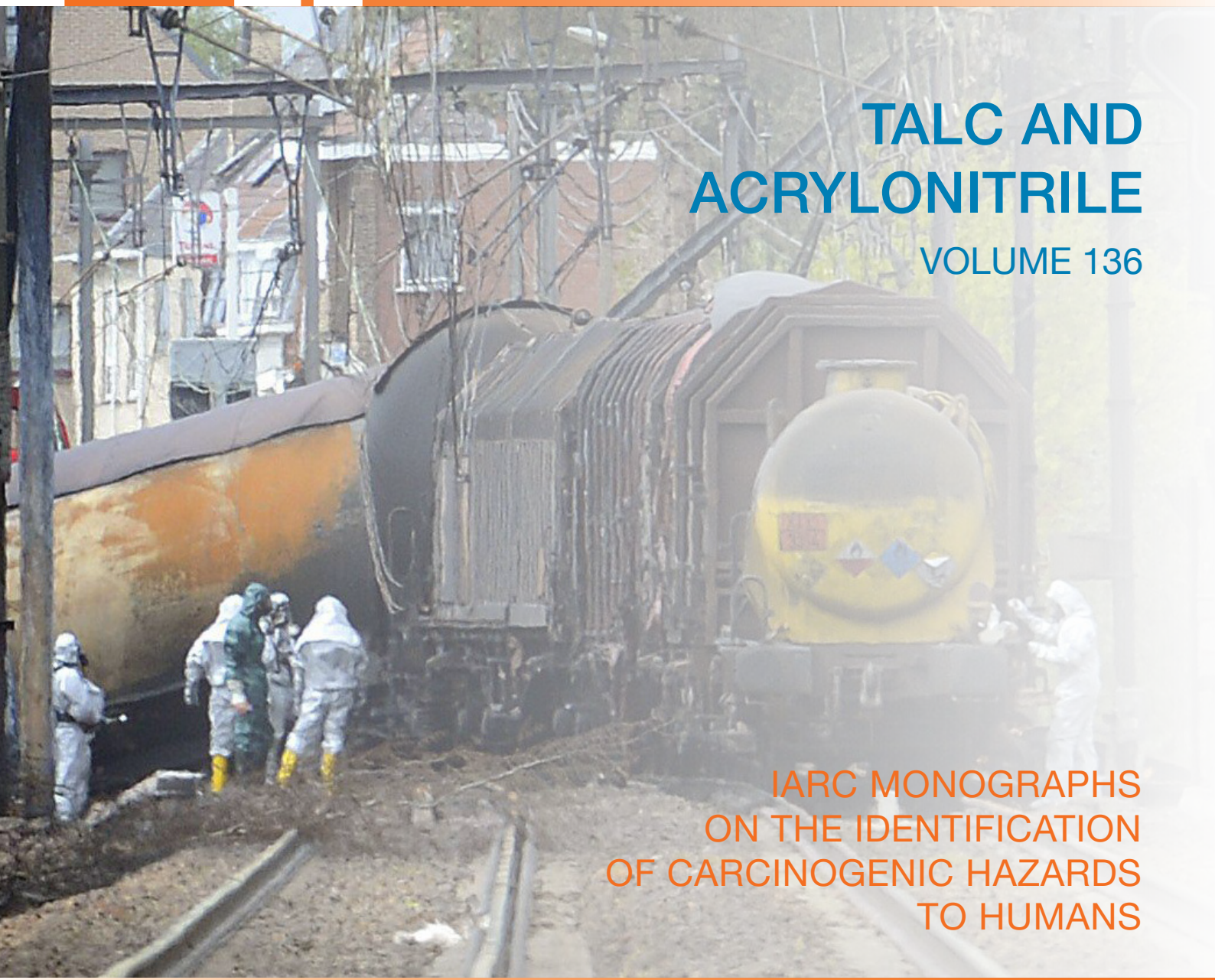
IARC MONOGRAPHS



TALC AND ACRYLONITRILE

VOLUME 136

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

Advance publication, 30 June 2025

International Agency for Research on Cancer

World Health Organization

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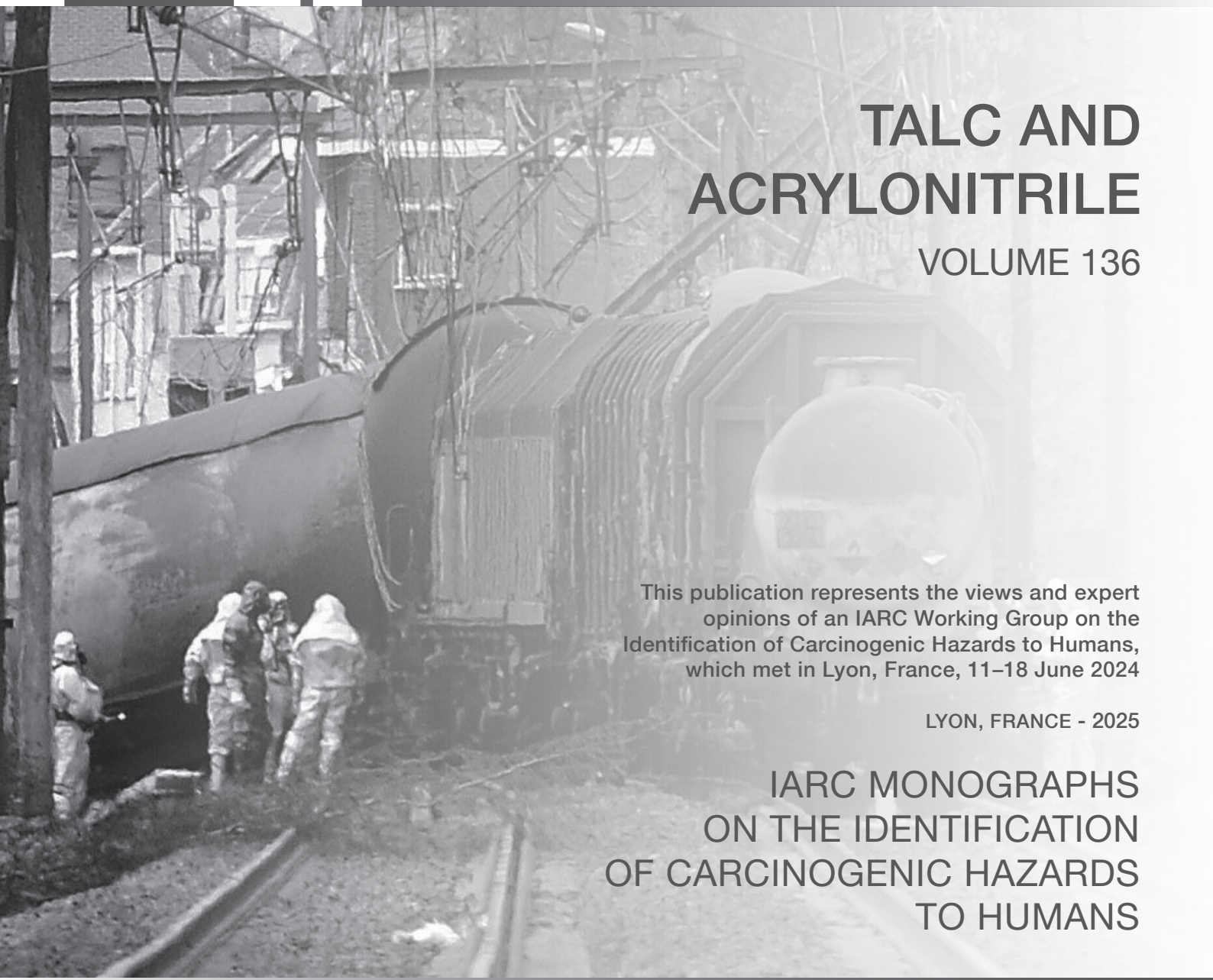
IARC MONOGRAPHS



TALC AND ACRYLONITRILE

VOLUME 136

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 11–18 June 2024

LYON, FRANCE - 2025

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

Advance publication, 30 June 2025

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic hazard of chemicals to humans, involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic hazards associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of cancer hazard to humans with the help of international working groups of experts in carcinogenesis and related fields; and to identify gaps in evidence. The lists of IARC evaluations are regularly updated and are available on the internet at https://monographs.iarc.who.int/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (for further information please consult: https://ec.europa.eu/social/easi). Support has also been provided since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

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About the cover: The cover photo shows draining activities at the wreck of a train that was transporting acrylonitrile and that derailed in Wetteren, Belgium, in May 2013. The incident led to the emergency evacuation of some 500 local residents.

Source: © Belga News Agency / Alamy Stock Photo

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The *IARC Monographs* Working Group and Secretariat for Volume 136, Talc and Acrylonitrile, who met in Lyon, France, on 11–18 June 2024.

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NOTE TO THE READER

The evaluations of carcinogenic hazard in the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* series are made by international working groups of independent scientists. The *IARC Monographs* classifications do not indicate the level of risk associated with a given level or circumstance of exposure. The *IARC Monographs* do not make recommendations for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic hazard of an agent to humans is encouraged to make this information available to the *IARC Monographs* programme, International Agency for Research on Cancer, 25 avenue Tony Garnier, CS 90627, 69366 Lyon Cedex 07, or via email at imo@iarc.who.int, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Monographs* programme. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.who.int/).

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[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Invited Specialists do not serve as Meeting Chair or Subgroup Chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. Each participant was asked to declare potentially relevant research, employment, and financial interests that are current or that have occurred during the past 4 years. Minimal interests are not disclosed here, and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All other non-publicly funded grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are disclosed as potentially significant conflicts of interests.

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[2] Dr Stewart reported being employed by Stewart Exposure Assessments, LLC, but the work conducted by this company does not involve competing interests for the topics covered by the present *IARC Monographs* Meeting.

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Mary Schubauer-Berigan *(Programme Head; Rapporteur, Cancer in Humans)*
Sanam Shah

[3] Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Working Group members, draft any part of a monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.
[4] Dr Bandli reported being employed by RJ Lee Group, an analytical laboratory and scientific consulting firm with business interests that may be affected by the outcome of this present meeting, and providing expert opinion on behalf of law firms in connection with expert testimony for defendants in talc litigation.
[5] Dr Jameson reported being employed by CWJ Consulting and providing expert opinion on behalf of law firms in connection with expert testimony for plaintiffs in talc litigation.
[6] Dr Kirman reported being employed by SciPinion and consulting for and receiving research support from the Acrylonitrile Group, which is also sponsoring his travel to and attendance at the present *IARC Monographs* meeting, and from EUROTALC.
[7] Dr Mundt was employed by the University of Massachusetts and as an independent consultant; he declared benefiting from personal consultancy fees from EUROTALC (current) and CTiS (past); providing expert opinion on behalf of entities producing, marketing, and retailing cosmetic products in connection with talc litigations; receiving support for travel and accommodation from EUROTALC to participate in the present *IARC Monographs* meeting, as well as support for travel and stipend from the Acrylonitrile Group in order to observe the proceedings on their behalf; and benefiting from research support from a tobacco company in his capacity of science advisory group member to summarize the epidemiological literature on non-combusted tobacco products.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, general principles and procedures, and scientific review and evaluations. The *IARC Monographs* embody principles of scientific rigour, impartial evaluation, transparency, and consistency. The Preamble should be consulted when reading a *Monograph* or a summary of a *Monograph*'s evaluations. Separate Instructions for Authors describe the operational procedures for the preparation and publication of a volume of the *Monographs*.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after the International Agency for Research on Cancer (IARC) was established in 1965, it started to receive frequent requests for advice on the carcinogenicity of chemicals, including requests for lists of established and suspected human carcinogens. In 1970, an IARC Advisory Committee on Environmental Carcinogenesis recommended "that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented." The next year, the IARC Governing Council adopted a resolution that IARC should prepare "monographs on the evaluation of carcinogenic risk of chemicals to man", which became the initial title of the series.

In succeeding years, the scope of the programme broadened as *Monographs* were developed for complex mixtures, occupational exposures, physical agents, biological organisms, pharmaceuticals, and other exposures. In 1988, "of chemicals" was dropped from the title, and in 2019, "evaluation of carcinogenic risks" became "identification of carcinogenic hazards", in line with the objective of the programme.

Identifying the causes of human cancer is the first step in cancer prevention. The identification of a cancer hazard may have broad and profound implications. National and international authorities and organizations can and do use information on causes of cancer in support of actions to reduce exposure to carcinogens in the workplace, in the environment, and elsewhere. Cancer prevention is needed as much today as it was when IARC was established, because the global burden of cancer is high and continues to increase as a result of population growth and ageing and upward trends in some exposures, especially in low- and middle-income countries (https://publications.iarc.who.int/Non-Series-Publications/World-Cancer-Reports).

IARC's process for developing *Monographs*, which has evolved over several decades, involves

the engagement of international, interdisciplinary Working Groups of expert scientists, the transparent synthesis of different streams of evidence (exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis), and the integration of these streams of evidence into an overall evaluation and classification according to criteria developed and refined by IARC. Since the *Monographs* programme was established, the understanding of carcinogenesis has greatly deepened. Scientific advances are incorporated into the evaluation methodology. In particular, strong mechanistic evidence has had an increasing role in the overall evaluations since 1991.

The Preamble is primarily a statement of the general principles and procedures used in developing a *Monograph*, to promote transparency and consistency across *Monographs* evaluations. In addition, IARC provides Instructions for Authors (https://monographs.iarc.who.int/preamble-instructions-for-authors/), which specify more detailed working procedures. IARC routinely updates these Instructions for Authors to reflect advances in methods for cancer hazard identification and accumulated experience, including input from experts.

2. Objective and scope

The objective of the programme is to prepare, with the engagement of international, interdisciplinary Working Groups of experts, scientific reviews and evaluations of evidence on the carcinogenicity of a wide range of agents.

The *Monographs* assess the strength of the available evidence that an agent can cause cancer in humans, based on three streams of evidence: on cancer in humans (see Part B, Section 2), on cancer in experimental animals (see Part B, Section 3), and on mechanistic evidence (see Part B, Section 4). In addition, the exposure to each agent is characterized (see Part B, Section 1). In this Preamble, the term "agent" refers to any chemical, physical, or biological entity or exposure circumstance (e.g. occupation as a painter) for which evidence on the carcinogenicity is evaluated.

A cancer *hazard* is an agent that is capable of causing cancer, whereas a cancer *risk* is an estimate of the probability that cancer will occur given some level of exposure to a cancer hazard. The *Monographs* assess the strength of evidence that an agent is a cancer hazard. The distinction between hazard and risk is fundamental. The *Monographs* identify cancer hazards even when risks appear to be low in some exposure scenarios. This is because the exposure may be widespread at low levels, and because exposure levels in many populations are not known or documented.

Although the *Monographs* programme has focused on hazard identification, some epidemiological studies used to identify a cancer hazard are also used to estimate an exposure–response relationship within the range of the available data. However, extrapolating exposure–response relationships beyond the available data (e.g. to lower exposures, or from experimental animals to humans) is outside the scope of *Monographs* Working Groups (IARC, 2014). In addition, the *Monographs* programme does not review quantitative risk characterizations developed by other health agencies.

The identification of a cancer hazard should trigger some action to protect public health, either directly as a result of the hazard identification or through the conduct of a risk assessment. Although such actions are outside the scope of the programme, the *Monographs* are used by national and international authorities and organizations to inform risk assessments, formulate decisions about preventive measures, motivate effective cancer control programmes, and choose among options for public health decisions. *Monographs* evaluations are only one part of the body of information on which decisions to control exposure to carcinogens may be based.

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Options to prevent cancer vary from one situation to another and across geographical regions and take many factors into account, including different national priorities. Therefore, no recommendations are given in the *Monographs* with regard to regulation, legislation, or other policy approaches, which are the responsibility of individual governments or organizations. The *Monographs* programme also does not make research recommendations. However, it is important to note that *Monographs* contribute significantly to the science of carcinogenesis by synthesizing and integrating streams of evidence about carcinogenicity and pointing to critical gaps in knowledge.

3. Selection of agents for review

Since 1984, about every five years IARC convenes an international, interdisciplinary Advisory Group to recommend agents for review by the *Monographs* programme. IARC selects Advisory Group members who are knowledgeable about current research on carcinogens and public health priorities. Before an Advisory Group meets, IARC solicits nominations of agents from scientists and government agencies worldwide. Since 2003, IARC also invites nominations from the public. IARC charges each Advisory Group with reviewing nominations, evaluating exposure and hazard potential, and preparing a report that documents the Advisory Group's process for these activities and its rationale for the recommendations.

For each new volume of the *Monographs*, IARC selects the agents for review from those recommended by the most recent Advisory Group, considering the availability of pertinent research studies and current public health priorities. On occasion, IARC may select other agents if there is a need to rapidly evaluate an emerging carcinogenic hazard or an urgent need to re-evaluate a previous classification. All evaluations consider the full body of available evidence, not just information published after a previous review.

A *Monograph* may review:

(a) An agent not reviewed in a previous *Monograph*, if there is potential human exposure and there is evidence for assessing its carcinogenicity. A group of related agents (e.g. metal compounds) may be reviewed together if there is evidence for assessing carcinogenicity for one or more members of the group.

(b) An agent reviewed in a previous *Monograph*, if there is new evidence of cancer in humans or in experimental animals, or mechanistic evidence to warrant re-evaluation of the classification. In the interests of efficiency, the literature searches may build on previous comprehensive searches.

(c) An agent that has been established to be carcinogenic to humans and has been reviewed in a previous *Monograph*, if there is new evidence of cancer in humans that indicates new tumour sites where there might be a causal association. In the interests of efficiency, the review may focus on these new tumour sites.

4. The Working Group and other meeting participants

Five categories of participants can be present at *Monographs* meetings:

(i) *Working Group* members are responsible for all scientific reviews and evaluations developed in the volume of the *Monographs*. The Working Group is interdisciplinary and comprises subgroups of experts in the fields of (a) exposure characterization, (b) cancer in humans, (c) cancer in experimental animals, and (d) mechanistic evidence. IARC selects Working Group members on the basis of expertise related to the subject matter and relevant methodologies, and absence

of conflicts of interest. Consideration is also given to diversity in scientific approaches and views, as well as demographic composition. Working Group members generally have published research related to the exposure or carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Since 2006, IARC also has encouraged public nominations through its Call for Experts. IARC's reliance on experts with knowledge of the subject matter and/or expertise in methodological assessment is confirmed by decades of experience documenting that there is value in specialized expertise and that the overwhelming majority of Working Group members are committed to the objective evaluation of scientific evidence and not to the narrow advancement of their own research results or a pre-determined outcome (Wild and Cogliano, 2011). Working Group members are expected to serve the public health mission of IARC, and should refrain from consulting and other activities for financial gain that are related to the agents under review, or the use of inside information from the meeting, until the full volume of the *Monographs* is published.

IARC identifies, from among Working Group members, individuals to serve as Meeting Chair and Subgroup Chairs. At the opening of the meeting, the Working Group is asked to endorse the selection of the Meeting Chair, with the opportunity to propose alternatives. The Meeting Chair and Subgroup Chairs take a leading role at all stages of the review process (see Part A, Section 7), promote open scientific discussions that involve all Working Group members in accordance with normal committee procedures, and ensure adherence to the Preamble.

(ii) *Invited Specialists* are experts who have critical knowledge and experience but who also have a conflict of interest that warrants exclusion from developing or influencing the evaluations of carcinogenicity. Invited Specialists do not draft any section of the *Monograph* that pertains to the description or interpretation of cancer data, and they do not participate in the evaluations. These experts are invited in limited numbers when necessary to assist the Working Group by contributing their unique knowledge and experience to the discussions.

(iii) *Representatives of national and international health agencies* may attend because their agencies are interested in the subject of the meeting. They do not draft any section of the *Monograph* or participate in the evaluations.

(iv) *Observers* with relevant scientific credentials may be admitted in limited numbers. Attention is given to the balance of Observers from constituencies with differing perspectives. Observers are invited to observe the meeting and should not attempt to influence it, and they agree to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers do not draft any section of the *Monograph* or participate in the evaluations.

(v) The *IARC Secretariat* consists of scientists who are designated by IARC and who have relevant expertise. The IARC Secretariat coordinates and facilitates all aspects of the evaluation and ensures adherence to the Preamble throughout development of the scientific reviews and classifications (see Part A, Sections 5 and 6). The IARC Secretariat organizes and announces the meeting, identifies and recruits the Working Group members, and assesses the declared interests of all meeting participants. The IARC Secretariat supports the activities of the Working Group (see Part A, Section 7) by searching the literature and performing title and abstract screening, organizing conference calls to coordinate the development of pre-meeting

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Table 1 Roles of participants at *IARC Monographs* meetings

Category of participant	Role			
	Prepare text, tables, and analyses	Participate in discussions	Participate in evaluations	Eligible to serve as Chair
Working Group members	✓	✓	✓	✓
Invited Specialists	✓[a]	✓		
Representatives of health agencies		✓[b]		
Observers		✓[b]		
IARC Secretariat	✓[c]	✓	✓[d]	

[a] Only for the section on exposure characterization.
[b] Only at times designated by the Meeting Chair and Subgroup Chairs.
[c] When needed or requested by the Meeting Chair and Subgroup Chairs.
[d] Only for clarifying or interpreting the Preamble.

drafts and discuss cross-cutting issues, and reviewing drafts before and during the meeting. Members of the IARC Secretariat serve as meeting rapporteurs, assist the Meeting Chair and Subgroup Chairs in facilitating all discussions, and may draft text or tables when designated by the Meeting Chair and Subgroup Chairs. Their participation in the evaluations is restricted to the role of clarifying or interpreting the Preamble.

All participants are listed, with their principal affiliations, in the front matter of the published volume of the *Monographs*. Working Group members and Invited Specialists serve as individual scientists and not as representatives of any organization, government, or industry (Cogliano et al., 2004).

The roles of the meeting participants are summarized in Table 1.

5. Working procedures

A separate Working Group is responsible for developing each volume of the *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year before the meeting of a Working Group, a preliminary list of agents to be reviewed, together with a Call for Data and a Call for Experts, is announced on the *Monographs* programme website (https://monographs.iarc.who.int/).

Before a meeting invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests form to report financial interests, employment and consulting (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests such as public statements and positions related to the subject of the meeting. IARC assesses the declared interests to determine whether there is a conflict that warrants any limitation on participation (see Table 2).

Approximately two months before a *Monographs* meeting, IARC publishes the names and affiliations of all meeting participants together with a summary of declared interests, in the interests of transparency and to provide an opportunity for undeclared conflicts of interest to be brought to IARC's attention. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

The Working Group meets at IARC for approximately eight days to discuss and finalize the scientific review and to develop summaries

Table 2 Public engagement during *Monographs* development

Approximate timeframe	Engagement
Every 5 years	IARC convenes an Advisory Group to recommend high-priority agents for future review
~1 year before a *Monographs* meeting	IARC selects agents for review in a new volume of the *Monographs* IARC posts on its website: Preliminary List of Agents to be reviewed Call for Data and Call for Experts Request for Observer Status WHO Declaration of Interests form
~8 months before a *Monographs* meeting	Call for Experts closes
~4 months before a *Monographs* meeting	Request for Observer Status closes
~2 months before a *Monographs* meeting	IARC posts the names of all meeting participants together with a summary of declared interests, and a statement discouraging contact of the Working Group by interested parties
~1 month before a *Monographs* meeting	Call for Data closes
~2–4 weeks after a *Monographs* meeting	IARC publishes a summary of evaluations and key supporting evidence
~9 months after a *Monographs* meeting	IARC Secretariat publishes the verified and edited master copy of plenary drafts as a *Monographs* volume

and evaluations. At the opening of the meeting, all participants update their Declaration of Interests forms, which are then reviewed by IARC. Declared interests related to the subject of the meeting are disclosed to the meeting participants during the meeting and in the published volume (Cogliano et al., 2004). The objectives of the meeting are peer review and consensus. During the first part of the meeting, subgroup sessions (covering exposure characterization, cancer in humans, cancer in experimental animals, and mechanistic evidence) review the pre-meeting drafts, develop a joint subgroup draft, and draft subgroup summaries. During the last part of the meeting, the Working Group meets in plenary session to review the subgroup drafts and summaries and to develop the consensus evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections. After the meeting, the master copy is verified by the IARC Secretariat and is then edited and prepared for publication. The aim is to publish the volume within approximately nine months of the Working Group meeting. A summary of the evaluations and key supporting evidence is prepared for publication in a scientific journal or is made available on the *Monographs* programme website soon after the meeting.

In the interests of transparency, IARC engages with the public throughout the process, as summarized in Table 2.

6. Overview of the scientific review and evaluation process

The Working Group considers all pertinent epidemiological studies, cancer bioassays in experimental animals, and mechanistic evidence, as well as pertinent information on exposure in humans. In general, for cancer in humans, cancer in experimental animals, and mechanistic evidence, only studies that have been published or accepted for publication in the openly available scientific literature are reviewed. Under some circumstances, materials that are publicly available and whose content is final may be reviewed if there is sufficient information to permit an evaluation of the quality of the methods and results of the studies (see Step 1,

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below). Such materials may include reports and databases publicly available from government agencies, as well as doctoral theses. The reliance on published and publicly available studies promotes transparency and protects against citation of premature information.

The principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence related to cancer in humans, cancer in experimental animals, and mechanistic evidence (as described in Part B, Sections 2–4 and as detailed in the Instructions for Authors). Each *Monograph* specifies or references information on the conduct of the literature searches, including search terms and inclusion/exclusion criteria that were used for each stream of evidence.

In brief, the steps of the review process are as follows:

Step 1. Comprehensive and transparent identification of the relevant information: The IARC Secretariat identifies relevant studies through initial comprehensive searches of literature contained in authoritative biomedical databases (e.g. PubMed, PubChem) and through a Call for Data. These literature searches, designed in consultation with a librarian and other technical experts, address whether the agent causes cancer in humans, causes cancer in experimental systems, and/or exhibits key characteristics of established human carcinogens (in humans or in experimental systems). The Working Group provides input and advice to IARC to refine the search strategies, and identifies literature through other searches (e.g. from reference lists of past *Monographs*, retrieved articles, and other authoritative reviews).

For certain types of agents (e.g. regulated pesticides and pharmaceuticals), IARC also provides an opportunity to relevant regulatory authorities, and regulated parties through such authorities, to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to permit an independent evaluation of (a) whether there has been selective reporting (e.g. on outcomes, or from a larger set of conducted studies); (b) study quality (e.g. design, methodology, and reporting of results), and (c) study results.

Step 2. Screening, selection, and organization of the studies: The IARC Secretariat screens the retrieved literature for inclusion based on title and abstract review, according to pre-defined exclusion criteria. For instance, studies may be excluded if they were not about the agent (or a metabolite of the agent), or if they reported no original data on epidemiological or toxicological end-points (e.g. review articles). The Working Group reviews the title and abstract screening done by IARC, and performs full-text review. Any reasons for exclusion are recorded, and included studies are organized according to factors pertinent to the considerations described in Part B, Sections 2–4 (e.g. design, species, and endpoint). Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results.

Step 3. Evaluation of study quality: The Working Group evaluates the quality of the included studies based on the considerations (e.g. design, methodology, and reporting of results) described in Part B, Sections 2–4. Based on these considerations, the Working Group may accord greater weight to some of the included studies. Interpretation of the results and the strengths and limitations of a study are clearly outlined in square brackets at the end of study descriptions (see Part B).

Step 4: *Report characteristics of included studies, including assessment of study*

quality: Pertinent characteristics and results of included studies are reviewed and succinctly described, as detailed in Part B, Sections 1–4. Tabulation of data may facilitate this reporting. This step may be iterative with Step 3.

Step 5: *Synthesis and evaluation of strength of evidence*: The Working Group summarizes the overall strengths and limitations of the evidence from the individual streams of evidence (cancer in humans, cancer in experimental animals, and mechanistic evidence; see Part B, Section 5). The Working Group then evaluates the strength of evidence from each stream of evidence by using the transparent methods and defined descriptive terms given in Part B, Sections 6a–c. The Working Group then develops, and describes the rationale for, the consensus classification of carcinogenicity that integrates the conclusions about the strength of evidence from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic evidence (see Part B, Section 6d).

7. Responsibilities of the Working Group

The Working Group is responsible for identifying and evaluating the relevant studies and developing the scientific reviews and evaluations for a volume of the *Monographs*. The IARC Secretariat supports these activities of the Working Group (see Part A, Section 4). Briefly, the Working Group's tasks in developing the evaluation are, in sequence:

(i) Before the meeting, the Working Group ascertains that all appropriate studies have been identified and selected, and assesses the methods and quality of each individual study, as outlined above (see Part A, Section 6). The Working Group members prepare pre-meeting working drafts that present accurate tabular or textual summaries of informative studies by extracting key elements of the study design and results, and highlighting notable strengths and limitations. They participate in conference calls organized by IARC to coordinate the development of working drafts and to discuss cross-cutting issues. Pre-meeting reviews of all working drafts are generally performed by two or more subgroup members who did not participate in study identification, data extraction, or study review for the draft. Each study summary is written or reviewed by someone who is not associated with the study.

(ii) At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary. A proposed classification of the strength of the evidence reviewed in the subgroup using the *IARC Monographs* criteria (see Part B, Sections 6a–c) is then developed from the consensus subgroup drafts of the evidence summaries (see Part B, Section 5).

(iii) During the plenary session, each subgroup presents its drafts for scientific review and discussion to the other Working Group members, who did not participate in study identification, data extraction, or study review for the drafts. Subgroup Chairs ensure that someone who is not associated with the study leads the discussion of each study summary. After review, discussion, and revisions as needed, the subgroup drafts are adopted as a consensus Working Group product. The summaries and classifications of the strength of the evidence, developed in the subgroup in line with the *IARC Monographs* criteria

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(see Part B, Sections 6a–c), are considered, revised as needed, and adopted by the full Working Group. The Meeting Chair proposes an overall evaluation using the guidance provided in Part B, Section 6d.

The Working Group strives to achieve consensus evaluations. Consensus reflects broad agreement among the Working Group, but not necessarily unanimity. The Meeting Chair may poll the Working Group to determine the diversity of scientific opinion on issues where consensus is not apparent.

Only the final product of the plenary session represents the views and expert opinions of the Working Group. The entire *Monographs* volume is the joint product of the Working Group and represents an extensive and thorough peer review of the body of evidence (individual studies, synthesis, and evaluation) by an interdisciplinary expert group. Initial working papers and subsequent revisions are not released, because they would give an incomplete and possibly misleading impression of the consensus developed by the Working Group over a full week of deliberation.

B. SCIENTIFIC REVIEW AND EVALUATION

This part of the Preamble discusses the types of evidence that are considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations. In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and any key issues encountered during the meeting.

1. Exposure characterization

This section identifies the agent and describes its occurrence, main uses, and production locations and volumes, where relevant. It also summarizes the prevalence, concentrations in relevant studies, and relevant routes of exposure in humans worldwide. Methods of exposure measurement and analysis are described, and methods of exposure assessment used in key epidemiological studies reviewed by the Working Group are described and evaluated.

Over the course of the *Monographs* programme, concepts of exposure and dose have evolved substantially with deepening understanding of the interactions of agents and biological systems. The concept of exposure has broadened and become more holistic, extending beyond chemical, physical, and biological agents to stressors as construed generally, including psychosocial stressors (National Research Council, 2012; National Academies of Sciences, Engineering, and Medicine, 2017). Overall, this broader conceptualization supports greater integration between exposure characterization and other sections of the *Monographs*. Concepts of absorption, distribution, metabolism, and excretion are considered in the first subsection of mechanistic evidence (see Part B, Section 4a), whereas validated biomarkers of internal exposure or metabolites that are routinely used for exposure assessment are reported on in this section (see Part B, Section 1b).

(a) Identification of the agent

The agent being evaluated is unambiguously identified. Details will vary depending on the type of agent but will generally include physical and chemical properties relevant to the agent's identification, occurrence, and biological activity. If the material that has been tested in experimental animals or in vitro systems is different from that to which humans are exposed, these differences are noted.

For chemical agents, the Chemical Abstracts Service Registry Number is provided, as well as the latest primary name and other names in common use, including important trade names,

along with available information on the composition of common mixtures or products containing the agent, and potentially toxic and/or carcinogenic impurities. Physical properties relevant to understanding the potential for human exposure and measures of exposure used in studies in humans are summarized. These might include physical state, volatility, aqueous and fat solubility, and half-life in the environment and/or in human tissues.

For biological agents, taxonomy and structure are described. Mode of replication, life-cycle, target cells, persistence, latency, and host responses, including morbidity and mortality through pathologies other than cancer, are also presented.

For foreign bodies, fibres and particles, composition, size range, relative dimensions, and accumulation, persistence, and clearance in target organs are summarized. Physical agents that are forms of radiation are described in terms of frequency spectrum and energy transmission.

Exposures may result from, or be influenced by, a diverse range of social and environmental factors, including components of diet, sleep, and physical activity patterns. In these instances, this section will include a description of the agent, its variability across human populations, and its composition or characteristics relevant to understanding its potential carcinogenic hazard to humans and to evaluating exposure assessments in epidemiological studies.

(b) Detection and analysis

Key methods of detection and quantification of the agent are presented, with an emphasis on those used most widely in surveillance, regulation, and epidemiological studies. Measurement methods for sample matrices that are deemed important sources of human exposure (e.g. air, drinking-water, food, residential dust) and for validated exposure biomarkers (e.g. the agent or its metabolites in human blood, urine, or saliva) are described. Information on detection and quantification limits is provided when it is available and is useful for interpreting studies in humans and in experimental animals. This is not an exhaustive treatise but is meant to help readers understand the strengths and limitations of the available exposure data and of the epidemiological studies that rely on these measurements.

(c) Production and use

Historical and geographical patterns and trends in production and use are included when they are available, to help readers understand the contexts in which exposures may occur, both within key epidemiological studies reviewed by the Working Group and in human populations generally. Industries that produce, use, or dispose of the agent are described, including their global distribution, when available. National or international listing as a high-production-volume chemical or similar classification may be included. Production processes with significant potential for occupational exposure or environmental pollution are indicated. Trends in global production volumes, technologies, and other data relevant to understanding exposure potential are summarized. Minor or historical uses with significant exposure potential or with particular relevance to key epidemiological studies are included. Particular effort may be directed towards finding data on production in low- and middle-income countries, where rapid economic development may lead to higher exposures than those in high-income countries.

(d) Exposure

A concise overview of quantitative information on sources, prevalence, and levels of exposure in humans is provided. Representative data from research studies, government reports and websites, online databases, and other citable, publicly available sources are tabulated. Data

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from low- and middle-income countries are sought and included to the extent feasible; information gaps for key regions are noted. Naturally occurring sources of exposure, if any, are noted. Primary exposure routes (e.g. inhalation, ingestion, skin uptake) and other considerations relevant to understanding the potential for cancer hazard from exposure to the agent are reported.

For occupational settings, information on exposure prevalence and levels (e.g. in air or human tissues) is reported by industry, occupation, region, and other characteristics (e.g. process, task) where feasible. Information on historical exposure trends, protection measures to limit exposure, and potential co-exposures to other carcinogenic agents in workplaces is provided when available.

For non-occupational settings, the occurrence of the agent is described with environmental monitoring or surveillance data. Information on exposure prevalence and levels (e.g. concentrations in human tissues) as well as exposure from and/or concentrations in food and beverages, consumer products, consumption practices, and personal microenvironments is reported by region and other relevant characteristics. Particular importance is placed on describing exposures in life stages or in states of disease or nutrition that may involve greater exposure or susceptibility.

Current exposures are of primary interest; however, information on historical exposure trends is provided when available. Historical exposures may be relevant for interpreting epidemiological studies, and when agents are persistent or have long-term effects. Information gaps for important time periods are noted. Exposure data that are not deemed to have high relevance to human exposure are generally not considered.

(e) Regulations and guidelines

Regulations or guidelines that have been established for the agent (e.g. occupational exposure limits, maximum permitted levels in foods and water, pesticide registrations) are described in brief to provide context about government efforts to limit exposure; these may be tabulated if they are informative for the interpretation of existing or historical exposure levels. Information on applicable populations, specific agents concerned, basis for regulation (e.g. human health risk, environmental considerations), and timing of implementation may be noted. National and international bans on production, use, and trade are also indicated.

This section aims to include major or illustrative regulations and may not be comprehensive, because of the complexity and range of regulatory processes worldwide. An absence of information on regulatory status should not be taken to imply that a given country or region lacks exposure to, or regulations on exposure to, the agent.

(f) Critical review of exposure assessment in key epidemiological studies

Epidemiological studies evaluate cancer hazard by comparing outcomes across differently exposed groups. Therefore, the type and quality of the exposure assessment methods used are key considerations when interpreting study findings for hazard identification. This section summarizes and critically reviews the exposure assessment methods used in the individual epidemiological studies that contribute data relevant to the *Monographs* evaluation.

Although there is no standard set of criteria for evaluating the quality of exposure assessment methods across all possible agents, some concepts are universally relevant. Regardless of the agent, all exposures have two principal dimensions: intensity (sometimes defined as concentration or dose) and time. Time considerations include

duration (time from first to last exposure), pattern or frequency (whether continuous or intermittent), and windows of susceptibility. This section considers how each of the key epidemiological studies characterizes these dimensions. Interpretation of exposure information may also be informed by consideration of mechanistic evidence (e.g. as described in Part B, Section 4a), including the processes of absorption, distribution, metabolism, and excretion.

Exposure intensity and time in epidemiological studies can be characterized by using environmental or biological monitoring data, records from workplaces or other sources, expert assessments, modelled exposures, job-exposure matrices, and subject or proxy reports via questionnaires or interviews. Investigators use these data sources and methods individually or in combination to assign levels or values of an exposure metric (which may be quantitative, semi-quantitative, or qualitative) to members of the population under study.

In collaboration with the Working Group members reviewing human studies (of cancer and of mechanisms), key epidemiological studies are identified. For each selected study, the exposure assessment approach, along with its strengths and limitations, is summarized using text and tables. Working Group members identify concerns about exposure assessment methods and their impacts on overall quality for each study reviewed (see Part B, Sections 2d and 4d). In situations where the information provided in the study is inadequate to properly consider the exposure assessment, this is indicated. When adequate information is available, the likely direction of bias due to error in exposure measurement, including misclassification (overestimated effects, underestimated effects, or unknown) is discussed.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part B, Section 2b) that include cancer as an outcome. These studies encompass certain types of biomarker studies, for example, studies with biomarkers as exposure metrics (see Part B, Section 2) or those evaluating histological or tumour subtypes and molecular signatures in tumours consistent with a given exposure (Alexandrov et al., 2016). Studies that evaluate early biological effect biomarkers are reviewed in Part B, Section 4.

(a) Types of study considered

Several types of epidemiological studies contribute to the assessment of carcinogenicity in humans; they typically include cohort studies (including variants such as case–cohort and nested case–control studies), case–control studies, ecological studies, and intervention studies. Rarely, results from randomized trials may be available. Exceptionally, case reports and case series of cancer in humans may also be reviewed. In addition to these designs, innovations in epidemiology allow for many other variants that may be considered in any given *Monographs* evaluation.

Cohort and case–control studies typically have the capacity to relate individual exposures under study to the occurrence of cancer in individuals, and provide an estimate of effect (such as relative risk) as the main measure of association. Well-conducted cohort and case–control studies provide most of the evidence of cancer in humans evaluated by Working Groups. Intervention studies are much less common, but when available can provide strong evidence for making causal inferences.

In ecological studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary

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measure of the exposure in the population under study. In ecological studies, data on individual exposure and outcome are not available, which renders this type of study more prone to confounding and exposure misclassification. In some circumstances, however, ecological studies may be informative, especially when the unit of exposure is most accurately measured at the population level (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

Exceptionally, case reports and case series may provide compelling evidence about the carcinogenicity of an agent. In fact, many of the early discoveries of occupational cancer hazards came about because of observations by workers and their clinicians, who noted a high frequency of cancer in workers who share a common occupation or exposure. Such observations may be the starting point for more structured investigations, but in exceptional circumstances, when the risk is high enough, the case series may in itself provide compelling evidence. This would be especially warranted in situations where the exposure circumstance is fairly unusual, as it was in the example of plants containing aristolochic acid (IARC, 2012a).

The uncertainties that surround the interpretation of case reports, case series, and ecological studies typically make them inadequate, except in rare instances as described above, to form the sole basis for inferring a causal relationship. However, when considered together with cohort and case–control studies, these types of study may support the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, pre-neoplastic lesions, malignant precursors, and other end-points are also reviewed when they relate to the agents reviewed. On occasion they can strengthen inferences drawn from studies of cancer itself. For example, benign brain tumours may share common risk factors with those that are malignant, and benign neoplasms (or those of uncertain behaviour) may be part of the causal path to malignancies (e.g. myelodysplastic syndromes, which may progress to acute myeloid leukaemia).

(b) Identification of eligible studies of cancer in humans

Relevant studies of cancer in humans are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Eligible studies include all studies in humans of exposure to the agent of interest with cancer as an outcome. Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single cohort, from analyses focused on different aspects of an exposure–disease association, or from inclusion of overlapping populations. Usually in such situations, only the most recent, most comprehensive, or most informative report is reviewed in detail.

(c) Assessment of study quality and informativeness

Epidemiological studies are potentially susceptible to several different sources of error, summarized briefly below. Qualities of individual studies that address these issues are also described below.

Study quality is assessed as part of the structured expert review process undertaken by the Working Group. A key aspect of quality assessment is consideration of the possible roles of chance and bias in the interpretation of epidemiological studies. Chance, which is also called random variation, can produce misleading study results. This variability in study results is strongly influenced by the sample size: smaller studies are more likely than larger studies to have effect estimates that are imprecise. Confidence intervals

around a study's point estimate of effect are used routinely to indicate the range of values of the estimate that could easily be produced by chance alone.

Bias is the effect of factors in study design or conduct that lead an association to erroneously appear stronger or weaker than the association that really exists between the agent and the disease. Biases that require consideration are varied but are usually categorized as selection bias, information bias (e.g. error in measurement of exposure and diseases), and confounding (or confounding bias) (Rothman et al., 2008). Selection bias in an epidemiological study occurs when inclusion of participants from the eligible population or their follow-up in the study is influenced by their exposure or their outcome (usually disease occurrence). Under these conditions, the measure of association found in the study will not accurately reflect the association that would otherwise have been found in the eligible population (Hernán et al., 2004). Information bias results from inaccuracy in exposure or outcome measurement. Both can cause an association between hypothesized cause and effect to appear stronger or weaker than it really is. Confounding is a mixing of extraneous effects with the effects of interest (Rothman et al., 2008). An association between the purported causal factor and another factor that is associated with an increase or decrease in incidence of disease can lead to a spurious association or absence of a real association of the presumed causal factor with the disease. When either of these occurs, confounding is present.

In assessing study quality, the Working Group consistently considers the following aspects:

- **Study description:** Clarity in describing the study design and its implementation, and the completeness of reporting of all other key information about the study and its results.
- **Study population:** Whether the study population was appropriate for evaluating the association between the agent and cancer. Whether the study was designed and carried out to minimize selection bias. Cancer cases in the study population must have been identified in a way that was independent of the exposure of interest, and exposure assessed in a way that was not related to disease (outcome) status. In these respects, completeness of recruitment into the study from the population of interest and completeness of follow-up for the outcome are essential measures.
- **Outcome measurement:** The appropriateness of the cancer outcome measure (e.g. mortality vs incidence) for the agent and cancer type under consideration, outcome ascertainment methodology, and the extent to which outcome misclassification may have led to bias in the measure(s) of association.
- **Exposure measurement:** The adequacy of the methods used to assess exposure to the agent, and the likelihood (and direction) of bias in the measure(s) of association due to error in exposure measurement, including misclassification (as described in Part B, Section 1f).
- **Assessment of potential confounding:** To what extent the authors took into account in the study design and analysis other variables (including co-exposures, as described in Part B, Section 1d) that can influence the risk of disease and may have been related to the exposure of interest. Important sources of potential confounding by such variables should have been addressed either in the design of the study, such as by matching or restriction, or in the analysis, by statistical adjustment. In some instances, where direct information on confounders is unavailable, use of indirect methods to evaluate the potential impact of confounding on exposure–disease associations is appropriate (e.g. Axelson and Steenland, 1988; Richardson et al., 2014).

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- **Other potential sources of bias:** Each epidemiological study is unique in its study population, its design, its data collection, and, consequently, its potential biases. All possible sources of bias are considered for their possible impact on the results. The possibility of reporting bias (i.e. selective reporting of some results and the suppression of others) should be explored.
- **Statistical methodology:** Adequacy of the statistical methods used and their ability to obtain unbiased estimates of exposure–outcome associations, confidence intervals, and test statistics for the significance of measures of association. Appropriateness of methods used to investigate confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders. Detailed analyses of cancer risks in relation to summary measures of exposure such as cumulative exposure, or temporal variables such as age at first exposure or time since first exposure, are reviewed and summarized when available.

For the sake of economy and simplicity, in this Preamble the list of possible sources of error is referred to with the phrase "chance, bias, and confounding", but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality.

These sources of error do not constitute and should not be used as a formal checklist of indicators of study quality. The judgement of experienced experts is critical in determining how much weight to assign to different issues in considering how all of these potential sources of error should be integrated and how to rate the potential for error related to each of these considerations.

The informativeness of a study is its ability to show a true association, if there is one, between the agent and cancer, and the lack of an association, if no association exists. Key determinants of informativeness include: having a study population of sufficient size to obtain precise estimates of effect; sufficient elapsed time from exposure to measurement of outcome for an effect, if present, to be observable; presence of an adequate exposure contrast (intensity, frequency, and/or duration); biologically relevant definitions of exposure; and relevant and well-defined time windows for exposure and outcome.

(d) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to inconsistent results that are difficult to interpret or reconcile. Combined analyses of data from multiple studies may be conducted as a means to address this ambiguity. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis), and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland and O'Rourke, 2008).

The strengths of combined analyses are increased precision because of increased sample size and, in the case of pooled analyses, the opportunity to better control for potential confounders and to explore in more detail interactions and modifying effects that may explain heterogeneity among studies. A disadvantage of combined analyses is the possible lack of comparability of data from various studies, because of differences in population characteristics, subject recruitment, procedures of data collection, methods of measurement, and effects of unmeasured covariates that may differ among studies. These differences in study methods and quality can influence results of either meta-analyses or pooled analyses. If published meta-analyses are to be considered by the Working Group, their adequacy needs to be carefully evaluated, including the methods used to identify eligible studies

and the accuracy of data extracted from the individual studies.

The Working Group may conduct ad hoc meta-analyses during the course of a *Monographs* meeting, when there are sufficient studies of an exposure–outcome association to contribute to the Working Group's assessment of the association. The results of such unpublished original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies, or de novo analyses.

Irrespective of the source of data for the meta-analyses and pooled analyses, the following key considerations apply: the same criteria for data quality must be applied as for individual studies; sources of heterogeneity among studies must be carefully considered; and the possibility of publication bias should be explored.

(e) Considerations in assessing the body of epidemiological evidence

The ability of the body of epidemiological evidence to inform the Working Group about the carcinogenicity of the agent is related to both the quantity and the quality of the evidence. There is no formulaic answer to the question of how many studies of cancer in humans are needed from which to draw inferences about causality, although more than a single study in a single population will almost always be needed. The number will depend on the considerations relating to evidence described below.

After the quality of individual epidemiological studies of cancer has been assessed and the informativeness of the various studies on the association between the agent and cancer has been evaluated, a judgement is made about the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several aspects of the body of evidence (e.g. Hill, 1965; Rothman et al., 2008; Vandenbroucke et al., 2016).

A strong association (e.g. a large relative risk) is more likely to indicate causality than is a weak association, because it is more difficult for confounding to falsely create a strong association. However, it is recognized that estimates of effect of small magnitude do not imply lack of causality and may have impact on public health if the disease or exposure is common. Estimates of effect of small magnitude could also contribute useful information to the assessment of causality if level of risk is commensurate with level of exposure when compared with risk estimates from populations with higher exposure (e.g. as seen in residential radon studies compared with studies of radon from uranium mining).

Associations that are consistently observed in several studies of the same design, or in studies that use different epidemiological approaches, or under different circumstances of exposure are more likely to indicate a causal relationship than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (e.g. differences in study informativeness because of latency, exposure levels, or assessment methods). Results of studies that are judged to be of high quality and informativeness are given more weight than those of studies judged to be methodologically less sound or less informative.

Temporality of the association is an essential consideration: that is, the exposure must precede the outcome.

An observation that cancer risk increases with increasing exposure is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship, and there are several reasons why the shape of the exposure–response association may be non-monotonic (e.g. Stayner et al., 2003). The demonstration of a decline in risk after cessation of or reduction in exposure

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in individuals or in whole populations also supports a causal interpretation of the findings.

Confidence in a causal interpretation of the evidence from studies of cancer in humans is enhanced if it is coherent with physiological and biological knowledge, including information about exposure to the target organ, latency and timing of the exposure, and characteristics of tumour subtypes.

The Working Group considers whether there are subpopulations with increased susceptibility to cancer from the agent. For example, molecular epidemiology studies that identify associations between genetic polymorphisms and inter-individual differences in cancer susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. Such studies may be particularly informative if polymorphisms are found to be modifiers of the exposure–response association, because evaluation of polymorphisms may increase the ability to detect an effect in susceptible subpopulations.

When, in the process of evaluating the studies of cancer in humans, the Working Group identifies several high-quality, informative epidemiological studies that clearly show either no positive association or an inverse association between an exposure and a specific type of cancer, a judgement may be made that, in the aggregate, they suggest evidence of lack of carcinogenicity for that cancer type. Such a judgement requires, first, that the studies strictly meet the standards of design and analysis described above. Specifically, the possibility that bias, confounding, or misclassification of exposure or outcome could explain the observed results should be considered and ruled out with reasonable confidence. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of relative effect of unity (or below unity) for any observed level of exposure, (b) when considered together, provide a combined estimate of relative risk that is at or below unity, and (c) have a narrow confidence interval. Moreover, neither any individual well-designed and well-conducted study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It must be noted that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the exposure levels reported and the timing and route of exposure studied, to the intervals between first exposure and disease onset observed in these studies, and to the general population(s) studied (i.e. there may be susceptible subpopulations or life stages). Experience from studies of cancer in humans indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; therefore, latency periods substantially shorter than about 30 years cannot provide evidence of lack of carcinogenicity. Furthermore, there may be critical windows of exposure, for example, as with diethylstilboestrol and clear cell adenocarcinoma of the cervix and vagina (IARC, 2012a).

3. Studies of cancer in experimental animals

Most human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species. For some agents, carcinogenicity in experimental animals was demonstrated before epidemiological studies identified their carcinogenicity in humans. Although this observation cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, such as strong evidence that a given agent causes cancer in

experimental animals through a species-specific mechanism that does not operate in humans (see Part B, Sections 4 and 6; Capen et al., 1999; IARC, 2003), these agents are considered to pose a potential carcinogenic hazard to humans. The inference of potential carcinogenic hazard to humans does not imply tumour site concordance across species (Baan et al., 2019).

(a) Types of studies considered

Relevant studies of cancer in experimental animals are identified by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below. Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (or possibly metabolites or derivatives of the agent) (see Part A, Section 7) after a thorough evaluation of the study features (see Part B, Section 3b). Those studies that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2018).

In addition to conventional long-term bioassays, alternative studies (e.g. in genetically engineered mouse models) may be considered in assessing carcinogenicity in experimental animals, also after a critical evaluation of the study features. For studies of certain exposures, such as viruses that typically only infect humans, use of such specialized experimental animal models may be particularly important; models include genetically engineered mice with targeted expression of viral genes to tissues from which human cancers arise, as well as humanized mice implanted with the human cells usually infected by the virus.

Other types of studies can provide supportive evidence. These include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies); studies in which the end-point was not cancer but a defined precancerous lesion; and studies of cancer in non-laboratory animals (e.g. companion animals) exposed to the agent.

(b) Study evaluation

Considerations of importance in the interpretation and evaluation of a particular study include: (i) whether the agent was clearly characterized, including the nature and extent of impurities and contaminants and the stability of the agent, and, in the case of mixtures, whether the sample characterization was adequately reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration and frequency of treatment, duration of observation, and route of exposure were appropriate; (iv) whether appropriate experimental animal species and strains were evaluated; (v) whether there were adequate numbers of animals per group; (vi) whether animals were allocated randomly to groups; (vii) whether the body weight, food and water consumption, and survival of treated animals were affected by any factors other than the test agent; (viii) whether the histopathology review was adequate; and (ix) whether the data were reported and analysed adequately.

(c) Outcomes and statistical analyses

An assessment of findings of carcinogenicity in experimental animals involves consideration of (i) study features such as route, doses, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age, and duration of follow-up; (ii) the spectrum of neoplastic response, from pre-neoplastic lesions and benign tumours to malignant neoplasms; (iii) the incidence, latency, severity, and multiplicity of neoplasms and pre-neoplastic

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lesions; (iv) the consistency of the results for a specific target organ or organs across studies of similar design; and (v) the possible role of modifying factors (e.g. diet, infection, stress).

Key factors for statistical analysis include: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type or lesion, and (iii) duration of survival.

Benign tumours may be combined with malignant tumours in the assessment of tumour incidence when (a) they occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) they appear to represent a stage in the progression to malignancy (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed.

Evidence of an increased incidence of neoplasms with increasing level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms. The form of the dose–response relationship can vary widely, including non-linearity, depending on the particular agent under study and the target organ. The dose–response relationship can also be affected by differences in survival among the treatment groups.

The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier and Bailer, 1989; Bieler and Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life and a survival-adjusted analysis would be warranted. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time that the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel–Haenszel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the poly-*k* test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other, more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

The concurrent control group is generally the most appropriate comparison group for statistical analysis; however, for uncommon tumours, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, sex, and strain, as well as other factors, such as basal diet and general laboratory environment, which may affect tumour response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003). It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls.

Meta-analyses and pooled analyses may be appropriate when the experimental protocols are sufficiently similar.

4. Mechanistic evidence

Mechanistic data may provide evidence of carcinogenicity and may also help in assessing the relevance and importance of findings of cancer in experimental animals and in humans (Guyton et al., 2009; Parkkinen et al., 2018) (see Part B, Section 6). Mechanistic studies have gained in prominence, increasing in their volume, diversity, and relevance to cancer hazard evaluation, whereas studies pertinent to other streams of evidence evaluated in the *Monographs* (i.e. studies of cancer in humans and lifetime cancer bioassays in rodents) may only be available for a fraction of agents to which humans are currently exposed (Guyton et al., 2009, 2018). Mechanistic studies and data are identified, screened, and evaluated for quality and importance to the evaluation by using systematic review principles as described in Part A, further elaborated in the Instructions for Authors, and as detailed below.

The Working Group's synthesis reflects the extent of available evidence, summarizing groups of included studies with an emphasis on characterizing consistencies or differences in results within and across experimental designs. Greater emphasis is given to informative mechanistic evidence from human-related studies than to that from other experimental test systems, and gaps are identified. Tabulation of data may facilitate this review. The specific topics addressed in the evidence synthesis are described below.

(a) Absorption, distribution, metabolism, and excretion

Studies of absorption, distribution, metabolism, and excretion in mammalian species are addressed in a summary fashion; exposure characterization is addressed in Part B, Section 1. The Working Group describes the metabolic fate of the agent in mammalian species, noting the metabolites that have been identified and their chemical reactivity. A metabolic schema may indicate the relevant metabolic pathways and products and whether supporting evidence is from studies in humans and/or studies in experimental animals. Evidence on other adverse effects that indirectly confirm absorption, distribution, and/or metabolism at tumour sites is briefly summarized when direct evidence is sparse.

(b) Evidence relevant to key characteristics of carcinogens

A review of Group 1 human carcinogens classified up to and including *IARC Monographs* Volume 100 revealed several issues relevant to improving the evaluation of mechanistic evidence for cancer hazard identification (Smith et al., 2016). First, it was noted that human carcinogens often share one or more characteristics that are related to the multiple mechanisms by which agents cause cancer. Second, different human carcinogens may exhibit a different spectrum of these key characteristics and operate through distinct mechanisms. Third, for many carcinogens evaluated before Volume 100, few data were available on some mechanisms of recognized importance in carcinogenesis, such as epigenetic alterations (Herceg et al., 2013). Fourth, there was no widely accepted method to search systematically for relevant mechanistic evidence, resulting in a lack of uniformity in the scope of mechanistic topics addressed across *IARC Monographs* evaluations.

To address these challenges, the key characteristics of human carcinogens were introduced to facilitate systematic consideration of mechanistic evidence in *IARC Monographs* evaluations (Smith et al., 2016; Guyton et al., 2018). The key characteristics described by Smith et al. (2016) (see Table 3), such as "is genotoxic", "is immunosuppressive", or "modulates receptor-mediated effects", are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by

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Table 3 The key characteristics of carcinogens

	Ten key characteristics of carcinogens
1.	Is electrophilic or can be metabolically activated to an electrophile
2.	Is genotoxic
3.	Alters DNA repair or causes genomic instability
4.	Induces epigenetic alterations
5.	Induces oxidative stress
6.	Induces chronic inflammation
7.	Is immunosuppressive
8.	Modulates receptor-mediated effects
9.	Causes immortalization
10.	Alters cell proliferation, cell death, or nutrient supply

From Smith et al. (2016).

the *IARC Monographs* programme up to and including Volume 100. The list of key characteristics and associated end-points may evolve, based on the experience of their application and as new human carcinogens are identified. Key characteristics are distinct from the "hallmarks of cancer", which relate to the properties of cancer cells (Hanahan and Weinberg, 2000, 2011). Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis. As such, the evaluation approach based on key characteristics, outlined below, "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence" (National Academies of Sciences, Engineering, and Medicine, 2017).

Studies in exposed humans and in human primary cells or tissues that incorporate end-points relevant to key characteristics of carcinogens are emphasized when available. For each key characteristic with adequate evidence for evaluation, studies are grouped according to whether they involve (a) humans or human primary cells or tissues or (b) experimental systems; further organization (as appropriate) is by end-point (e.g. DNA damage), duration, species, sex, strain, and target organ as well as strength of study design. Studies investigating susceptibility related to key characteristics of carcinogens (e.g. of genetic polymorphisms, or in genetically engineered animals) can be highlighted and may provide additional support for conclusions on the strength of evidence. Findings relevant to a specific tumour type may be noted.

(c) Other relevant evidence

Other informative evidence may be described when it is judged by the Working Group to be relevant to an evaluation of carcinogenicity and to be of sufficient importance to affect the overall evaluation. Quantitative structure–activity information, such as on specific chemical and/or biological features or activities (e.g. electrophilicity, molecular docking with receptors), may be informative. In addition, evidence that falls outside of the recognized key characteristics of carcinogens, reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms, may also be included. Available evidence relevant to criteria provided in authoritative publications (e.g. Capen et al., 1999; IARC, 2003) on thyroid, kidney, urinary bladder, or other tumours in experimental animals induced by mechanisms that do not operate in humans is also described.

(d) Study quality and importance to the evaluation

Based on formal considerations of the quality of the studies (e.g. design, methodology, and reporting of results), the Working Group may give greater weight to some included studies.

For observational and other studies in humans, the quality of study design, exposure assessment, and assay accuracy and precision are considered, in collaboration with the Working Group members reviewing exposure characterization and studies of cancer in humans, as are other important factors, including those described above for evaluation of epidemiological evidence (García-Closas et al., 2006, 2011; Vermeulen et al., 2018) (Part B, Sections 1 and 2).

In general, in experimental systems, studies of repeated doses and of chronic exposures are accorded greater importance than are studies of a single dose or time-point. Consideration is also given to factors such as the suitability of the dosing range, the extent of concurrent toxicity observed, and the completeness of reporting of the study (e.g. the source and purity of the agent, the analytical methods, and the results). Route of exposure is generally considered to be a less important factor in the evaluation of experimental studies, recognizing that the exposures and target tissues may vary across experimental models and in exposed human populations. Non-mammalian studies can be synthetically summarized when they are considered to be supportive of evidence in humans or higher organisms.

In vitro test systems can provide mechanistic insights, but important considerations include the limitations of the test system (e.g. in metabolic capabilities) as well as the suitability of a particular test article (i.e. because of physical and chemical characteristics) (Hopkins et al., 2004). For studies on some end-points, such as for traditional studies of mutations in bacteria and in mammalian cells, formal guidelines, including those from the Organisation for Economic Co-operation and Development, may be informative in conducting the quality review (OECD, 1997, 2016a, b). However, existing guidelines will not generally cover all relevant assays, even for genotoxicity. Possible considerations when evaluating the quality of in vitro studies encompass the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results). High-content and high-throughput in vitro data can serve as an additional or supportive source of mechanistic evidence (Chiu et al., 2018; Guyton et al., 2018), although large-scale screening programmes measuring a variety of end-points were designed to evaluate large chemical libraries in order to prioritize chemicals for additional toxicity testing rather than to identify the hazard of a specific chemical or chemical group.

The synthesis is focused on the evidence that is most informative for the overall evaluation. In this regard, it is of note that some human carcinogens exhibit a single or primary key characteristic, evidence of which has been influential in their cancer hazard classifications. For instance, ethylene oxide is genotoxic (IARC, 1994), 2,3,7,8-tetrachlorodibenzo-*para*-dioxin modulates receptor-mediated effects (IARC, 1997), and etoposide alters DNA repair (IARC, 2012a). Similarly, oncogenic viruses cause immortalization, and certain drugs are, by design, immunosuppressive (IARC, 2012a, b). Because non-carcinogens can also induce oxidative stress, this key characteristic should be interpreted with caution unless it is found in combination with other key characteristics (Guyton et al., 2018). Evidence for a group of key characteristics can strengthen mechanistic conclusions (e.g. "induces oxidative stress" together with "is electrophilic or can be metabolically activated to an

electrophile", "induces chronic inflammation", and "is immunosuppressive"); see, for example, 1-bromopropane (IARC, 2018).

5. Summary of data reported

(a) Exposure characterization

Exposure data are summarized to identify the agent and describe its production, use, and occurrence. Information on exposure prevalence and intensity in different settings, including geographical patterns and time trends, may be included. Exposure assessment methods used in key epidemiological studies reviewed by the Working Group are described and evaluated.

(b) Cancer in humans

Results of epidemiological studies pertinent to an evaluation of carcinogenicity in humans are summarized. The overall strengths and limitations of the epidemiological evidence base are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a positive association between the agent and cancer was observed are identified. Exposure–response and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed exposure, process, occupation, or industry, the Working Group seeks to identify the specific agent considered to be most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data permit.

(c) Cancer in experimental animals

Results pertinent to an evaluation of carcinogenicity in experimental animals are summarized to indicate how the evaluation was reached. For each animal species, study design, and route of administration, there is a statement about whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or pre-neoplastic lesions was observed, and the tumour sites are indicated. Special conditions resulting in tumours, such as prenatal exposure or single-dose experiments, are mentioned. Negative findings, inverse relationships, dose–response patterns, and other quantitative data are also summarized.

(d) Mechanistic evidence

Results pertinent to an evaluation of the mechanistic evidence on carcinogenicity are summarized to indicate how the evaluation was reached. The summary encompasses the informative studies on absorption, distribution, metabolism, and excretion; on the key characteristics with adequate evidence for evaluation; and on any other aspects of sufficient importance to affect the overall evaluation, including on whether the agent belongs to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans, and on criteria with respect to tumours in experimental animals induced by mechanisms that do not operate in humans. For each topic addressed, the main supporting findings are highlighted from exposed humans, human cells or tissues, experimental animals, or in vitro systems. When mechanistic studies are available in exposed humans, the tumour type or target tissue studied may be specified. Gaps in the evidence are indicated (i.e. if no studies were available in exposed humans, in in vivo systems, etc.). Consistency or differences of effects across different experimental systems are emphasized.

6. Evaluation and rationale

Consensus evaluations of the strength of the evidence of cancer in humans, the evidence of cancer in experimental animals, and the mechanistic evidence are made using transparent criteria and defined descriptive terms. The Working Group then develops a consensus overall evaluation of the strength of the evidence of carcinogenicity for each agent under review.

An evaluation of the strength of the evidence is limited to the agents under review. When multiple agents being evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single and unified evaluation of the strength of the evidence.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of carcinogenicity. After considering all relevant scientific findings, the Working Group may exceptionally assign the agent to a different category than a strict application of the framework would indicate, while providing a clear rationale for the overall evaluation.

When there are substantial differences of scientific interpretation among the Working Group members, the overall evaluation will be based on the consensus of the Working Group. A summary of the alternative interpretations may be provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

The categories of the classification refer to the strength of the evidence that an exposure is carcinogenic and not to the risk of cancer from particular exposures. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used as descriptors of different strengths of evidence of carcinogenicity in humans; *probably carcinogenic* signifies a greater strength of evidence than *possibly carcinogenic*.

(a) Carcinogenicity in humans

Based on the principles outlined in Part B, Section 2, the evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal association between exposure to the agent and human cancer has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.

***Limited evidence of carcinogenicity*:** A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence regarding carcinogenicity*:** The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer, or no data on cancer in humans are available. Common findings that lead to a determination of inadequate evidence of carcinogenicity include: (a) there are no data available in humans; (b) there are data available in humans, but they are of poor quality or informativeness; and (c) there are studies of sufficient quality available in humans, but their results are inconsistent or otherwise inconclusive.

***Evidence suggesting lack of carcinogenicity*:** There are several high-quality studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and the studied cancers at any observed level of exposure. The results from these studies

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alone or combined should have narrow confidence intervals with an upper limit below or close to the null value (e.g. a relative risk of unity). Bias and confounding were ruled out with reasonable confidence, and the studies were considered informative. A conclusion of *evidence suggesting lack of carcinogenicity* is limited to the cancer sites, populations and life stages, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

When there is *sufficient evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a causal interpretation has been established. When there is *limited evidence*, a separate sentence identifies the target organ(s) or tissue(s) for which a positive association between exposure to the agent and the cancer(s) was observed in humans. When there is *evidence suggesting lack of carcinogenicity*, a separate sentence identifies the target organ(s) or tissue(s) where evidence of lack of carcinogenicity was observed in humans. Identification of a specific target organ or tissue as having *sufficient evidence* or *limited evidence* or *evidence suggesting lack of carcinogenicity* does not preclude the possibility that the agent may cause cancer at other sites.

(b) Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity from studies in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols. An increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices (GLP), can also provide *sufficient evidence*.

Exceptionally, a single study in one species and sex may be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour, or age at onset, or when there are marked findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment and does not meet the criteria for *sufficient evidence*; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation–promotion studies; (e) the evidence of carcinogenicity is restricted to observational studies in non-laboratory animals (e.g. companion animals); or (f) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

***Inadequate evidence regarding carcinogenicity*:** The studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect because of major

qualitative or quantitative limitations, or no data are available on cancer in experimental animals.

***Evidence suggesting lack of carcinogenicity*:** Well-conducted studies (e.g. conducted under GLP) involving both sexes of at least two species are available showing that, within the limits of the tests used, the agent was not carcinogenic. The conclusion of *evidence suggesting lack of carcinogenicity* is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure covered by the available studies.

(c) Mechanistic evidence

Based on the principles outlined in Part B, Section 4, the mechanistic evidence is classified into one of the following categories:

***Strong mechanistic evidence*:** Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species. Quantitative structure–activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence.

Of note, "strong" relates not to potency but to strength of evidence. The classification applies to three distinct topics:

(a) Strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified as carcinogenic or probably carcinogenic to humans. The considerations can go beyond quantitative structure–activity relationships to incorporate similarities in biological activity relevant to common key characteristics across dissimilar chemicals (e.g. based on molecular docking, –omics data).

(b) Strong evidence that the agent exhibits key characteristics of carcinogens. In this case, three descriptors are possible:

1. The strong evidence is in exposed humans. Findings relevant to a specific tumour type may be informative in this determination.
2. The strong evidence is in human primary cells or tissues. Specifically, the strong findings are from biological specimens obtained from humans (e.g. ex vivo exposure), from human primary cells, and/or, in some cases, from other humanized systems (e.g. a human receptor or enzyme).
3. The strong evidence is in experimental systems. This may include one or a few studies in human primary cells and tissues.

(c) Strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Certain results in experimental animals (see Part B, Section 6b) would be discounted, according to relevant criteria and considerations in authoritative publications (e.g. Capen et al., 1999; IARC, 2003). Typically, this classification would not apply when there is strong mechanistic evidence that the agent exhibits key characteristics of carcinogens.

***Limited mechanistic evidence*:** The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.

***Inadequate mechanistic evidence*:** Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the studies; (c) the available results are negative.

(d) Overall evaluation

Finally, the bodies of evidence included within each stream of evidence are considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans. The three streams of evidence are integrated and the agent is classified into one of the following categories (see Table 4), indicating that the Working Group has established that:

The agent is carcinogenic to humans (Group 1)

This category applies whenever there is *sufficient evidence of carcinogenicity* in humans.

In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.

The agent is probably carcinogenic to humans (Group 2A)

This category generally applies when the Working Group has made at least *two of the following* evaluations, *including at least one* that involves either exposed humans or human cells or tissues:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,
- *Strong evidence that the agent exhibits key characteristics of carcinogens.*

If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems (i.e. *sufficient evidence of carcinogenicity* in experimental animals or *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens).*

Additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2A.

Separately, this category generally applies if there is *strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A*.

The agent is possibly carcinogenic to humans (Group 2B)

This category generally applies when only one of the following evaluations has been made by the Working Group:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,

Table 4 Integration of streams of evidence in reaching overall classifications (the evidence in *bold italic* represents the basis of the overall evaluation)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	
Sufficient	Not necessary	Not necessary	**Carcinogenic to humans (Group 1)**
Limited or Inadequate	***Sufficient***	***Strong (b)(1) (exposed humans)***	
Limited	***Sufficient***	Strong (b)(2–3), Limited, or Inadequate	**Probably carcinogenic to humans (Group 2A)**
Inadequate	***Sufficient***	***Strong (b)(2) (human cells or tissues)***	
Limited	Less than Sufficient	***Strong (b)(1–3)***	
Limited or Inadequate	Not necessary	***Strong (a) (mechanistic class)***	
Limited	Less than Sufficient	Limited or Inadequate	**Possibly carcinogenic to humans (Group 2B)**
Inadequate	***Sufficient***	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	***Strong (b)(1–3)***	
Limited	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	
Inadequate	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	**Not classifiable as to its carcinogenicity to humans (Group 3)**
All other situations not listed above			

[a] Human cancer(s) with highest evaluation.

[b] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.

• *Strong evidence that the agent exhibits key characteristics of carcinogens.*

Because this category can be based on evidence from studies in experimental animals alone, there is **no** requirement that the strong mechanistic evidence be in exposed humans or in human cells or tissues. This category may be based on *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens.*

As with Group 2A, additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2B.

The agent is not classifiable as to its carcinogenicity to humans (Group 3)

Agents that do not fall into any other group are generally placed in this category.

This includes the case when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of *sufficient evidence in experimental animals*, and other categories are not supported by data from studies in humans and mechanistic studies.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.

If the evidence suggests that the agent exhibits no carcinogenic activity, either through *evidence suggesting lack of carcinogenicity* in both humans and experimental animals, or through *evidence suggesting lack of carcinogenicity* in

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experimental animals complemented by strong negative mechanistic evidence in assays relevant to human cancer, then the Working Group may add a sentence to the evaluation to characterize the agent as well-studied and without evidence of carcinogenic activity.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. This section integrates the major findings from studies of cancer in humans, cancer in experimental animals, and mechanistic evidence. It includes concise statements of the principal line(s) of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence for each stream of evidence, an indication of the body of evidence that was pivotal to these conclusions, and an explanation of the reasoning of the Working Group in making its evaluation.

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PRELIMINARY GENERAL REMARKS

This one-hundred-and-thirty-sixth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of talc.

The present evaluation of talc supersedes the previous classifications of "talc not containing asbestos or asbestiform fibres" (Group 3) and "perineal use of talc-based body powder" (Group 2B) in Volume 93 of the *IARC Monographs* (IARC, 2010). "Talc containing asbestos" was not re-evaluated and retains its classification within "asbestos" (Group 1) from Volume 100C (IARC, 2012).

The Advisory Group to Recommend Priorities for the *IARC Monographs* that met in 2019 recommended that talc be evaluated with high priority (IARC, 2019a; Marques et al., 2019), largely on the basis of emerging evidence for cancer in humans and of mechanistic evidence related to the key characteristics of carcinogens (KCs).

A summary of the findings of the present volume appears in *The Lancet Oncology* (Stayner et al., 2024).

Potential asbestos contamination of commercial products containing talc

Several challenges arise when characterizing asbestos contamination in commercial products containing talc, which include cosmetic products, pharmaceuticals and food, and talc used in manufacturing. First, if the origin of the talc is known, it is possible, based on reports about the mineralogy of the talc deposits in a particular mine, to estimate the potential for asbestos contamination of the resulting products. Where such evidence was available, the Working Group summarized information about the exploited mines to draw conclusions as to the likelihood of asbestos contamination. However, for most commercial products, the origin of the talc used was not known or it was a mix from different sources. Second, the literature has not been consistent and precise in the terminology used to describe potential asbestos contamination. It was not always clear whether the reported fibres in talc were asbestiform talc (and therefore not asbestos), other fibrous non-asbestos minerals, or truly asbestos. It was therefore not always possible to rely on a given study's description of the talc to deduce whether the mineral was contaminated with asbestos. Third, the methods commonly used in the past to detect asbestos

in commercial talc samples, including cosmetic and pharmaceutical talc, were mostly not sufficiently sensitive to detect an asbestos content of < 0.5%. Therefore, samples that were reported to be free of asbestos according to these methods could potentially have contained asbestos at a significant level of contamination. Only recently has the use of sensitive methods that can detect asbestos at levels of < 0.5% and sometimes as low as 0.001%, such as transmission electron microscopy (TEM) and scanning electron microscopy (SEM), become more common. Fourth, there has been a lack of systematic testing for asbestos contamination of commercial products containing talc. The United States Food and Drug Administration (US FDA) has only recently published data on more systematic testing of cosmetic talc products in the USA, and very little information is available on asbestos contamination of pharmaceutical and food products globally.

For the studies on perineal use of talc, the Working Group determined that potential asbestos contamination of talc products for this use could not be discounted, regardless of the country and year of use. This information was crucial to the determination that the evidence for "talc" and ovarian cancer in humans was *limited* because, although positive associations were observed in the body of epidemiological evidence on personal use of talc-based body powder and ovarian cancer, confounding by asbestos contamination of the talc could not be ruled out, even in the more recent studies.

The Working Group clarified that, when considering the carcinogenicity of talc-based body powders, both the evaluation of "talc" in the present volume and the evaluation of "talc containing asbestos" in Volume 100C could be relevant. Talc contaminated with asbestos, even in small amounts, is classified as *carcinogenic to humans* (Group 1). Detection of asbestos contamination in small amounts in the talc requires more sensitive methods than those that were previously applied for talc used in cosmetic products.

The Working Group noted the lack of data available on the use of talc in food products, which is probably determined by country-specific regulations and may be higher than expected because of illicit supplementation. The resulting exposure of the general population to talc via food and the potential resulting exposure to asbestos through contaminated talc in food are difficult to estimate. Similarly, although it is known that talc is present in many pharmaceutical products, few data on the concentration of talc in the final products and the resulting exposure of patients to talc were available to the Working Group. Unless asbestos contamination is ruled out by testing with methods of sufficient sensitivity, it is possible that pharmaceutical-grade talc (which has the highest purity of all talc grades) may contain some asbestos.

Updated evaluation of talc and cancer in experimental animals

The evaluation of the carcinogenicity of talc in experimental animals (Section 3, Cancer in experimental animals) was updated from *limited* in Volume 93 to *sufficient* in the present volume on the basis of the following three considerations. First, the Working Group for the present volume considered that it was relevant to include pheochromocytomas (tumours of the adrenal medulla), which were disregarded in Volume 93 because the previous Working Group suggested that stress and hypoxia may contribute to chromaffin cell proliferation and potentially to the development of pheochromocytomas. Second, the occurrence of bilateral pheochromocytomas (both benign and malignant) was considered by this Working Group to be an important factor in the present evaluation. Third, the tumours occurred in an unusual site (adrenal medulla)

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after exposure by inhalation. This was considered especially relevant because adrenal medulla tumours are not a common outcome of inhalation exposure.

Type of talc used in the 2-year bioassay by the National Toxicology Program

In the 2-year bioassay carried out by the National Toxicology Program (NTP, 1993), the talc used (MP 10-52 grade), obtained in two lots, was one of the microtalc series of products manufactured by the Minerals, Pigments, and Metals Division of Pfizer, Inc. Both lots were from Pfizer's Barretts mine, which is a strip mine located between Barretts and Three Brothers, Montana, USA, and was the only source for MP 10-52 grade talc. The particle size was 10 µm and, according to the manufacturer, contained no tremolite or any asbestiform minerals. Both lots of talc were extensively characterized. The mineral used for the inhalation studies was a finely powdered white solid and was identified as talc by infrared spectroscopy, elemental analysis, thermogravimetric analyses, spark source mass spectrometry, automated scanning electron probe analyses, X-ray diffraction, polarized light microscopy, and TEM. Both lots were found to be asbestos-free by polarized light microscopy and TEM, which were state-of-the-science techniques for determining asbestos at the time of the study. Results of automated scanning electron microprobe analysis of one of the lots indicated that the sample was virtually free of silica (one particle of silica in 1466 particles examined).

Mechanistic evidence for talc related to KC6, "induces chronic inflammation"

The Working Group evaluated the mechanistic evidence of talc as *strong* on the basis of consistent and coherent evidence in experimental systems for end-points associated with KC6, "induces chronic inflammation", and in human primary cells and experimental systems for end-points related to KC10, "alters cell proliferation, cell death, or nutrient supply".

Chronic inflammation is a relevant property of several carcinogens, as demonstrated for several agents classified in Group 1 or Group 2A (e.g. welding fumes, occupational exposure as a firefighter, crotonaldehyde, acrolein, cobalt metal and cobalt compounds) and is often observed together with other KCs (DeMarini et al., 2025). Evidence of inflammation with persistence of the effects, including alteration of several systemic and in situ end-points, was available across numerous studies in rodents exposed to talc via different routes of administration and at a range of exposure levels. Some of the studies were conducted with very high doses, and the mechanism could have been ascribed to a foreign body reaction in the target organ, as happens with several types of particle. As for talc, thresholds for such particles and studies can be rather high. The Working Group noted that exposures to talc in the reviewed studies in humans, either as occupational (mining and secondary industries using talc), as long-term exposure to consumer products, or as a result of medical procedures (i.e. pleurodesis), were reported to be high. Of note, the evidence for KC6 was also supported by several case reports in exposed humans, reviewed by the Working Group, that linked continuous use of talc (not specifically at very high exposure levels) with inflammatory outcomes (e.g. talcosis). Evidence of chronic inflammation was considered together with evidence of cell proliferation

in human primary cells and in experimental systems both in vivo and in vitro. For the overall evaluation, the mechanistic evidence stream was integrated with the *sufficient* evidence for cancer in experimental animals and *limited* evidence for cancer in humans (as clearly described in the Preamble to the *IARC Monographs*, para. 6(d), in the present volume; IARC, 2019b). As such, this information is relevant to cancer hazard identification.

Scope of the systematic review

Standardized searches of the PubMed database (NCBI, 2024) were conducted for talc for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the KCs). The literature trees for talc, including the full set of search terms for the agent name and each outcome type, are available online.[a]

As described in the Preamble to the *IARC Monographs* (last revised in 2019; IARC, 2019b), the Working Group reviews publicly available scientific data, such as peer-reviewed papers in the scientific literature, and may also review unpublished reports, if made available in their final form by governmental agencies and if they contain enough detail for critical review. A public Call for Data was opened on the IARC website 1 year ahead of the meeting for Volume 136. Eligible studies were only those published or accepted for publication in the openly available scientific literature by the time of the Working Group meeting.

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[a] The literature tree for the monograph in the present volume is available at: https://hawcproject.iarc.who.int/assessment/703 (talc).

TALC

1. Exposure Characterization

1.1 Identification of the agent

The agent evaluated by the Working Group was talc. The term "talc" refers to mineral (natural) and synthetic products. The present section contains a description of the substance talc, followed by a systematic comprehensive list of forms of talc and talc products that were eligible for inclusion as part of the agent definition.

In 2006, for Volume 93 of the *IARC Monographs* (Carbon black, titanium dioxide, and talc; IARC, 2010), "talc not containing asbestos or asbestiform fibres" was classified in Group 3 and "perineal use of talc-based body powder" in Group 2B. Both of these classifications are superseded by the present evaluation of "talc", both lamellar and fibrous (which includes asbestiform) talc, as defined in Section 1.1.

Talc containing asbestos is not evaluated in the present volume. For the latest evaluation of talc containing asbestos, which was carried out in 2009, see *IARC Monographs* Volume 100C (IARC, 2012a). In Volume 100C, it was reported that "The studies on talc containing asbestiform fibres were considered when developing the *Monograph* on asbestos. Talc containing asbestos as well as other mixtures containing asbestos should be regarded as *carcinogenic to humans*". Therefore, talc containing asbestiform fibres of minerals other than talc was not evaluated in the present monograph. Talc containing asbestiform fibres that are identifiable as one of the six commonly recognized forms of asbestos is covered under the definition of "talc containing asbestos". However, fibrous (including asbestiform) talc is not asbestos (see Section 1.1.4(a)) and was considered as part of the agent definition in the present monograph. [The Working Group considered asbestiform talc to be a subgroup of fibrous talc. In the present monograph, the term "fibrous talc" shall be understood to include both asbestiform and non-asbestiform fibrous talc. Asbestiform talc is not asbestos. The Working Group used the term "fibrous talc" rather than "asbestiform talc" to avoid any confusion with asbestos. The Working Group also noted that some natural talc deposits may be contaminated with asbestos, see Section 1.1.6 and Table 1.1.]

1.1.1 Identification

Chem. Abstr. Serv. Reg. No.: 14807-96-6 (CAS, 2024)

Chem. Abstr. Serv. name: talc ($Mg_3H_2(SiO_3)_4$)

IUPAC systematic name: trimagnesium; *1,3,5,7*-tetraoxido-*2,4,6,8,9,10*-hexaoxa-*1,3,5,7*-tetrasilatricyclo[*3.3.1.1*^{3,7}]decane; dihydroxide (NCBI, 2024a)

EC/List No.: 238-877-9 (ECHA, 2024)

Synonyms: pulvis talci; talc powder; magnesium silicate monohydrate; purified talc; talcum powder; talc powder (NCBI, 2024; ECHA, 2024).

1.1.2 Crystal structure

The ideal chemical formula for talc is $Mg_3(OH)_2Si_4O_{10}$ (MgO, 31.88 percentage by weight, wt%; SiO_2, 63.37 wt%; and H_2O, 4.75 wt%) (Webmineral, 2024).

The ideal molecular mass of talc is 379.27 (Webmineral, 2024).

Talc is a trioctahedral 2:1 (or TOT) layer silicate, electrostatically neutral in the ideal configuration, with a structure composed of a magnesium-centred octahedral sheet (O in Fig. 1.1) sandwiched between two opposing silicon-centred tetrahedral sheets (T in Fig. 1.1) (Gruner, 1934; Stemple and Brindley, 1960; Rayner and Brown, 1966; Claverie et al., 2018). Each tetrahedron in the T sheets shares three planar oxygen atoms with neighbouring tetrahedra, and the fourth out-of-plane oxygen atom is coordinated to magnesium atoms in the O sheet such that the magnesium atoms are octahedrally coordinated by two oxygen atoms from each tetrahedral sheet and two hydroxyl groups. There is a misfit of the lateral dimensions of the O and T sheets compensated by O thinning and counter rotation of adjacent tetrahedra of the ditrigonal ring with a tilting angle α dependent upon the value of the crystallographic *b* axis (Radoslovich, 1962). The weak bonds between adjacent TOT layers, resulting from van der Waals forces, may be responsible for the variable degree of stacking disorder in talc (Gualtieri, 1999).

Although Gruner (1934) originally refined the crystal structure of talc as monoclinic (talc 2M; space group *C*2/*c* with $a = 5.26$ Å, $b = 9.10$ Å, $c = 18.81$ Å, $\alpha = 90°$, $\beta = 100.00°$, and $\gamma = 90°$), its real symmetry is triclinic (talc 1A; space group *C*-1 with $a = 5.1848–5.293$ Å, $b = 8.9230–9.179$ Å, $c = 9.19–9.496$ Å, $\alpha = 90.46–90.92°$, $\beta = 90.9–98.92°$, and $\gamma = 90.00–90.09°$) (Rayner and Brown, 1966; Ross et al., 1968; IARC, 2010; Drits et al., 2012).

1.1.3 Chemical and physical properties

Cleavage: {001} perfect (Deer et al., 2013)

Colour: white, pale green, bright emerald-green to dark green, brown, grey; talc is colourless in thin section (Deer et al., 2013)

Density: the measured density is 2.7–2.8 g/cm^3 at 20 °C (ECHA, 2024)

Hardness: Mohs scale, 1 (Deer et al., 2013)

Indices of refraction: talc is biaxial, with $\alpha = 1.539–1.550$, $\beta = 1.589–1.594$, and $\gamma = 1.589–1.600$; the indices of refraction increase with iron content (Deer et al., 2013)

Lustre: translucent; greasy or pearly (Webmineral, 2024; Deer et al., 2013)

Melting point: 1500 °C (ECHA, 2024)

Other properties: commonly, the crystal habit of talc is lamellar/platy (also known as platy) (Fig. 1.2), but it can be fibrous or, more rarely, asbestiform (Cressey et al., 1982; Wylie et al., 1997; Ferrage et al., 2003; IARC, 2010; Deer et al., 2013). [The Working Group noted that lamellar and fibrous (asbestiform) talc forms have the same chemical composition and, presumably, comparable chemical and physical properties, although the properties of the fibrous (asbestiform) form have never been specifically described. Both platy and fibrous (asbestiform) talc forms are part of the current definition of the agent.]

The biopersistence of a particle is defined by its biodurability (ability to resist chemical or biochemical alteration) and by its resistance to physical clearance in vivo. Talc is moderately biodurable (Jurinski and Rimstidt, 2001). The speed of the purely chemical dissolution of talc (biodurability) is faster than that of quartz

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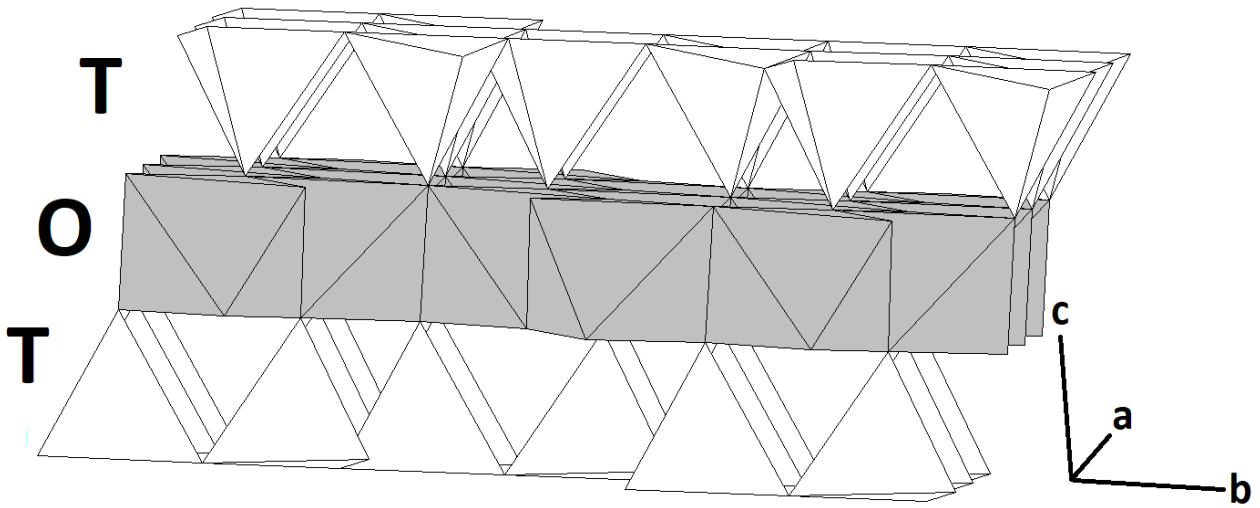
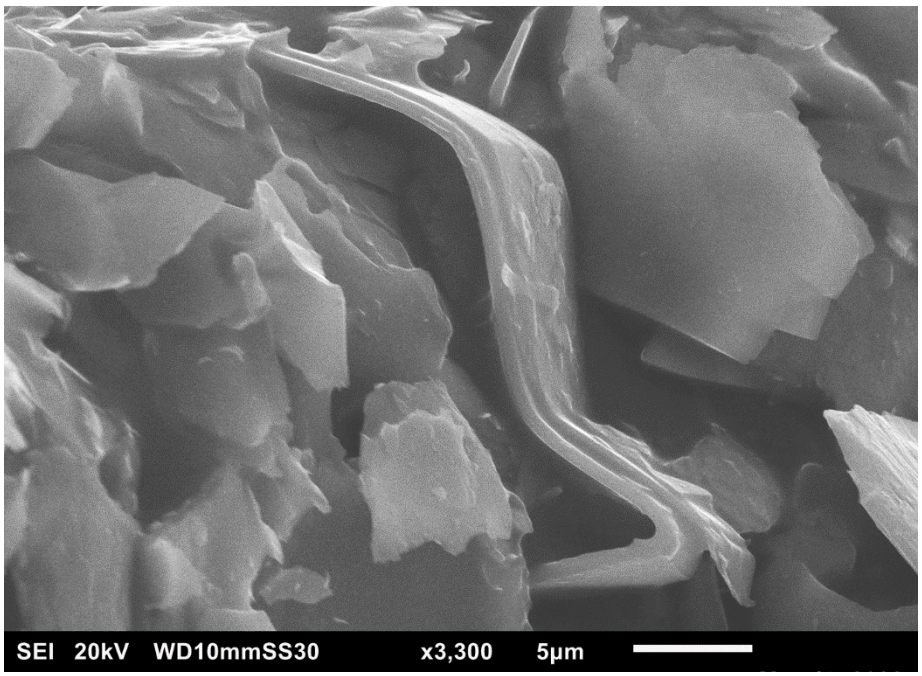
Fig. 1.1 Sketch of the ideal 2:1 structure of talc



The magnesium-centred octahedral (O) sheet (grey) is sandwiched between two silicon-centred tetrahedral (T) sheets (white). The periodicity of this layer silicate along the *c* axis is 10 Å.
Created by the Working Group.

Fig. 1.2 Scanning electron microscopy image of lamellar/platy aggregates of talc in a commercial talc product from Italy



Created by the Working Group.

but slower than that of chrysotile (see also Section 4.1). Talc dissolution in an acellular acidic environment takes place through the leaching of the magnesium octahedral sheet, with a dissolution reaction rate that is controlled by the destruction rate of the tetrahedral silica sheets (Lin and Cemency, 1981; Saldi et al., 2007).

The zeta potential (ζ) – the electrical or electrokinetic potential at the surface of particles, measured at the interface that separates mobile fluid from fluid attached to the surface – of talc is negative in the pH range 3–12, with the point-of-zero charge at pH 3 (Feng et al., 2012). Zeta potential is an important surface property of particles because it influences haemolytic potential, reactive oxygen species (ROS) production, and mitochondria-regulated apoptosis (Pollastri et al., 2014). The surface of talc platelets is naturally hydrophobic, with a sessile drop contact angle of nearly 80° with water. The sessile drop contact angle decreases with increased aluminium content, from about 80 ° for no substitution (talc) to 0 ° for extensive substitution (phlogopite) (Atluri et al., 2019).

1.1.4 Talc products

The umbrella term "talc" refers to different natural and synthetic industrial products:

(a) Pure natural talc

This is a mineral (a substance that is formed naturally) product that is assumed to contain talc at 100 wt% (Zazenski et al., 1995). Talc usually exhibits a lamellar crystal habitus. Under an optical or electron microscope, the crystal habitus may also appear as fibrous and/or asbestiform (elongate mineral particles composed of bundles readily separable into fibres or fibrils that are aligned parallel to their common fibre axis direction but randomly or semi-randomly in the perpendicular directions) (see for example, Wylie et al. (1997) for fibrous morphology and Cressey et al. (1982) for asbestiform pseudomorphs). Both macroscopically and microscopically, the fibre bundles can display frayed or splayed ends and can be flexible and bent (Gualtieri et al., 2023). [The Working Group noted that pure natural talc (100 wt% to the best of the detection limits of the analytical techniques used) is a rarity. The Working Group also noted that asbestiform talc is not classified as asbestos.]

(b) Synthetic talc

This is a man-made substance obtained via laboratory and/or industrial processes.

According to the preparation methods, properties, and applications, different synthetic products are prepared. In principle, all synthetic forms of talc may also exhibit a lamellar, fibrous, or asbestiform crystal habit.

(i) Pure synthetic talc

Worldwide, there are few industrial production sites for synthetic talc (Dumas et al., 2013). [The Working Group noted that since synthetic talc may contain amorphous phase of minor process residues, pure synthetic products (100 wt% to the best of the detection limits of the analytical techniques) are nearly impossible to obtain.]

(ii) Doped pure synthetic talc

This talc product is obtained at laboratory scale in the presence of ions generally substituting for magnesium in the crystal lattice (Stemple and Brindley, 1960; Wilkins and Ito, 1967; Petit et al., 2008). [No information indicating the production of these materials at industrial levels was available to the Working Group.]

(iii) Pure synthetic nanotalc or talc-like structures

These products are synthesized to obtain particles of nanometric size (Claverie et al., 2018). The different routes of synthesis can produce crystalline nanotalc, amorphous, and/or short-range order nanotalc (talc comprised of monolayers and few layers; Alencar et al., 2015), and

organic–inorganic hybrid talc-like structures. [The Working Group noted that no information indicating that these materials were produced at an industrial level was available.]

(c) Industrial talc

This is a natural or synthetic product that generally contains talc at 35–98 wt% (IARC, 2010). "Soapstone" generally contains ≥ 25 wt% minerals other than talc. "Talcite" generally contains ≥ 75 wt% talc (IARC, 2010). [The Working Group noted that industrial talc may contain asbestos. For details on potential contamination of talc from different locations see, for example, Table 1.1.]

(d) Cosmetic talc

This natural or synthetic product generally contains talc at a minimum of 90 wt% (Cosmetic Ingredient Review, 2013). [The Working Group noted that cosmetic talc may contain asbestos. For details and a historic perspective on the purity of talc and related industry standards, see Section 1.4.1(e).]

(e) Pharmaceutical talc

This is a natural or synthetic product that generally contains talc at > 98 wt% (Pharma Excipients, 2025). It is possible to have pure (to the best of the detection limits of the analytical techniques used) pharmaceutical talc. [As for cosmetic talc, the common industry methods used for detecting asbestos in pharmaceutical talc are not sufficiently sensitive to detect low-level contamination with asbestos, which is relevant because of the known potential for asbestos to cause cancer.]

Industrial, cosmetic, and pharmaceutical talcs can also exhibit a lamellar, fibrous (asbestiform) crystal habit. There is a very long list of trade names for talc products (IARC, 2010). Most of these are no longer used today. The term "steatite" was used in the past to indicate nearly pure talc (Piniazkiewicz et al., 1994). [The Working Group noted that "steatite" can contain amphibole minerals.] Another major commercial synonym of talc used in the past was "talcum". [The Working Group noted that the term "talcum" has also been used in the past for products that did not contain talc. Rohl et al. (1976), for example, reported that some "talcum" samples comprised three to five minerals, only one of which was talc. Other non-asbestos mineral phases included were chlorite, platy serpentine, pyrophyllite, mica, and carbonate minerals. In some studies the term "talcum powder" was used to indicate the final cosmetic product of talc powder. The Working Group used this terminology (talcum powder rather than talc powder) if such term was used in the original publication that the Working Group was citing]

A notable commercial product of pharmaceutical grade is micronized Talc E553B (containing < 0.1% respirable crystalline silica), which fulfils the criteria for a foodstuff, as defined in Article 2 of Regulation (EC) No. 178/2002 of the European Parliament and of the Council (European Commission, 2018a).

1.1.5 Chemical variability of natural talc

Natural pure talc usually displays isomorphic substitutions of aluminium and ferric iron for silicon or magnesium; and ferric/ferrous iron for magnesium. The degree of substitution is variable and can be complete in end-member isomorphs such as minnesotaite, ideally $Fe^{2+}_3(OH)_2Si_4O_{10}$ (Guggenheim and Eggleton, 1986). Fluorine may substitute for the hydroxyl group (Michot et al., 1994; Petit et al., 2004). Minor (< 0.02 afu, atoms per formula unit) substitution of chromium, manganese, nickel, and titanium for magnesium may also occur (Petit et al., 2004; Nkoumbou et al., 2008). Traces (< 100 ppm) of other metals like cobalt may be present in the crystal lattice of talc (e.g. Nkoumbou et al., 2008). Calcium is unlikely to be hosted in the crystal lattice of talc

(e.g. Deer et al., 2013), and its presence is probably because of minor contaminants like calcite.

The chemical composition of natural talc and the types of associated phase depend upon the nature of the pristine rock, type of hydrothermal alteration, and metamorphic history (IARC, 2010). When talc is formed during regional metamorphism (minor commercial talc-chlorite ores), it is accompanied by olivine (Basta and Abdel, 1969), phlogopite (Yun et al., 1994), amphiboles, chlorite (Prochaska, 1989; Ersoy et al., 2013) (including clinochlore, penninite, and sheridanite Blount and Vassiliou, 1983); iron, chromium and manganese oxides, pyrite, pyrrothite, and pentlandite (Pooley and Rowlands, 1975; Piniazkiewicz et al., 1994; Harben and Kužvart, 1996). Rare minerals like manganese-rich tourmaline (Ayuso and Brown, 1984) and stevensite (Basta and Abdel, 1969) can also be associated with talc. When talc originates from the alteration of carbonate rocks or in the presence of carbonation phenomena of magnesium-rich rocks (major commercial talc-carbonate industrial ores), two types are distinguished (Pooley and Rowlands, 1975; Piniazkiewicz et al., 1994): (i) deposits derived from hydrothermal alteration and/or retrograde metamorphism of siliceous dolomites in association with ankerite, breunnerite (Harben and Kužvart, 1996), calcite, dolomite, magnesite, siderite and quartz (Harben and Kužvart, 1996); and (ii) deposits derived from metamorphism (metasomatism or hydrothermal alteration) of magnesium-rich minerals such as olivine and serpentine that react with carbon dioxide and water showing an association with serpentine, kaolinite, mica, pyrophyllite (Rohl et al., 1976; Harben and Kužvart, 1996), sepiolite, palygorskite (Germine, 1987), amphiboles like tremolite-actinolite and anthophyllite (often as asbestos (Van Gosen et al., 2004), feldspars, quartz (Wylie et al., 1997), graphite, and apatite (Li et al., 2016a).

1.1.6 Contamination of natural talc with asbestos

Natural talcs may contain one or more of the six regulated asbestos species (IARC, 2012a). [The Working Group noted that regulations vary by country.] Here we define "asbestos" as a generic term applied to the (fibrous) asbestiform variety of serpentine (chrysotile) and the (fibrous) asbestiform variety of amphibole group minerals (anthophyllite, amosite (cummington-grunerite), tremolite, actinolite, and crocidolite (riebeckite)), which have been exploited, prospected, described in the literature, traded, and sold commercially for their unique physical properties that result from the fibril width of ≤ 0.5 µm. According to Wylie et al. (1997), fibrous talc has been used in the past as a general term that includes fibres composed entirely of the mineral talc as well as fibres that are composed of talc contaminated with amphiboles (Stemple and Brindley, 1960; Virta, 1985). [The Working Group noted that terminology has been inconsistent in the past, making it difficult to examine historical reports. The term "fibrous talc" has had four different interpretations in the past: (i) fibrous (asbestiform) talc that does not include asbestos; (ii) talc containing asbestos fibres; (iii) talc that contains asbestiform fibres other than asbestos; and (iv) talc containing non-specified fibres that could be any of the above.

The Working Group used the term "fibrous talc" to refer to (i), fibrous (asbestiform) talc that does not include asbestos; however, in many epidemiological studies, "fibrous talc" has been used for any of the above, and the original term used by the study authors may be cited in the study descriptions below.]

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1.2 Production and use

1.2.1 Overview of global talc production

(a) Types of talc deposits

There are basically three types of exploitable talc deposit worldwide (Chidester et al., 1964; Eurotalc, 2023).

(i) Talc-carbonate

Talc crystallizes from the metasomatism or hydrothermal alteration of magnesium-rich minerals such as olivine and serpentine that react with carbon dioxide and water:

$2\,Mg_3Si_2O_5(OH)_4$ (*serpentine*) + $3\,CO_2$ → $Mg_3(OH)_2Si_4O_{10}$ (*talc*) + $3\,MgCO_3$ (*magnesite*) + $3\,H_2O$

This process, known as "talc carbonation" or "steatization", generally forms pure and white talc (industrial- and cosmetic-grade talc), which is the basis for about 50% of world talc production (Pooley and Rowlands, 1975; Piniazkiewicz et al., 1994; IARC, 2010; New World Encyclopedia contributors, 2023).

Talc-carbonate deposits can also form from hydrothermal alteration and/or retrograde metamorphism of siliceous dolomites. This process is known as "skarnification" of dolomites by silica-flooding in contact metamorphic aureoles (Piniazkiewicz et al., 1994; Van Gosen et al., 2004; Lumitos, 2024):

$3\,CaMg(CO_3)_2$ (*dolomite*) + $4\,SiO_2$ + H_2O → $Mg_3(OH)_2Si_4O_{10}$ (*talc*) + $3\,CaCO_3$ (*calcite*) + $3\,CO_2$.

In these deposits (about 40% of world talc supplies), the crude ore is generally beneficiated by flotation (IARC, 2010).

(ii) Talc-chlorite

Talc can also form in aluminium-rich rocks during regional metamorphism (Chidester et al., 1964; IARC, 2010). Talc in these deposits (about 10% of world talc supplies) (Eurotalc, 2023) often occurs in association with serpentine, chlorite minerals (namely clinochlore), and pyroxenes (Handbook of Mineralogy, 2001). This talc is usually of industrial grade and may require beneficiation (flotation) to meet industrial standards. The basic metamorphic reaction leading to the formation of talc is:

$Mg_3Al_3(OH)_8Si_3AlO_{10}$ (*Al-rich chlorite*) + $3\,SiO_2$ (*quartz*) → $2\,Al_2SiO_5$ (*kyanite*) + $Mg_3(OH)_2Si_4O_{10}$ (*talc*) + $3\,H_2O$

(iii) Sedimentary talc

Talc can occur as a diagenetic mineral in sedimentary rocks where it can form from the transformation of metastable hydrated magnesium-clay precursors, such as sepiolite, precipitating from marine and lake water under some specific conditions. These deposits are less common and have a lower talc concentration (industrial talc) compared with the other types (i) and (ii). They typically occur as detrital or secondary talc and are often associated with impurities and contaminants (Chidester et al., 1964; Eurotalc, 2023).

In general, the mineral composition of talc deposits varies depending on geological setting and the genesis of the deposit (López-Galindo et al., 2007). It might be said that each talc deposit is unique in morphology and geochemistry (Piniazkiewicz et al., 1994). Even the metal content can be extremely variable both in talc deposits and in processed talc-based commercial products. Wudke et al. (2024) (and references therein) reported a compilation of vanadium, chromium, cobalt, and nickel concentrations in ultramafic- and carbonate-hosted talc deposits from Afghanistan, Cameroon, Egypt, India, Mexico, Poland, the Republic of Korea, and the United States of America (USA). These metals can be hosted in the crystal lattice of talc or be present in accessory minerals. For example, nickel is observed in iron sulfides (like pyrite) and chromium in chromite and/or chromium-magnetite. Wudke et al. (2024) also measured the concentration of trace elements analysed in three replicates (A, B, C) of a widely

used baby powder from 1985 (JNJ1985) and found: vanadium, 10.5–10.7 mg/kg; chromium, 394.7–404.3 mg/kg; cobalt, 52.7–56.9 mg/kg; and nickel, 1344–1447.5 mg/kg.

Minerals associated with talc deposits have been described in Section 1.1.

(iv) Exploited talc deposits

A list of the major past abandoned and active talc deposits of commercial interest worldwide is reported in Table 1.1. [The Working Group noted that this does not necessarily describe workers' exposure or products derived from this mine.] For each deposit, the table includes the presumed origin, the type of talc, and occurrence of asbestos and quartz. The table does not report deposits of sedimentary origin (iii) of minor importance. The indication of the presence of asbestos was based on the following data: "no" means that, in the surveyed literature describing that occurrence, the presence of one or more of the six mineral species classified as asbestos was not reported or that the absence of one or more of the six mineral species classified as asbestos was stated; "possible" means that presence of serpentine has been reported; and "probable" means that the presence of amphibole minerals tremolite, anthophyllite and actinolite has been reported, but not in the asbestiform habit. If these minerals were reported in the asbestiform habit, then this was marked as the type of asbestos (without "probable" or "possible").

(b) Mining and mineral processing of talc

Talc is mined from both open-pit and underground mines. The raw rock is drilled and blasted and then undergoes primary and/or secondary crushing by jaw crushers and screening. Hammer mills and jaw crushers are used to reduce the size of the largest ore received (Radosta and Trivedi, 1978; Virta, 1989). Eventually hand sorting or optical sorters are used to produce a high-grade feed for the mill (Virta, 1989). Sometimes the talc ore is washed to remove fine dust and impurities (Roe and Olson, 1983). Roller mills can be used to produce the final product. When used in conjunction with air classifiers, roller mills can grind talc to an approximate mean particle size of 5–10 μm (Virta, 1989). The grinding mills are sometimes equipped with heating combustion chambers to achieve simultaneous grinding and drying of the product (US EPA, 1995). Fluid-energy mills or pulverizing mills can be used for ultra-fine grinding of the talc product (Radosta and Trivedi, 1978; Clifton, 1985; Virta, 1989; Soln Pharma, 2024).

Beneficiation of talc usually involves grinding, froth flotation, and magnetic separation of the iron oxide minerals. Froth flotation is the preferred separation technique because talc is naturally floatable (Virta, 1989; Yehia and Al-Wakeel, 2000; Bazar et al., 2021), although a variety of mineral processing techniques (including gravity separation, electrostatic separation, and hydrometallurgy) have been employed to separate talc from other valuable minerals like sulfides (Yuan et al., 2019). Water and air surface interaction with talc has been extensively studied to understand and optimize talc behaviour in suspension and froth flotation yield. Talc is an anisotropic mineral considered to be hydrophobic in most cases (Atluri et al., 2019). The treated ore is passed through rougher and cleaner cells before being dewatered and thickened. The filter cake is dried in a flash dryer and ground in a pulverizer system (Virta, 1989; Clifton, 1985).

For some applications, additional processing of the talc products is desirable or required. For example, green or black talcs (containing higher contents of organic matter) are calcined to remove organic matter and increase their whiteness. Sometimes talc is surface-treated with organic compounds (Radosta and Trivedi, 1978; Virta, 1989).

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Table 1.1 Characteristics of talc ores of past or present commercial interest worldwide

Mine location	Mineral origin of talc	Talc type	Occurrence of asbestos[a]	Occurrence of quartz[b]	Estimated period of mine exploitation[c]	Reference	Reference for cancer or mechanistic study in humans with setting in the mine
Afghanistan, Nangarhar Province	Hydrothermal talc-carbonate	Industrial, cosmetic	Tremolite	Yes	1970?–to date	Tahir et al. (2018)	NA
Austria, Lassing, Liezen, Styria	Hydrothermal talc-carbonate	Industrial	No[d]	Probable	1901–1998	Prochaska (1989)	Wild et al. (2002)
Austria, Rabenwald, Pöllau, Hartberg-Fürstenfeld, Styria	Hydrothermal talc-carbonate	Industrial	No	Probable	1947?–to date	Prochaska (1989)	Wild et al. (2002)
Brazil, Bahia district	Hydrothermal talc-carbonate	Industrial	Chrysotile probable, actinolite, tremolite	Yes	1950?–to date	Gondim and Jiang (2004)	NA
Brazil, Brumado, Bahia	Hydrothermal talc-carbonate	Cosmetic, pharmaceutical	No	No	1969–to date	Xilolite (2012)	Vargas et al. (2001)
Brazil, Paranà district, Ponta Grossa and Castro	Ultramafic talc-carbonate	Industrial	Chrysotile probable, tremolite	Yes	1988–to date?	Gondim and Jiang (2004)	NA
Canada, Madoc, Ontario	Ultramafic talc-carbonate	Industrial	Tremolite, actinolite possible	Yes	1896–2010	Sabina (1987)	NA
Canada, Saint-Pierre-de-Broughton, Chaudière-Appalaches, Québec	Ultramafic talc-chlorite	Industrial	Actinolite probable, tremolite probable	probable	1938–2001	Horváth and Pfenninger Horváth (2010)	NA
China, Guangxi Province	Hydrothermal talc-carbonate	Industrial, cosmetic	Tremolite possible	Yes	1970?–to date	Schober (1998)	NA
China, Jiangxi Province	Contact metamorphism talc-carbonate	Industrial	No	Yes	< 2013–to date	Li et al. (2013)	NA
China, Liaoning Province	Hydrothermal talc-carbonate	Industrial	Chrysotile probable, tremolite possible	Yes	1995?–to date	Misch et al. (2018)	Fu and Zhang (1992)

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Table 1.1 (continued)

Mine location	Mineral origin of talc	Talc type	Occurrence of asbestos[a]	Occurrence of quartz[b]	Estimated period of mine exploitation[c]	Reference	Reference for cancer or mechanistic study in humans with setting in the mine
China, Shandong Province	Hydrothermal talc-carbonate	Industrial, cosmetic?	Tremolite possible	Yes	1970?–to date	Schober (1998)	NA
Finland, Sotkamo, Polvijarvi	Ultramafic talc-chlorite	Industrial	Tremolite probable	Yes	1967?–to date	Kuutila (2022)	NA
Finland, Vuonos, Polvijarvi	Ultramafic talc-chlorite	Industrial	Tremolite probable	Yes	1967?–to date	Kuutila (2022)	NA
France, Trimouns Arlège	Ultramafic talc-chlorite	Industrial	No	Yes	1905–to date	IARC (2010)	Wild et al. (2002)
India, Rajasthan[e]	Ultramafic talc-carbonate	Industrial, cosmetic, pharmaceutical	Chrysotile possible, tremolite	No	< 2012–to date	Shekhawat et al. (2010)	NA
Italy, Sa Matta, Sardinia	Ultramafic talc-chlorite	Industrial	Tremolite probable	Yes	1934–to date	Fiori and Grillo (2002)	NA
Italy, Val Germanasca/Val Chisone	Ultramafic talc-carbonate	Industrial	No	Probable	1907–1995	Ciocan et al. (2022)	Ciocan et al. (2022)
Italy, Val Germanasca, Nuova Fontane	Ultramafic talc-carbonate	Industrial	No	Yes	1933–to date	Cadoppi et al. (2016)	NA
Italy, Valmalenco	Ultramafic talc-carbonate	Industrial	Chrysotile probable	No	1936–to date	Cavallo (2020)	NA
Republic of Korea, Dongyang, Chungju[e]	Ultramafic talc-carbonate	Industrial	Tremolite	Yes	1970? –to date	Dongbok and Sang-Mo (2004)	NA
Norway, Altermark, Rana	Ultramafic talc-carbonate	Industrial	Anthophyllite, tremolite	Yes	1934–2009	Wergeland et al. (1990); Karlsen et al. (2000)	Wergeland et al. (2017)
Pakistan, Sherwan, Khyber Pakhtoonkhwa	Ultramafic talc-carbonate	Industrial, cosmetic	No	Yes	1952–to date	Calkins et al. (1973)	NA
Russian Federation, Krasnoyarsk, Yenisey, Siberia	Ultramafic talc-carbonate	Industrial	No	Yes	2004?–to date	Granovskaya and Kochergin (2020)	Katsnelson and Mokronosova (1979)

Table 1.1 (continued)

Mine location	Mineral origin of talc	Talc type	Occurrence of asbestos[a]	Occurrence of quartz[b]	Estimated period of mine exploitation[c]	Reference	Reference for cancer or mechanistic study in humans with setting in the mine
Spain, Fuentes de Respina, León, Puebla de Lillo	Hydrothermal talc-carbonate	Industrial to pharmaceutical	No	Yes	1920s–2000s	Tornos and Spiro (2000)	Montes et al. (2003)
Sweden, Handöl Köli, Asån	Ultramafic talc-chlorite	Industrial	Chrysotile probable, tremolite probable	Yes	? – to date	Bergman (1993)	NA
USA, Alabama, Dadeville	Ultramafic talc-chlorite	Industrial	Actinolite, anthophyllite, tremolite	No	1963–1991	Van Gosen et al. (2004)	NA
USA, Alabama, Winterboro	Hydrothermal talc-carbonate	Industrial, cosmetic	No	Yes	1943–1991	Greene (1995)	NA
USA, California, Silver Lake and Yukka Grove, Death Valley	Ultramafic talc-chlorite	Industrial	Tremolite	Yes	1916?–1955	Van Gosen et al. (2004)	NA
USA, California, Grantham-Warm Spring and Alexander Hills, Death Valley	Ultramafic talc-chlorite	Industrial	Tremolite	Yes	1916–1978	Van Gosen et al. (2004)	NA
USA, California, Inyo, Northern Panamint Range district	Hydrothermal talc-carbonate	Industrial, cosmetic	Tremolite probable	Yes	1912/1918–1955?	Greene (1995); Van Gosen et al. (2004)	NA
USA, California, Talc city District	Hydrothermal talc-carbonate	Industrial	No	Yes	1912/1918–1968?	Van Gosen et al. (2004)	NA
USA, Georgia, Chatsworth district, Murray County	Ultramafic talc-chlorite	Industrial, cosmetic	Actinolite, anthophyllite, chrysotile	Yes	1907–1998	Furcron et al. (1947)	NA
USA, Georgia, Soapstone Ridge	Ultramafic talc-chlorite	Industrial	Anthophyllite, tremolite	No	1883?–1990	Van Gosen et al. (2004)	NA
USA, Maryland, Piedmont belt	Ultramafic talc-chlorite	Industrial	Chrysotile possible	Yes	1852–1985	Cleaves et al. (1974); Greene (1995)	NA

Table 1.1 (continued)

Mine location	Mineral origin of talc	Talc type	Occurrence of asbestos[a]	Occurrence of quartz[b]	Estimated period of mine exploitation[c]	Reference	Reference for cancer or mechanistic study in humans with setting in the mine
USA, Montana, Dillon-Ennis district, Treasure and Regal mines	Hydrothermal talc-carbonate	Industrial, cosmetic	No	Quartz probable	1940–2023	Chidester (1962); Buzon and Gunter (2017)	NA
USA, Montana, Dillon-Ennis district, Yellowstone	Hydrothermal talc-carbonate	Industrial	Tremolite probable	Yes	1940–2019	IARC (2010); Van Gosen et al. (2004)	NA
USA, Montana, Dillon-Ennis district, Willow creek and Beaverhead mine	Hydrothermal talc-carbonate	Industrial	Tremolite probable	Yes	1940?–1979	Van Gosen et al. (2004)	NA
USA, Nevada, Palmetto and Sylvania Districts	Hydrothermal talc-carbonate	Industrial	No	Yes	1903–1980	Greene (1995)	NA
USA, New Mexico, Red Rock	Ultramafic talc-chlorite	Industrial	No	Yes	1926–1945	Fitzsimmons and Kelly (1980)	NA
USA, New York, Gouverneur District, St Lawrence County, Talcville[e]	Ultramafic talc-chlorite)	Industrial	Anthophyllite, tremolite	Yes	1878–2012?	Chidester (1962); Van Gosen et al. (2004); IARC (2010); Gunter et al. (2018)	Honda et al. (2002) (mine and millers' facilities in upper state New York)
USA, New York, Gouverneur District, St Lawrence County, Fowler[e]	Ultramafic talc-chlorite)	Industrial	Chrysotile possible, anthophyllite, tremolite	Yes	1878–2008	Wylie et al. (1997); IARC (2010); Van Gosen et al. (2004); Gunter et al. (2018)	Honda et al. (2002) (mine and millers' facilities in upper state New York)
USA, New York, Lewis County, Natural Bridge	Ultramafic talc-chlorite	Industrial	Chrysotile possible	Yes	1900–1970	Engel (1949), IARC (2010); Van Gosen et al. (2004)	Honda et al. (2002) (mine and millers' facilities in upper state New York)

Table 1.1 (continued)

Mine location	Mineral origin of talc	Talc type	Occurrence of asbestos[a]	Occurrence of quartz[b]	Estimated period of mine exploitation[c]	Reference	Reference for cancer or mechanistic study in humans with setting in the mine
USA, North Carolina, Blue Ridge, Day Book and Murphy District[e]	Hydrothermal talc-carbonate	Industrial	Anthophyllite, tremolite probable	Quartz probable	1859–1990	Chidester (1962); Greene (1995); Van Gosen et al. (2004)	NA
USA, North Carolina, Piedmont belt	Contact or hydrothermal talc-chlorite	Industrial, cosmetic	Tremolite possible	No	1859–1991	Greene (1995)	NA
USA, Texas, Allamoore district[e]	Hydrothermal talc-carbonate	Industrial	Tremolite	Quartz	1952–to date	Van Gosen et al. (2004)	NA
USA, Texas, Llano district	Ultramafic talc-chlorite	Industrial	Actinolite probable, anthophyllite probable, tremolite, chrysotile	No	1946–1994	Van Gosen et al. (2004)	NA
USA, Vermont (Blackwall talc)[e]	Ultramafic talc-chlorite	Industrial, cosmetic	Actinolite probable Anthophyllite possible, chrysotile Tremolite probable	Quartz	1903–1983	IARC (2010); Van Gosen et al. (2004); Gunter et al. (2018); Egilman et al. (2020)	Fordyce et al. (2019)
USA, Virginia, Schuyler	Ultramafic talc-chlorite	Industrial	Actinolite probable	No	1893–2014	Chidester (1962); Greene (1995)	NA

NA, not available; USA, United States of America.

[a] Fibrous–asbestiform form [the Working Group assumed the possible presence of chrysotile when presence of serpentine has been reported. "Probable" means that the presence of amphibole minerals tremolite, anthophyllite and actinolite has been reported, but not in the asbestiform habit. If these minerals were reported in the asbestiform habit, then this is marked as the type of asbestos (without "probable" or "possible"). "Possible" tremolite means that the presence of tremolite has been reported for the geological formation forming the deposit or in contact with the deposit.]

[b] The presence of quartz does not imply that it is carcinogenic respirable quartz (silica).

[c] Some data taken from mindat.org (Hudson Institute of Mineralogy, 2024).

[d] "No" indicates that, in the surveyed literature describing that occurrence, the presence of one or more of the six mineral species classified as asbestos was not reported or that the absence of one or more of the six mineral species classified as asbestos was stated.

[e] Presence of fibrous talc is reported.

Table 1.2 Estimated production of talc in mines in selected countries and worldwide, 2018–2023

Country	Estimated production (thousand metric tonnes)					
	2018	2019	2020	2021	2022	2023
Afghanistan	ND	ND	ND	628	370	370
Brazil[a, b]	660	660	650	650	600	600
Canada[c]	210	240	230	150	200[a]	200[a]
China[c]	1800	1400	1300	1100	1100	1100
Finland	380	330	300	297	242	240
France	450	450	450	350	350	400
India[a]	920	920	1670	1750	1630	1600
Italy	170	165	165	165	180	180
Japan[a]	160	160	160	160	136	140
Pakistan	ND	183	126	140	300	300
Republic of Korea[a]	350	330	476	355	323	320
South Africa[a]	ND	ND	126	ND	439	370
Türkiye	ND	ND	ND	220[a]	43	40
United States of America	650	578	490[d]	577[d]	511	450
Other countries[a]	815	728	600	690	707	700
World total (rounded)[a]	6600	6140	6720[d]	7240[d]	7130	7000

ND, no data.
[a] Includes pyrophyllite.
[b] Crude and beneficiated.
[c] Unspecified minerals.
[d] Excludes production of pyrophyllite in the USA.
From US Geological Survey (2020, 2021, 2022, 2023, 2024).

Expensive talc beneficiation processes (Bazar et al., 2021) are used to produce "powder talc", whereas cheap talc mineral processing results in "talc lumps" and "talc granules".

(c) Talc production

Estimates of the world mine production of talc are reported in Table 1.2 (modified after US Geological Survey, 2020, 2021, 2022, 2023, 2024). The Asia–Pacific region dominates the global talc market, owing to the rising domestic market in China and India. In India, talc reserves are mainly located in Rajasthan state, where local companies supply the cosmetics and polymer industry (Fitzgerald et al., 2019; Mordor Intelligence, 2023). Rapid industrialization in emerging economies such as Thailand, Malaysia, Mexico, Brazil, Argentina, the Russian Federation, and South Africa is driving the growth of the market for talc to be used in various end-use industries (MarketsandMarkets, 2023). The COVID-19 (SARS-CoV-2) pandemic affected the market in 2020 and 2021, forcing manufacturers of ceramics, paper, paints, and coatings to reduce or close their operations (Mordor Intelligence, 2023). This was evidenced by a decrease in production in China and France (Fig. 1.3) in that period. At the present time, the major producers in the global talc market are India, China, and Brazil (Fig. 1.3).

(d) Synthetic talc

Although much more limited than the natural talc market [probably < 1% of the global talc market], there is industrial production and distribution of synthetic talc. Industrial sites for the production of synthetic talc, via hydrothermal synthesis in a continuous process, can

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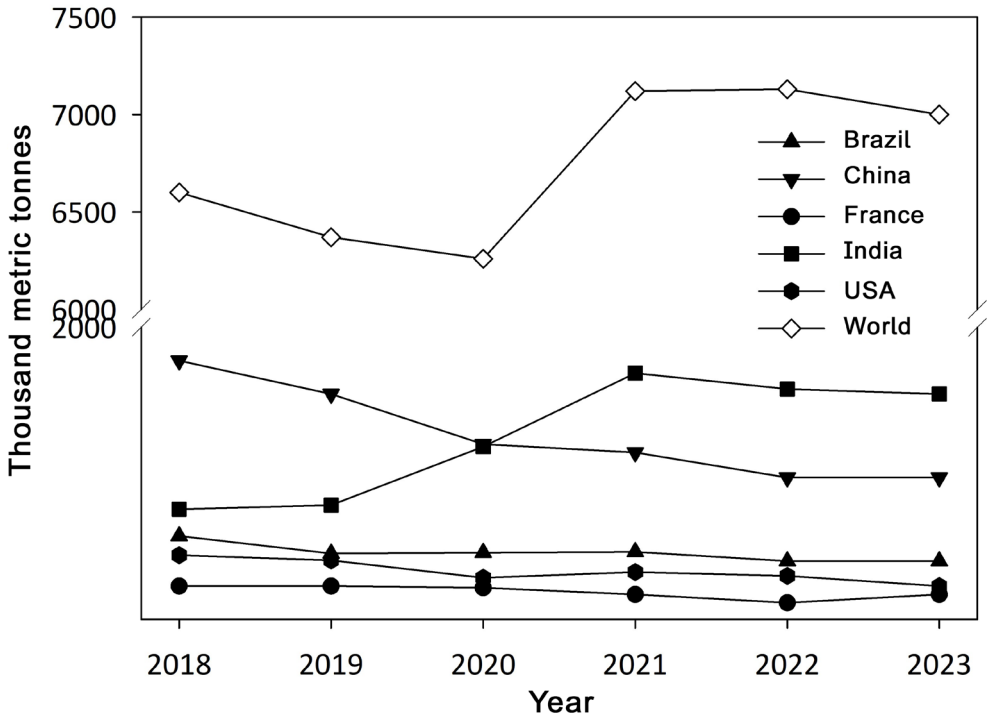
Fig. 1.3 Trends in estimated production of talc in mines in 2018–2023, selected countries leading the talc market and world overall trend



Pyrophyllite is included for Brazil and India.
Averaged and plotted from US Geological Survey (2020, 2021, 2022, 2023, 2024).

be found in the USA and France (Aymonier et al., 2019; Imerys, 2022). [The Working Group noted that market distribution of this synthetic product is also conveyed through online sites; see, for example, Rio Grande (2024).]

1.2.2 Uses of talc

Talc has unique chemical, physical, and technological properties, including affinity for organic molecules, high specific surface area, hydrophobicity, insolubility, platyness, refractoriness, softness, and more (Ferrage et al., 2003; IARC, 2010), that have been exploited for more than a century for use in many industrial products and applications, such as animal feed, ceramics, cosmetics, fertilizers, paints, paper, pharmaceuticals, polymers, roofing, and rubber. In 2023, in the USA for example, talc was used in: plastics, 30%; ceramics (including automotive catalytic converters), 27%; paint, 17%; paper, 9%; roofing, 8%; and rubber, 5%. The remaining 4% was for agriculture, cosmetics, export, insecticides, and other miscellaneous uses (US Geological Survey, 2024). A non-exhaustive list of talc industrial applications, mostly in end-use industry, is reported below in alphabetical order.

[The Working Group noted that it is very difficult to determine whether the talc used in a broad range of consumer and industrial products and settings is contaminated with asbestos or other carcinogens without knowing from which deposit the talc originated. This information was very rarely available to the Working Group.]

(a) Agriculture and treatment of wastewater

Talc is used as anticaking agent, dispersing agent, and die lubricant in animal feed and fertilizers (IARC, 2010; McCarthy, 2013), as an active substance for plant protection (EFSA, 2017), or as inert carrier in premixes and agricultural chemicals (Essential Minerals Association, 2023), and can be used in oils and greases to reduce wear and friction (Rudenko and Bandyopadhyay, 2013; Kumar et al., 2021).

Talc is a functional carrier in agricultural products, in garden dusts, flea and tick powders, seed treatments and biocides. Talc improves the flowability of oil-seed meal and finished products, and animal feeds containing sticky ingredients such as molasses, oil, fatty products, urea, milk powder, and sugar (IARC, 2010). Talc acts as a die lubricant especially for high-fibre, high-sugar, high-mineral formulations, and pelleted feeds. Talc is also used as anticaking agent in ammonium nitrate and granular fertilizers (IARC, 2010). In mushrooms, addition of talc was shown to control mycelial morphologies to improve mycelial growth and the production of secondary metabolites (Tao et al., 2018).

Talc improves the performance of biological wastewater treatment plants, favouring flocs of bacteria and accelerating their sedimentation (Essential Minerals Association, 2023). Talc-mediated bioleaching could also facilitate the precipitation of metals (Wakeman et al., 2011). Decontamination of metals like lead, cadmium, cobalt, and zinc onto polyacrylic acid acrylonitrile–talc nanocomposite has been recently accomplished (Abass et al., 2022).

(b) Ceramics

After the dehydroxylation reaction, $Mg_6Si_8O_{20}(OH)_4 \rightarrow 6\ MgSiO_3 + 2\ SiO_2 + 2H_2O$, which occurs in the temperature range 700–1000 °C (Wesołowski, 1984), talc renders magnesium and silicon available for high-temperature ceramic processes. For example, talc is used as a major component in the formulation of magnesium-based cordierite-mullite refractories (Maiti and Singh, 2001). It is added to the mixes for the preparation of white stoneware tiles, generally in percentages below 5 wt%, to promote sintering of the ceramic body and enabling the reduction of firing temperatures and cycles (Ferrari et al., 2004; IARC, 2010). This is possible because magnesium from talc promotes the formation of eutectic points (reducing the melting temperature) when it reacts with potassium and sodium made available from the feldspar fluxes. [The Working Group remarked that China is a great consumer of talc because it is the leading producer and consumer of ceramics worldwide.] Talc is also used in sanitary ware, tableware, and technical ceramic products (IARC, 2010). Talc lumps with a very low iron content are particularly suitable for the manufacture of ceramic frits, glass ceramics, engobes, and glazes (IARC, 2010). Alumina ceramics are also prepared with titania as nucleating agent and talc as fluxing agent (Yu et al., 2018).

Recently, Wu et al. (2021) formulated stoneware tiles prepared from graphite tailings, kaolin, shale, potash feldspar, and albite; the firing temperature range was broadened by using talc as an additive.

(c) Cosmetics and personal care

Talc has been used as the main component of many body powders. Talc is an important component of many cosmetic products, providing silkiness in blushes, powder compacts, and eye shadows; transparency in foundations; and the sheen in beauty creams. The addition of talc to cosmetic products also allows the progressive gradual release of fragrances. For example, talc can be present in body and shower products, lotions, feminine hygiene products, eyeshadow, foundation, lipstick, deodorants, and face masks (IMA Europe, 2024). Soap manufacturers also use talc to enhance the performance of skin care products (IARC, 2010; Essential Minerals

Association, 2023). Talc is found in antiperspirants and deodorants; bath and shower products; beauty aids like aerosol talc products, face masks, foundations, body oils, make-up bases, concealers, blushes, body powders, rouge, make-up, compact powders, eye shadows, dusting powders, eyebrow pencils, pressed powder products, face powders, mascaras, liquid talc products and powder cleansers, creams, foot powders, hair care products, lipsticks, lotions, shampoos, and shaving products; sun care products like lipsticks; and wound ointments (Lundeen et al., 1985; IARC, 2010).

Talc-based baby powder has long been used for the prevention of irritant contact diaper dermatitis (Sinniah, 2011).

The problem of asbestos contamination of talcs used in products for the cosmetics and personal care industry is well known (see Section 1.4.1(e)) (Stoiber et al., 2020; Reuters, 2023).

(d) Food industry

Talc is an anti-stick coating agent used in several foods, such as chewing-gum, candies, and cured meats. Talc acts as a natural processing aid that improves extraction and increases the yield and quality of virgin olive oil (IARC, 2010; Caponio et al., 2014) and nutmeg oil (Hang and Yang, 2007).

Talc has also been used as inert carrier for active premix ingredients, as an antisticking agent on conveyor belts that carry foodstuffs (IARC, 2010), and as a rice additive (Merliss, 1971a).

(e) Paints and coatings

Talc improves the hiding power and efficiency of titania-based decorative paints. In anti-corrosion primers, talc improves resistance to corrosion and adhesion of the paint. Talc is also used in inks, jointing compounds, putties (where it can be the major component), adhesives, and stucco (Yazicioglu et al., 1980; IARC, 2010; Joannès et al., 2010).

(f) Pharmaceuticals and health care

Talc has been used as an agent in pleurodesis (see Section 4.2.6), a therapeutic treatment applied by intrapleural administration to create adhesion between the parietal and visceral pleura (Gonzalez et al., 2010; Sweatt and Sung, 2014). The first use of talc in the treatment of lung pleural effusions dates back to 1935 (Kennedy et al., 1995). Talc pleurodesis is also used in the management of primary spontaneous pneumothorax (Mendogni et al., 2020). Use of talc still is well accepted for pleurodesis, as evidenced by the inclusion of talc in multiple therapeutic guidelines (Feller-Kopman et al., 2018; Gilbert and Haouzi, 2019).

Qureishi et al. (2012) reported the successful use of talc sclerotherapy in the management of spontaneous cervical lymphocoele, obviating the need for high-risk surgical procedures.

In pharmaceutical products, talc is an important excipient used as a glidant, lubricant, and diluent. Talc powder is added as an excipient in the preparation of tablets, capsules, powders, topical and oral suspensions (Pharma Excipients, 2025), granules, lozenges, (Takenaka et al., 1980; Jadhav et al., 2013; Lääkeinfo, 2022), intra-oral matting sprays for dental chairside systems (Ochsmann et al., 2020), oily drugs (e.g. zedoary turmeric oil, ZTO, microspheres with self-emulsifying ability; You et al., 2005), in surgery gloves (IARC, 2010), as powder placebo in some clinical tests (Magnolfi et al., 1996), for the prevention of athlete's foot (Ramsey, 1989), in condoms (Kasper and Chandler, 1995), and to counterfeit drugs (Jackson et al., 2010). Talc-coated pellets obtained with the standardized liquid extract of *Brosimum gaudichaudii* were prepared for the treatment of vitiligo (Filho et al., 2015).

In traditional Chinese medicine, talc has therapeutic functions as an antipyretic and diuretic agent in herbal applications (Chang et al., 2019).

(g) Plastics and rubber

Talc is added as filler to polypropylene mixes and thermoplastic foams (e.g. Loypetch et al., 2019), copolymer polypropylene produced through low-pressure foam-injection moulding (Llewelyn et al., 2019), polyoxymethylene composites (Kailasanathan et al., 2022), nanocomposites used for surface modification of polyester fabric (Oikawa et al., 2015), generally to improve stiffness and size stability as reinforcing filler in automotive parts, household appliances, white goods, and food packaging applications (Imerys, 2024). A synthetic nickel-talc was used as filler in the synthesis of polyurethane nanocomposites (Prado et al., 2015). Talc is also used for antiblocking of linear low-density polyethylene and as a nucleating agent in semi-crystalline polymers (IARC, 2010).

In rubber, talc reduces the viscosity of rubber compounds, easing the processing of moulded parts. Talc is added to extrudates to enhance resistance to ultraviolet (UV) irradiation of exterior parts such as automotive profiles and to provide compression resistance to sealants and gaskets. Talc is used as an insulator in cables and as a processing aid in tyre manufacture (IARC, 2010; Essential Minerals Association, 2023). Poly(lactic acid) was modified with poly(butylene succinate) and talc to obtain formulations with good toughness and high crystallization rate for biodegradable injection-moulding products (Petchwattana et al., 2021).

Talc was used in the pretreatment of radioactive sections for quantitative radioluminography (Maas et al., 2000), as an electrochemical sensor (Pecheu et al., 2022), and as a catalyst for the synthesis of 1,3-butadiene from ethanol (Miyaji et al., 2018).

(h) Pulp, paper, and paper products

Talc is used in the pulp industry to prevent pitch deposition and in the paper industry as both a filler and a coating pigment. Talc is also suitable for liquid and food packaging, where it acts as an ingredient of the sealing layer (Nordic talc, 2023). Talc is added to the pulp for both uncoated and coated gravure papers in order to improve printability, reduce surface friction, and enhance handling characteristics (IARC, 2010; Marzbani et al., 2013).

Talc is also used as a smooth filler in the "pigmented core" of colouring pencils (IARC, 2010).

(i) Roofing and various building materials

Talc is used in back surfacing of asphalt and laminated shingles (IARC, 2010). Fabrication of white one-part alkali-activated magnesia-based cements using the vitrification of talc in the presence of sodium hydroxide (NaOH) or sodium aluminate ($NaAlO_2$) was shown to be possible, demonstrating the potential use of this mixture as a lightweight and a rapid-hardening cement in prestige construction projects and decorative works (Abdel-Gawwad, 2021).

(j) Other uses

Talc is also used in air bags, in combination with NaOH (Swanson-Biearman et al., 1993).

1.3 Detection and quantification

Ensuring the detection, purity, and quantification of talc in commercial, geological, and industrial hygiene samples is essential for quality control, safety, and resource assessment. Talc is commonly used in cosmetics and pharmaceuticals. Assessment of the purity of talc used in these products is mandatory to ensure consumer safety (IARC, 2010). For example, Paoletti et al. (1984) analysed 29 industrial, cosmetic, and pharmaceutical talc powders from Italian and international markets. In 8 out of 15 talc samples from Italy, asbestos fibres were found to be present. Accurate quantification of talc in ceramics and plastics is critical for the

optimization of product formulations and to achieve the desired properties (Beuguel et al., 2015). Talc in geological samples is analysed to understand its source, mineral composition, economic potential, and possible contamination with asbestos (Van Gosen et al., 2004). On-site detection and quantification of talc for resource assessment using a portable X-ray diffraction and X-ray fluorescence (XRD/XRF) analyser in geological samples is also possible (Ahonen et al., 1988; Sarala and Koskinen, 2018).

1.3.1 *Methods for talc sampling and preparation*

Talc detection and quantification are downstream of the sampling procedure and preparation of the collected sample. Distinct methods for the collection of the solid constituents (including talc) must be applied to gaseous (air), solid (soil), and aqueous (water) media.

(a) Air

In the medium of air, where talc is generally treated as a general dust, the primary analytical method is aimed at determining the airborne inhalable (entering the nose and mouth during breathing and available for deposition anywhere in the respiratory tract), thoracic (particles with a nominal mean aerodynamic diameter of ≤ 10 µm, generally referred to as PM_{10}, that penetrate beyond the larynx; Office of the Federal Register, 1987b), or respirable (particles with a nominal mean aerodynamic diameter of ≤ 4 µm that are able to penetrate the alveolar region) dust concentrations. The three fractions can be collected using different types of aerosol sampler (Health and Safety Executive, 2014). For the inhalable fraction, the Institute of Occupational Medicine (IOM) sampler (flow rate, 2.0 L/minute) is the preferred method. The conical inhalable sampler (CIS) (3.5 L/minute), the button sampler (4.0 L/minute), and the multi-orifice sampler (2.0 L/minute) are also used. For the thoracic fraction, the GK2.69 cyclone sampler (1.6 L/minute) (recommended) and the parallel particle impactor (PPI2) (2.0 L/minute) are used. For the respirable fraction, the generic Higgins–Dewell type cyclone sampler (2.2 L/minute) (recommended for use in the United Kingdom, UK), the GS-3 cyclone (2.75 L/minute), and the GK2.69 cyclone (4.2 L/minute) are used. Multifraction samplers allow simultaneous measurement of inhalable, thoracic, and respirable fractions (Health and Safety Executive, 2014).

An earlier method of airborne dust collection that has been used for talc (see Section 1.4.2) is liquid impinger sampling, in which dust-laden air is drawn through a liquid. After collection, the liquid is analysed by light microscopy to count the number of particles present. Using this method, dust concentration in the air was reported as million particles per cubic foot (mppcf) (mg/m^3 are generally used at the present time). [The Working Group noted that some studies used a conversion factor to adjust mppcf values to respirable mass concentration values. These conversion factors ranged from 0.38 mppcf = 0.1 mg/m^3 respirable dust (Oestenstad et al., 2002) to 1 mppcf = 0.1 mg/m^3 respirable dust (Rossner et al., 2020).]

Many guidance documents for the sampling and analysis of air samples exist today (see for example, the Health and Safety Executive (HSE) guidance document MDHS14/4; Health and Safety Executive, 2014) and the "General considerations for sampling airborne contaminants" of the National Institute for Occupational Safety and Health (NIOSH) (NIOSH, 2020). Specifically, the HSE guidance document MDHS14/4 reports a procedure to collect the respirable, thoracic, and inhalable aerosol fractions in air for monitoring workplace exposure and describes analysis of the fractions using gravimetric analysis. In this technique, a volume (in cubic metres) of air is pumped through a pre-weighed collection medium (for example, a filter) mounted in a suitable sampler. The mass concentration of the aerosol in air (in

mg/m^3) can be calculated from the mass of the aerosol collected and the sampled air volume (Health and Safety Executive, 2014). The guide recommended specific sampling parameters, with indications for the sampling times and positions, sampled air volume, selection of suitable sampler type, and relative collection medium. In some samplers, the collection medium is held in cassettes to be weighed together. In other samplers, the collection medium may be held within a holder that is not weighed (Health and Safety Executive, 2014). The most frequently used collection media are membrane filters (made of polyvinyl chloride, Teflon, silver, and mixed cellulose esters) (NIOSH, 2020). Other commonly used filters are glass and quartz fibre filters, and polycarbonate pore filters (good for collecting particles to be analysed with scanning electron microscopy (SEM) or transmission electron microscopy (TEM) and XRF. Fibre loss from glass fibre filters may occur during handling and could be significant if not weighed within a cassette (Health and Safety Executive, 2014). The filters are usually removed from the sampler and conserved in laboratory desiccators, and usually a small fragment is cut out and weighed for subsequent laboratory analyses, such as electron microscopy measurements.

The "General considerations for sampling airborne contaminants" (NIOSH, 2020) instead focuses on the sampling objectives, including sampling pump and flow rates, sampling filter, definition of humidity and temperature conditions, sampling strategy, addition of bulk air, solid and liquid samples, and more.

(b) Soil

In soil medium, various sampling methods and strategies are available (see for example US EPA, 1992; Arshad et al., 1997). The United States Environmental Protection Agency (US EPA) operating procedure for soil sampling (US EPA, 2023) describes the sampling methods to collect surface and shallow subsurface (about 15–30 cm deep) soil samples. Another recent US EPA guideline is specific for asbestos-contaminated soils (US EPA, 2021a).

Sampling methods include the use of manual soil samplers such as stainless-steel spoons and hand augers; direct push soil samplers; split spoon/drill rig methods; Shelby tube/thin-walled sampling methods; and Backhoe sampling methods (US EPA, 2023).

The main soil-sampling strategies are the random, the judgemental, and the systematic. The latter is based on geometric grid patterns but is not suitable for small areas or spot sampling (Malinconico et al., 2022). [The Working Group noted that this method was developed for asbestos.] Incremental sampling methodology (ISM) (see the guidance document delivered by the Interstate Technology Regulatory Council, 2024) is based on a systematic strategy designed to estimate the mean contaminant concentration over a given area (US EPA, 1992). It provides representative samples of specific soil volumes, defined as decision units (DUs), by collecting several increments of soil (typically 30–100 in triplicate) that are combined, processed, and subsampled according to specific protocols (US EPA, 2023).

For field sample preparation, sieving with 4.72 mm or 2.0 mm screens may be conducted to discard rock or plant fragments and man-made materials. If the sample is collected in relation to concerns regarding human exposures, the US EPA recommends subsequently sieving to a fine fraction (< 150 µm) to best represent that portion of the soil that is most likely to adhere to human skin (US EPA, 2021b). Usually, a volume of 250 mL or a mass of 1 kg is collected and coning and quartering allow the sample volume to be reduced, both on site and in the laboratory (Malinconico et al., 2022).

Treatment of soil samples before identification and quantification usually includes drying/conditioning and crushing (Malinconico et al., 2022). Comminution (reduction of average

particle size) results in homogenization of the soil sample. However, its effectiveness is strongly dependent on the crystal–chemical nature of the mineral species composing the sample (Malinconico et al., 2022). Milling the whole sample allows the inclusion of fibres that may be embedded in the skeleton. When the sample has been homogenized, it is usually subsampled (US EPA, 1997). Methods of gravimetric matrix reduction include ashing; dissolution in acid; or separation of larger aggregates and particles by sedimentation, which can be followed by filtration sonication (i.e. ultrasonication), usually in alcohol, to further dismantle the particle aggregates (Malinconico et al., 2022).

(c) Water

Many recommendations given for soil also apply to the liquid matrix, i.e. water (US EPA, 1994; Webber et al., 1999).

Preparation of the water samples is also a determining factor for the subsequent analytical steps, and many different procedures are described in the literature (e.g. Pierce et al., 1971). When the samples are stored for a long time and/or have a high organic load, ozone and UV treatments are used (Malinconico et al., 2022). Later, sonication and filtration can be carried out to deposit the solid residue onto membranes. Dilution with distilled water is carried out when high particle loadings are noticed in the sample (Malinconico et al., 2022). Further preparation of specimens for microscopy follows the same procedure as that for air samples (Malinconico et al., 2022). When a high organic load is present, the subsample should be dried and ashed in a muffle furnace, plasma asher, or microwave system, and the residue then remobilized in particle-free water (Malinconico et al., 2022).

1.3.2 Methods for the detection and quantification of talc

Several analytical techniques are used for talc detection and quantification, each of which has advantages and limitations. The choice of method depends on the specific application and the level of information required.

Common mineralogical, chemical, and spectroscopic methods for the detection and quantification of talc are listed below.

(a) X-ray powder diffraction

X-ray powder diffraction (XRPD) is a widely used technique for identifying and quantifying minerals and synthetic phases in natural and industrial materials; however, the identification of mixed mineral assemblages may be difficult because of the overlap of diffraction peaks (Krause, 1977). Although the limit of detection (LOD) with this technique for talc in bulk samples is around 1 wt%, modern quantitative analysis methods can reach levels of about 0.1 wt% (Bish and Plötze, 2011).

XRPD cannot distinguish fibrous–asbestiform minerals from other habits, so it is not possible to assess whether the talc identified (and eventually quantified) displays a fibrous–asbestiform crystal habit. Krause and Ashton (1978) pointed out that the fact that it is impossible to distinguish minerals with a fibrous (asbestiform) habit from minerals with lamellar habits continues to be overlooked by responsible investigators claiming to have identified asbestos by XRPD.

If the presence of asbestos minerals has been assessed independently, quantification is possible by XRPD. Rohl and Langer (1974) reported LODs of 0.10 wt% and 0.25 wt% for amphibole tremolite and chrysotile, respectively, in consumer talcum products. In a more recent publication, Hu et al. (2014) reported the detection of asbestos in traditional pharmaceutical talc at levels of 0.3–0.8 wt%. Block et al. (2014)

stated that there is a need to update the current United States Pharmacopeia (USP) monograph because both methods currently listed (the Fourier transform infrared spectroscopy, FTIR (Section 1.3.2(d)), and XRPD) have relatively high LODs for asbestos (nominal LODs, 1% and 0.5%, respectively) (Office of the Federal Register, 2024a). [The Working Group noted that the limitations of these experimental methods make it hard to rule out asbestos contamination in pharmaceutical-grade talc.]

(b) X-ray fluorescence

The chemical analysis of talc samples is generally carried out using XRF data (e.g. Ferrage et al., 2002; Dumas et al., 2015). Volatiles such as structural water must be determined independently (see Section 1.3.2(c)), and the outcome of the analysis is usually expressed in wt% oxides (values for an ideally pure talc sample are: MgO, 1.9 wt%; SiO_2, 63.4 wt%, and H_2O, 4.8 wt%; Piniazkiewicz et al., 1994). XRF can detect impurities and contaminants in talc samples (with a lower LOD of about 0.35 wt% for silicon and 10 µg/g for magnesium from pressed powder pellets (CRB, 2024)) but is not suitable for the identification or quantification of talc, except to establish the composition of almost pure talc. In fact, in mixed samples, XRF cannot discriminate between the various magnesium silicates (e.g. talc versus serpentine minerals).

(c) Thermal analysis

Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) are used to determine the behaviour of talc when it is subjected to temperature changes. This includes information on decomposition, phase transformation, and the presence of impurities that affect the thermal properties of talc (Piga et al., 1992). The identification and quantification of talc is possible by detecting the endothermic event related to the dehydroxylation reaction, $Mg_3(Si_2O_5)_2(OH)_2 \rightarrow {}_3MgSiO_3$(enstatite) + SiO_2 (amorphous silica) + H_2O, which occurs in the temperature range 800–1000 °C (Wesołowski, 1984; Belgacem and Trabelsi-Ayadi, 2011). By using calibration curves, quantification of the talc content is possible by measuring the endothermic peak area from the DTA, which is proportional to the talc content (Keattch et al., 1980; Wesołowski, 1984). The detection of that endothermic event may be prevented by overlap with other endothermic events related to the dehydroxylation of layer silicates such as mica, illite, or chlorite, or decomposition reactions such as decarbonation.

With the use of reference standard materials, the minimum LOD for minerals (e.g. quartz) by DTA is around 0.5 wt% (Schelz, 1976). Chrysotile has been quantified in pharmaceutical-grade talc with a minimum LOD of 1.0 wt% (Schelz, 1974) and in cosmetic-grade talc with a minimum LOD of 0.5 wt% (Luckewicz, 1975).

(d) Fourier transform infrared spectroscopy

The identification and quantification of talc from FTIR spectra is possible by inspecting the typical bands in the hydroxyl stretching region at 3677, 3661, and 3643 cm^{-1} (Wilkins and Ito, 1967; Farmer, 1974). [The Working Group noted that discrimination between lamellar and fibrous talc is possible only by FTIR combined with microscopy, but not with conventional FTIR for bulk sample powders. Micro-FTIR has not been applied to exposure assessment in epidemiological studies.] An application of near- and mid-FTIR infrared spectroscopy was reported by Blanchard et al. (2018), who investigated synthetic nickel-doped talc by focusing on the four main hydroxyl stretching bands, which represent good probes of their local physical and chemical environment. Talc has been detected in wheat flour by near-infrared spectroscopy (NIRS) using a method developed for rapid detection in real time (Bao et al., 2022).

The presence of layer silicates, the absorption bands for which may overlap with those of talc,

may bias the identification or quantification of talc, and analysis requires careful discrimination by robust deconvolution fitting procedures. In complex natural systems, the LOD for this technique is about 1.0 wt% (Chen et al., 2014; Malinconico et al., 2022).

Contamination of talc with asbestos minerals can also be detected and quantified using FTIR. The estimated LOD for chrysotile in soil can be as low as 0.01 wt% (Foresti et al., 2003) using a standard laboratory elutriator in sedimentation analysis for detecting enrichment of chrysotile fibres. [The Working Group noted that the method described by Foresti et al. (2003) has been applied to soil matrices. A similar LOD was not commonly achieved in other studies using this method for exposure assessment.]

(e) Optical microscopy

Common microscopy methods for the detection and quantification of talc are listed in the present section. Talc can be identified from its optical properties by polarized light optical microscopy (PLOM). Talc is biaxial, negative, and the three indices of refraction increase with iron content. Because β and γ are approximately equal, talc appears to be uniaxial (Nesse, 2004; Deer et al., 2013). The identification of talc particles can be complicated because accompanying minerals, such as muscovite, chlorite, and pyrophyllite, can display similar optical properties. However, talc has a higher-order interference colour and lower 2V than do muscovite and pyrophyllite (Nesse, 2004; Deer et al., 2013; Perkins et al., 2023). In particular, given the small size of the crystals, the distinction between talc and pyrophyllite is almost impossible to discern (UFRGS, 2022). Moreover, assessing whether the talc particles display a lamellar or fibrous crystal habit can be very difficult.

Using PLOM combined with SEM, Johnson et al. (2020) measured the size and shape of talc particles in samples of talc-containing baby powder and surgically resected pelvic tissues from talc-exposed patients with ovarian carcinoma.

Quantification of talc is usually carried out using XRPD or SEM (Section 1.3.2(a), Section 1.3.2(f)), but optical microscopy can also be used via the "point counting" technique (used to count each individual particle of a phase in a certain statistically representative area of a sample and calculate the relative volume percentages). Although less common than SEM, optical microscopy is an effective tool for mineralogical quantitative characterization and can be automated (De Castro et al., 2022). Moreover, optical microscopy with a nominal size resolution of 200 nm (Nesse, 2004) can discriminate particles with a resolution of as high as about 1 μm.

Elongate particles of minerals other than talc have long been screened for using PLOM or phase contrast optical microscopy (PCOM) in combination with electron microscopy (Chatfield, 2018; Sanchez et al., 2023). Optical microscopy is susceptible to misidentification of talc and asbestos (Krause and Ashton, 1978). For details, advantages, and disadvantages of the optical method, mostly applied to air samples, see, for example, Stanley (1978), US EPA (1993), OSHA (1995), ISO (2014a, b), Health and Safety Executive (2021). Recently, Nishimura et al. (2023) reported that a point-counting method using fluorescence microscopy images enabled semiquantitative analysis of asbestos contamination of 0.01–1.0 wt% in talc.

(f) Scanning electron microscopy

SEM provides high-resolution images that can reveal impurities, contaminants, and particle size distribution in talc samples. Morphological analysis using both secondary and back-scattered electrons provides a clear indication as to whether the talc particles are lamellar or fibrous (Catalano et al., 2014; Gilbert et al., 2018; Klein and Krekeler, 2020). Lapenas et al. (1982) showed how exogenous materials such as talc in biopsy and autopsy tissues can be detected by PLOM,

but confident identification of these materials is obtained only by the morphological and chemical information provided by SEM-EDX analysis. McDonald et al. (2019) attempted to determine talc resulting from in vivo exposure in pelvic lymph nodes using SEM-EDX and concluded that, because PLOM and in situ SEM-EDX permit the identification of particles in cells and tissues, these techniques were recommended for the assessment of talc in lymph nodes.

Although it is possible to assure an LOD for talc of 100 mg/kg (0.01 wt%) using SEM in bulk matrices, quantitative SEM determinations usually involve the inspection of impurities (e.g. asbestos) in talc samples and not the talc samples themselves. The asbestos content of talc-rich samples of air or bulk material can be determined using various protocols, as described in Health and Safety Executive (2021). The criteria for fibre definition are compliant with the World Health Organization (WHO) standard (WHO, 1997).

(g) Transmission electron microscopy

TEM is also used for the identification of talc in bulk and airborne samples. TEM high-resolution (nanometre) morphological analysis combined with energy-dispersive X-ray spectroscopy (EDS) or other spectroscopic spot analyses (e.g. electron energy loss spectroscopy, EELS) can be used for the analysis of the shape of the talc particles (lamellar or fibrous). Talc is identified from selected area electron diffraction (SAED) patterns, although talc platelets and talc intergrown with amphibole in fibrous talc have complex electron diffraction patterns that may resemble those of other silicates, including amphiboles (Stemple and Brindley, 1960). Kremer and Millette (1990) developed a standard method for the preparation of powdered talc for TEM analysis to identify and quantify small quantities of asbestos and related minerals. The presence of asbestos fibres in commercial talc powders was later confirmed by TEM with an X-ray diffraction microanalysis probe (Scancarello et al., 1996) and TEM-SAED analysis (e.g. Gordon et al., 2014). Talc in bulk materials is quantified by bulk methods (Section 1.3.2(a)) other than TEM-SAED but, on the basis of the existing data in the literature, the estimated LOD for talc using the TEM-SAED method is 0.00005 wt% of fibrous particles with length of 3 μm, width of 0.2 μm, and thickness of 0.06 μm (Kremer and Millette, 1990).

The use of TEM-SAED and related analytical protocols to detect the presence of asbestos fibres in talc samples is well documented in the literature (Rohl and Langer, 1974; Kremer and Millette, 1990; Asbestos Hazard Emergency Response Act, Office of the Federal Register, 1987a; American Society for Testing and Materials, ASTM, 1998, 1999, 2023; and International Organization for Standardization, ISO, 2019a, b).

Stanley (1978) reported an LOD for asbestos fibres in talc using TEM-SAED of about 0.1 wt%, but theoretically much lower limits can be achieved (Millette, 2015).

(h) Electron probe microanalysis

Electron probe microanalysis (EPMA) is used for the calculation of the structural formulae of mineral or synthetic phases including trace elements, and benefits from the improved stability of spectrometers, an electron column that operates at high probe current, new large-area crystal monochromators, spectrometers with an ultra-high count rate, full integration of energy-dispersive/wavelength-dispersive X-ray spectroscopy (EDS/WDS) signals, and the development of powerful software packages. For phases that are stable under a dense electron beam, the LOD and precision for the elements of which the sample is composed can be decreased to the level of parts per million (Batanova et al., 2018). The structural formulae of both lamellar and/or fibrous–asbestiform talc and asbestos minerals can be computed by EPMA data, which allows unambiguous phase identification. Numerous examples of the application of EPMA analysis to

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talc (e.g. Li et al., 2013) and asbestos phases (e.g. chrysotile, Di Giuseppe et al., 2021) are found in the literature.

(i) Micro-Raman spectroscopy

In micro-Raman spectroscopy, individual particles in a complex matrix can be selected and irradiated with a laser beam to produce a diagnostic Raman spectrum that allows phase identification. This is a qualitative method that is not used for the quantitative analysis of talc in bulk samples.

The Raman spectra of microscopic lamellar and/or fibrous talc particles exhibited no differences uniquely associated with their form, whereas the Raman spectra of microscopic particles of talc and tremolite exhibited very sharp, well-defined peaks that allowed their identification (Blaha and Rosasco, 1978). The position of the peak near 360 cm^{-1}, related to specific metal–oxygen vibrations, as well as the integrated intensities of the hydroxyl stretching Raman signals (3600–3750 cm^{-1}) can be used to determine the amount of octahedral magnesium and iron/manganese in talc with a precision similar to that of EPMA (Aspiotis et al., 2023). Near-field synchrotron infrared nano-spectroscopy, Raman spectroscopy, and first-principle calculations have been used to investigate the structural and vibrational properties of talc crystals, ranging from monolayers to bulk, in the 300–750 and < 60 cm^{-1} spectral windows (Longuinhos et al., 2023).

Micro-Raman spectroscopy can be used for the recognition and evaluation of talc crystallinity in human lung tissues (Rinaudo et al., 2010; Campion et al., 2018). With this aim, Campion et al. (2018) obtained high-quality Raman spectra specific for talc in unstained tissue samples (pleural tissue after talc pleurodesis, and ovarian tissue after long-term perineal exposure to talc). From the Raman analysis, Rinaudo et al. (2010) found that the abundant fibrous material observed in the pleural area was talc; the results were confirmed by variable pressure scanning electron microscopy (VPSEM) with annexed EDS analyses.

The detection limits of the technique depend upon the magnification of the microscope lens used for the focalization of the beam on the selected object but, in general, micrometric particles can be detected. For example, a spatial resolution of 2 μm can be obtained using a 50× objective (Fornasini et al., 2022).

Pharmaceutical-grade talc is usually analysed using XRPD, FTIR, and optical microscopy, whereas cosmetic talc is usually analysed with XRPD and optical microscopy (see Tables 1.17 and 1.18, described in Section 1.5). Industrial-grade talc is generally analysed using XRPD, XRF, and optical microscopy. [The Working Group noted that the only way to reliably determine the presence of mineral impurities such as asbestos in all grades of talc is accomplished using electron microscopy (both SEM and TEM). Less reliable methods have been and are still used to determine asbestos. The high LODs (between 0.5% and 2%) for these less reliable methods imply that asbestos contamination cannot be excluded even at the present time.]

(j) Other state-of-the art analytical methods

Several chemical–spectroscopic methods, although not routinely used, can be employed for the identification and study of the crystal structure of talc. Characterization of iron (oxidation state and chemical environment) in talc is possible by ^{57}Fe Mössbauer spectroscopy (Blaauw et al., 1980).

Fiorentino et al. (2013) studied the dispersion and orientation of talc lamellae by SEM and wide-angle X-ray scattering (WAXS).

The 14 MeV neutron activation method has been used successfully to measure talc in flour. The neutron yield of a deuterium-tritium (D-T) neutron generator was used to irradiate flour samples (Xu et al., 2020). Wehner and Wilkerson (1981) used neutron activation to estimate

pulmonary deposition, translocation, and clearance of inhaled particles of talc and fly ash in hamsters.

Hyperion hyperspectral remote sensing data from the visible and near-infrared (VNIR) operating bands (B008–B057, 426.82–925.41 nm) and short-wavelength infrared (SWIR) bands (B077–B224, 912.45–2395.50 nm) can be used to identify minerals, including talc, on a geographical or geological scale (Govil et al., 2019; Tripathi et al., 2019).

In patients, high-resolution computed tomography (HRCT) can detect small centrilobular nodules associated with heterogeneous conglomerate masses containing high-density amorphous areas suggestive of pulmonary talcosis (Marchiori et al., 2010). The CT findings for talc pneumoconiosis overlap those for silicosis and asbestosis (Akira et al., 2007).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

(a) Air

The presence of mineral dusts in the atmosphere before such minerals were in global commercial use has long been demonstrated (Bowes et al., 1977), and fine particles of talc have been shown to contribute to such dusts. Airborne talc dust has been the focus of a large body of scientific investigation particularly concerning occupational and environmental exposures (see Section 1.4.2). However, little is known about background concentrations of airborne talc in the natural environment. Understanding the sources, dispersion mechanisms, and implications of talc in airborne dust is crucial for addressing safety concerns and developing mitigation strategies to safeguard ambient air quality.

Talc in the environmental airborne particulate can be of (i) natural origin, when released from talc-containing rocks or sediments or from parent talc-rich rocks that underwent alteration processes (litho-genetic cycle) and transported by wind action for short or long distances (Klein, 1993), or (ii) anthropogenic origin (Windom et al., 1967; Hillier, 2001), when released during mining or mining-related activities (Webber et al., 2006) in areas near the exploitation site or from human-manufactured talc-containing products. Talc can also be a component of dust from indoor pollution. Indoor pollution comes from many sources, including household products, cosmetics, combustion used to heat homes or cook food, smoking, and hobbies (Vincent and Chemarin, 2011). Vincent and Chemarin (2011) reported that 5% of homes in France have levels of pollution of > 180 μg/m^3 for PM_{10} and 2% for $PM_{2.5}$ (particles with an aerodynamic diameter of ≤ 2.5 μm), with the main particle air pollutants probably comprising silica, talc, asbestos, and carbon. [The Working Group noted that these values are for total particulate matter and that the proportion of talc was not known.]

Talc found in airborne particulate from the Valmalenco valley, central Alps, in northern Italy, associated with naturally occurring asbestos, may be released from huge outcrops of serpentinite and widespread quarrying of the talc-rich greenstone (Cavallo and Petriglieri, 2020).

The talc observed by Windom et al. (1967) in dusts recovered directly from the atmosphere and in the solid fraction of rain and snow from various localities worldwide is probably of both natural and anthropogenic origin. Considering that the authors reported the mean talc content to be in the order of 1 wt% in the solid phase (Windom et al., 1967), the Working Group calculated the following talc concentrations based on the proportion of talc: [0.016 mg/L] in rain solid fraction from San Diego, California, USA; [0.0052 mg/L] in glacier solid fraction from Yukon, Canada; [1.82 mg/L] in glacier solid fraction from Orizaba, Mexico; [1.66 mg/L] in glacier solid fraction from Popocatepetl, Mexico; [0.045 mg/L] in glacier solid fraction from Washington, USA; [0.018 mg/L] in glacier solid

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fraction from Palomar, Mexico; [0.029 mg/L] in snow solid fraction from Julian, San Diego, California; and [0.3 mg/L] in snow solid fraction from Mount Rainier, Washington, USA. Although talc was present, no concentration data were reported by Windom et al. (1967) for atmospheric dust from San Diego, California, or Scotts Bluff, Nebraska, in the USA; Minicoy Island, India; or a dust storm from Baghdad, Iraq.

Airborne talc-containing dust can be associated with farming activities in rural areas, because talc has long been used as a filler and/or lubricant in treated seeds, pesticides (as a dry carrier of active chemicals), and powders for foliar or soil applications. For example, in mixes for treated seeds, talc helps prevent the seeds from sticking together but also abrades the seed and creates dust (Bowes et al., 1977; Krupke et al., 2012; Stoner, 2015). For these applications, Krupke et al. (2012) reported that the recommended level of talc addition was about 240 mL of talc per 75 kg of maize seed. According to Windom et al. (1967), the presence of as much as 1 wt% talc in rural air samples is the result of contamination from such agricultural sources (Bowes et al., 1977). In particular, it is possible that in the USA this high concentration of talc was mostly because of extensive use of talc-containing pesticides since the late 1930s, when talc and other natural fillers were introduced as carriers (Windom et al., 1967).

Airborne talc can also be found in tyre debris or dust produced by the normal wear of tyres in urban or metropolitan areas. Talc-rich particulate matter produced by motor vehicles mainly originates from the wear of tyres, brakes, and the road surface (Camatini et al., 2001; de Lira Lixandrão and Ferreira, 2019). Talc has been shown to be a component of particulate dust in various European urban environments, such as the Swiss city of Zurich, Switzerland, and the cities of Girona and Barcelona, Spain (Amato et al. (2011). In Barcelona, Amato et al. (2011) detected talc (and other mineral particles), especially in airborne dust collected at construction work sites, probably because of its use in building materials.

Talc detected in airborne particulate collected from the highly populated city of Lahore, Pakistan, is probably of anthropogenic origin (Hussain et al., 1990). For samples of airborne particulate collected from Lahore, Ahmad et al. (2013) reported an average mass concentration of 1130 μg/m^3, with a talc concentration of 8.5 wt% (96.05 μg/m^3). The talc detected in air samples from the industrial city of Faisalabad, Pakistan, was certainly of anthropogenic origin, resulting from crushing of marble rocks when building property (Ajmal et al., 2018).

(b) Water

Talc has been found in groundwater in Sri Lanka (Shi et al., 2023); in the River Don in the UK (Hillier, 2001), in the Amazon River, Brazil (Milliman et al., 1975); in Lake Neuchâtel, Switzerland (Ruch et al., 1989); in rainwater in San Diego, California, (Windom et al., 1967), and Cape Cod, Massachusetts (Poppe et al., 1983), in the USA; and in glaciers and snow in North America (Windom et al., 1967). It has also been found in the Mediterranean (Pierce and Stanley, 1975; Sartori and Tomadin, 1977) and Caribbean (Jacobs and Ewing, 1965, 1969) Seas; the Gulf of Mexico (Jacobs and Ewing, 1969); the waters of the north-eastern and north-western Atlantic Ocean (Meade et al., 1975; Poppe et al., 1983; Ruch et al., 1989); and the Atlantic coast of the south-eastern USA (Pierce et al., 1971, 1972).

A variety of explanations has been proposed as to its source, including as a natural component of suspended sediment, e.g. from soil erosion (Jacobs and Ewing, 1965; Shi et al., 2023), that was then transported to other areas by wind (Ruch et al., 1989) or water currents (Pierce et al., 1971, 1972), or via resuspension from bottom water (Milliman et al., 1975). Anthropogenic sources have been suggested as being industrial or agricultural (e.g. from pesticides) processes

(Windom et al., 1967; Pierce et al., 1971; Ruch et al., 1989; Hillier, 2001), or paint from the ship collecting the water samples (Van Baren and Von Harmse, 1969). [The Working Group noted that two other anthropogenic sources – talc used to remove algae in lakes (Pan et al., 2006) or lead in wastewater (Rashed, 2001) – are unlikely to have been sources of talc in the above-mentioned studies, as these uses are likely to be rare and not performed at the sampled locations of these studies.]

Two artefacts regarding these studies should be noted. Quantification has not been carried out in any of these studies, often because of the small sample size (Hillier, 2001) or small amount of material in the samples, which made it difficult to distinguish between talc and pyrophyllite (Jacobs and Ewing, 1965; Pierce et al., 1971, 1972; Sartori and Tomadin, 1977). In addition, Sartori and Tomadin (1977) reported that the presence of talc in their study and in other studies was probably because of contamination of the sampling and analytical equipment. [The Working Group noted that generally the studies reported here provided no indication that the equipment was evaluated, although the few that did (Pierce et al., 1971; Poppe et al., 1983; Ruch et al., 1989) reported that such contamination was not an issue.]

(c) Soil and sediments

[The Working Group noted that none of the studies in the literature describing the occurrence of talc in soil and sediments seemed to contain quantitative information on talc concentrations.]

The presence of talc in soil is linked to the weathering and/or pedogenesis of magnesium-rich parent rocks (Lee et al., 2001). A parent talc-rich rock that undergoes alteration processes can release residual (primary) talc particles or magnesium into the soil medium. Although subordinate and still poorly described in the literature, secondary or newly formed talc can also arise during pedogenesis (e.g. in slightly weathered bedrock profiles). This is the case, for example, in zones adjacent to fractures in ultramafic parent rocks, where talc could also form from magnesium released from the fracture zones (Sharma and Rajamani, 2000).

In clay fractions of soil in south-western Spain, talc was found to be a residual phase from the pristine rock, its persistence in the profile being promoted by coatings of iron oxides, which inhibit further weathering (Pérez-Rodríguez et al., 1996). Rozanov et al. (2017) analysed soil profiles from the Letaba River valley, South Africa, and found that traces of talc originating from greenstone were present throughout the valley. Ajiboye et al. (2018) claimed that, in tropical environments, intense weathering prompts the formation of soils with complex mineral assemblages including talc. Such complex assemblages are not observed in other geological and climate environments such as in the pedons, formed on glaciofluvial and glaciolacustrine deposits, of north-eastern British Columbia, Canada (Arocena and Sanborn, 1999), where talc is found as a residual phase from the pristine rocks.

Secondary accumulations of talc arise from alteration processes within the soil matrix. An example was reported by Villanova-de-Benavent et al. (2016), who described nickel- and magnesium-bearing layered silicates in the lower saprolite horizons of the Falcondo nickel-laterite deposit, Central Dominican Republic.

In Sarigkiol, Greece, hexavalent chromium in soil, sediments, and groundwater associated with layered silicates like talc was reported by Kazakis et al. (2018). Soils derived from talc at Ejiba in Kogi State, Nigeria, were evaluated by Ajiboye et al. (2008), who found that the clay fraction of the soils contained talc and had the greatest levels of all forms of potassium, adequate for the sustainable crop production.

Talc can also be found as a common anthropogenic contaminant in sediments, even in remote snowfields in the Alps, because of emissions into the atmosphere by various processes

(Hillier, 2001). In mine wastes, the soils formed may contain talc. High levels of trace elements can hamper the process of revegetation to stabilize the tailings (Vega et al., 2004). Talc has been found in biosolids in sewage sludge: Jaynes and Zartman (2005) found talc in the inorganic fraction of biosolids from New York City and in rangeland and research plot soil in western Texas, USA, where the biosolids had been applied between 1992 to 1999 and postulated that the talc derived from cosmetic products. Adamo et al. (2002) found talc in the clay fraction of the horizons of a soil profile representative of an area devoted to stocking raw materials in the dismantled iron-steel industrial plant of Bagnoli in Naples, Italy. Schaafsma et al. (2018) described an anthropogenic talc-rich soil dust from vacuum-type planters that is produced by abrasion of talc, which is added as a lubricant during planting.

(d) Food and feed

The presence of talc in food is linked to its use as an anticaking agent, glazing agent, or thickener (FAO/WHO, 2024). Specific uses include as a filtering aid, coating agent, surface-finishing agent, texturizing agent, and component of chewing-gum base. For these uses there are specific requirements concerning purity, such as being free from asbestos (defined as testing negative by infrared absorption or by XRD, and optical microscopy) (European Commission, 2018b) and not containing lead at > 2 mg/kg (JECFA, 2003). A commercial alimentary talc product sold online contained 98% talc, 1% chlorite, 0.5% dolomite, and 0.5% magnesite (Mon-Droguiste.Com, 2022). Talc has been used as a dusting powder in chewing-gum and in coated rice (Merliss, 1971a). When used as a filler in confectionery food products, the talc volume can be up to one third of the base used (Zazenski et al., 1995). In chewing-gum coating, talc constituted 12.5 wt% of inorganic matter (Dudefoi et al., 2018). Talc has been used to whiten flour and increase yield because of its bleaching and antisticking properties (Liu et al., 2019; Bao et al., 2022). According to United States Food and Drug Administration (US FDA) regulations, talc may be used as an additive in table salt at a maximum level of 2% (Office of the Federal Register, 2024b). The ministry of health of China stipulated in food additive standard GB2760-2015 that talc powder may be added only in preserved surface-drying fruit and liquorice-flavoured products, at a maximum level of 20.0 g/kg (USDA, 2015).

As a food additive, talc can be present in the following food categories under the conditions of Good Manufacturing Practice (GMP): flavoured fluid milk drinks, condensed milk and analogues, clotted cream, milk and cream powder, several cheese products, dairy-based deserts, processed fruit, dried, cooked or fried vegetables, breakfast cereals, and many more. Talc could also be used in heat-treated butter milk and spices (FAO/WHO, 2024). It is also used in confectionaries and baked goods as a glaze, providing a smooth, shiny finish to the product (1Source, 2025). Industry provided the European Food Safety Agency (EFSA) with data on use levels of calcium silicate, magnesium silicate, magnesium trisilicate, and talc in 292 food products. These were included in 7 out of the 28 food categories in which these food additives are authorized. Most of the data provided to EFSA referred to talc (n = 287). Also, according to the Mintel Global New Product Database, silicates were labelled on more than 1000 food products, mostly in food supplements, between January 2013 and January 2018. The food additive labelled was talc in 89% of these foods (EFSA, 2018a). The main food category labelled with one of these food additives is food supplements. [The Working Group noted that talc can be expected to be present in many foods and, in some instances, in substantial amounts when used as a filler. However, there is a lack of data on actual use levels in foods, and no quantitative data were available to the Working Group.]

The presence of talc in food can also result from the use of talc E553B in plant protection as a repellent (fungifuge and insectifuge) on fruit trees and grapevines. In addition, sometimes it is added to product formulations as a carrier. However, since talc E553B is assumed to comply with the specification as food additive and since the applied talc is partly removed by rain and by washing, the authors of the EFSA (2016) report stated that no residues of concern were expected to be present in plant commodities at harvest that could result in consumer exposure (EFSA, 2016). [The Working Group noted that partial removal by rain or washing may still leave substantial amounts of talc on products.]

The illicit use of talc as a filler to replace other ingredients such as wheat flour and rice flour has been reported (Xu et al., 2013; Nath et al., 2014; Du et al., 2022; Ma et al., 2022; He et al., 2023). Chili powder and other spices may be adulterated with talc (Daszykowski et al., 2023; Momtaz et al., 2023; Balasasirekha, 2024). In China, talc has been added to tea (Li et al., 2016b). [The Working Group noted that talc might be present in food to a higher extent than would be expected assuming maximal allowed use levels. However, there was a lack of data on the illicit use of talc in food.]

Talc has been approved as a technological additive in the animal feed industry under European code E560. In 2005, a report described four experiments in broiler chickens to study the effects of the addition of 1% or 2% of talc to the feed compared with those of control feed containing avilamycin at 5 mg/kg and unsupplemented feed. Both additives improved bird performance, weight gain, and feed conversion ratio, especially when poor performances were observed for the unsupplemented control group (Mallet et al., 2005). Talc can be used in feed at concentrations of up to 100 000 mg/kg of a natural mixture of talc and chlorite (NMTC), containing 74% talc, although no safe dietary level of NMTC could be identified for piglets, chickens for fattening, and dairy cows (EFSA, 2018b). [The Working Group noted the paucity of measured concentration values. No evidence was presented that talc additives to animal feed were harmless to consumers.]

Asbestos fibres were found in talc used in food (Eisenberg, 1974). [The Working Group noted a paucity of data on asbestos contamination of talc used in food.]

(e) Commercial and consumer products

[The Working Group noted that although talc is known to be used in many products, there are very few quantitative data available on actual concentrations of talc and the composition of these products.] Reports published between the 1960s and the 1980s aiming to examine the mineralogy of talc in consumer products in the USA (although with several analytical limitations) concluded that the presence of anthophyllite, tremolite, pyrophyllite, or chrysotile was possible (Cralley et al., 1968; Rohl et al., 1976). Ferret and Moreau (1990) published a comprehensive review of the average mineralogical content of commercial products "sold under the name of talc" in North America and Europe. This was referenced in *IARC Monographs* Volume 93 (IARC, 2010), and those summary tables are reproduced in the present volume (Table 1.3, Table 1.4).

More recently, Pi-Puig et al. (2020) compared the physical, chemical, and mineralogical characteristics of talc from two Mexican ore deposits that were not commercially exploited with those of nine samples of imported cosmetic talc. The imported talc was classified according to price and whether it was packed in the country of origin or in Mexico. Talc content in products of low price was low, 23–40%, and the impurities most probably rendered them unsuitable for cosmetic use (Table 1.5). Asbestos was not detected in any of the samples. However, the researchers reported relatively high levels of lead (5–172 ppm), vanadium (22–47 ppm), and barium (9–1800 ppm)

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Table 1.3 Average mineralogical composition of commercial products sold under the name of talc in North America

	Canada			USA								
				Vermont			California		Texas	Montana		New York
Talc production (thousand tonnes)	**40 floated**	**10**	**30**	**70**	**30 floated**	**200**	**12 floated**	**10**	**307**	**326**	**20**	**140**
Mineral (%)												
Talc	92.5	64.5	60.5	55	90	52.5	94.5	54	80	94	8	25
Chlorite	3	11.5	10.5	7	7	9	1.5	5	1	4.5	85.5	
Dolomite	1	4	8	2	0.5	2	0.5	9	12.5	0.5	0.5	
Magnesite	1.5	17	18	34	2	33.5	0.5	16		T	T	
Serpentine			T									25
Quartz									T	T	T	
Mica	T	T							T	T	T	
Calcite	T											
Tremolite												44
Anthophyllite												5

USA, United States of America.
T, Identified mineral that could not be measured by the methods of analysis used.
From Ferret and Moreau (1990).

Table 1.4 Average mineralogical composition of commercial products sold under the name of talc in Europe

	Finland		Sweden	Norway	UK	France	Austria		Italy				Spain	
Talc production (thousand tonnes)	**75 floated**	**250 floated**	**15**	**50**	**17**	**320**	**80**	**20**	**40**	**46**	**17**	**33**	**20**	**28**
Mineral (%)														
Talc	93	88	64	55	54	59	51.5	51.5	86	51	47	89	80.5	53
Chlorite	3.5	8.5	16.5	11	9	39	42	43	9.5	19.5	22.5	6	12	18.5
Dolomite	0.5	T	11.5	2	2	1.5	1	2	1.5	12	14.5	2	1.5	6
Magnesite	1.5	2		29	30.5		1		0.5	10	14.5			18.5
Serpentine										T	T			
Quartz			T	T	T		T	T		T			T	
Mica			T				T	T				1.5	1.5	
Calcite			T	T				T		T		0.5	T	
Tremolite			T											

T, identified mineral that could not be measured by the methods of analysis used; UK, United Kingdom.
From Ferret and Moreau (1990).

Table 1.5 Mineralogical composition of cosmetic talc samples in Mexico, determined by XRD and refined by the Rietveld method

Sample	Price	Mineralogical composition (%)[a]									Type
		1A talc	2M talc	Cl	Q	Cc	Ma	Do	Clay	Zin	
Oaxaca	NA	40.0	31.4	26.1	2.6	–	–	–	–	–	Green-white
Puebla	NA	20.4	47.0	8.3	5.3	–	–	19.0	–	–	Green-white
I	High	15.3	63.4	–	5.5	–	–	5.1	3.5	7.2	White
II	High	14.6	68.6	5.5	4.1	–	5.9	–	–	1.3	White
III	High	32.8	16.7	5.7	9.4	28.0	2.1	1.3	–	4.0	White
IV	High	39.6	50.5	–	6.9	–	0.9	1.7	–	0.4	White
V	L/M	28.6	2.7	38.2	13.6	3.1	1.6	6.8	4.1	1.3	Green
VI	L/M	15.6	7.6	49.7	4.4	0.2	15.2	6.5	–	0.8	Green
VII	L/M	27.9	9.3	34.4	20.4	13.9	–	3.7	–	0.4	Green
VIII	L/M	28.2	10.8	29.4	23.6	1.7	–	6.3	–	–	Green
IX	L/M	29.4	10.3	19.8	20.5	6.7	–	12.7	–	–	Green

ICSD, Inorganic Crystal Structure database; ICDD, International Centre for Diffraction Data; L/M, low/medium price; NA, not applicable; XRD, X-ray diffraction.

[a] 1A (triclinic) talc (ICSD 98-002-1017); 2M (monoclinic) talc (ICSD 98-002-6741); Cl, chlorite group, clinochlore (ICDD 01-078-1997 and ICDD 01-087-2496); Q, quartz (ICSD 98-008-3849); Cc, calcite (ICSD 98-016-9919); Ma, magnesite (ICSD 98-006-3663); Do, dolomite (ICDD 01-075-1654); Clay, clay minerals of smectite (ICSD 98-016-1171) and kaolinite (ICDD 01-078-2110) groups; Zin, zincite (ICSD 98-005-2362).

From Pi-Puig et al. (2020).

in the low/medium-priced talc samples (Pi-Puig et al., 2020). Rehman et al. (2013) and Nnorom (2011) detected lead at concentrations up to 1 ppm and 5 ppm in talcum powders on sale in Pakistan and Nigeria, respectively.

(i) Ceramics

Talc has been identified as a key component of ceramics (McCarthy, 2013), its principal uses being in the production of wall tiles, sanitaryware, tableware, refractories, and technical ceramics. [The Working Group noted that exposure to talc from ceramics is likely to be restricted to occupational settings involving processing and handling of raw materials during the production of ceramic products. After firing, talc is no longer present in the final product.] In electrical porcelains (often called steatite bodies), high-purity talc products with low levels of alkali metals are preferred. A typical steatite is made from 85% talc and 10% plastic kaolin (kaolin mixed with 25–30% water). Steatites are used as insulators on high voltage equipment such as automotive starters, microwave oven generators, and laser generators. Talc–clay bodies are used for wall tiles and hobby-ware. McCarthy (2013) reported that talc containing tremolite and carbonate is preferred to ensure good porosity, although the morphology of the tremolite was not specified, i.e. whether this was tremolite asbestos or not. Another ceramic, cordierite ($Mg_4Al_4Si_5O_{18}$), is made from talc (25%), kaolin (65%), and aluminium oxide (Al_2O_3) (10%). It has the lowest thermal expansion coefficient of any commercial ceramic and therefore has a high thermal shock resistance. Cordierite ceramics have traditionally been used for kiln furniture and more recently for automotive exhaust catalyst substrates (McCarthy, 2013). Cordierite is also used in some finishing glazes and engobes (coloured or white slip applied to pottery for decorative or textural purposes) (Mooney, 1996). Typical formulae were reported for different types of commercially produced ceramic wall tile, one of which contains 60% of talc and 15%, 15%, and 10% of ball clay A, ball clay B, and wollastonite, respectively (Mooney, 1996).

The formulation of a selection of talc-containing commercial glazes and slips with talc content ranging from 4% to 15% is reported in Burleson (2003) (Table S1.6, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646).

In ceramics, talc provides a readily available source of magnesium and silica, which results in opaque matte glaze surfaces, because of the formation of magnesium silicate crystals (Lithos Industrial Minerals, 2024). Up to 50% of slips could be talc, particularly when it is used to increase the whiteness of the finished product. Talc is also used to improve thermal expansion to resist crazing. A much smaller percentage was commonly used to flux stoneware clays to change the melt and vitrification point. Talc is also commonly used in a wide variety of glazes to improve melt points or produce better results (Dogwood Ceramic Supply, 2024).

(ii) Coatings and paints

[The Working Group noted that there were very few quantitative data available on the use of talc in coatings and paint; however, this industry is one of the major users of talc (see Section 1.2).]

(iii) Paper

The global paper industry uses around 30 million tonnes of mineral-based fillers, of which some 90% is used in the manufacture of printing and writing paper. Hubbe and Gill (2016) investigated the role of mineral fillers in the papermaking industry. They defined fillers and water-insoluble particulate substances in the size range 0.1–10 μm. Fillers are generally one of the main constituents of paper, second only to cellulosic fibres. Worldwide usage of mineral-based fillers was estimated to be at least 6–8 million metric tonnes per year (Mackie and MacKenzie,

1999). The most used mineral fillers are kaolin and calcium carbonate, with talc representing > 7% of the total (Harris, 2004). Talc is a relatively recent addition to the main mineral fillers. However, its use as a coating pigment has grown steadily, particularly in Europe, where it is used in the production of coated mechanical grades used in the rotogravure printing market. Talc is less commonly used in North America, partly because of the investment required to install suitable preparation tanks and to adjust well-established furnish and coating mixes (Harris, 2004).

The platy morphology, softness, hydrophobicity, and chemical inertness of talc contribute to its widespread application as a filler in papermaking industry. However, to be effective, talc must be well dispersed throughout the paper slurry. Chauhan and Bhardwaj (2017) investigated the efficacy of talc dispersion in the papermaking process. Five dry powders of talc filler with five different particle sizes were sourced from a talc manufacturer in north India. The talc fillers were designated as Talc-1, Talc-2, Talc-3, Talc-4, and Talc-5 on the basis of decreasing particle size. The variation in particle size distribution (PSD) decreased from Talc-1 to Talc-5. The percentage of particles of < 10 µm in size in Talc-1, Talc-2, Talc-3, Talc-4, and Talc-5 fillers was 56.9%, 76.9%, 92.5%, 93.3%, and 95.6%, respectively. Similarly, the percentage of particles of < 3 µm in size in Talc-1, Talc-2, Talc-3, Talc-4, and Talc-5 fillers was 0.5%, 1.3%, 2.8%, 6.4%, and 7.9%, respectively. The median particle size of Talc-1, Talc-2, Talc-3, Talc-4, and Talc-5 was 9.3, 7.6, 6.0, 5.7 and 5.4 µm, respectively. The researchers focused on the effect of different particle sizes of talc and the use of a wetting agent (non-ionic triblock copolymer) and an anionic dispersant (sodium salt of polyacrylic acid). The PSD and shape of fillers were identified as the most important factors determining the retention of filler and light scattering in paper (Chauhan and Bhardwaj, 2017).

Talc is mainly used as a "detackying" agent to reduce the effects of pitch and sticky materials in papermaking processes (Valero and Holton, 1995). It is widely used in countries that have high-quality talc deposits, i.e. China, France, Finland, and Japan (Biza, 1999). In the USA, industrial-grade talc from Montana is mainly used. Fine-particle talc is preferred and a level of about 5–7.5 kg of talc per tonne of paper is recommended, or < 1.0% by mass (Hubbe and Gill, 2016).

(iv) Pharmaceuticals

Talc is widely used in a broad range of pharmaceutical products. Pharmaceutical talc is specified as having a purity of 98% (see Section 1.1.4(e) and Section 1.5). It is present at a wide range of different concentrations or strengths, depending on the purpose of the product. In the Finnish pharmaceuticals database, 24% of all products (including infusion liquids, oils etc.; n = 4913) contained talc, and 44% of tablets (n = 1880) included talc as an excipient (Duodecim, 2024).

Table 1.7, Table 1.8, and Table 1.9 present the characteristics of a selection of talc-containing pharmaceutical and over-the-counter products available in the USA (Knox et al., 2024); these include "brand name consumer and prescription products".

(v) Cosmetics and personal care products

A chemical and mineralogical analysis of 21 consumer powders containing talc, including baby powders, body powders, facial powders, and a pharmaceutical talc was undertaken by Rohl et al. (1976). The various consumer powders containing talc were purchased from retail stores in the New York City area, USA, during 1971–1975. A range of analytical techniques were employed to determine their mineralogical and chemical characteristics, including optical microscopy, TEM with SAED and SEM, spectroscopy, atomic absorption, and XRF. Talc was the major mineral phase in all except one of the

Table 1.7 Characteristics of selected prescription products containing talc

Product name	Dosage form	Strength	Route	Marketing start	Marketing end
Sclerosol	Aerosol, powder	4 g/25.0 g	Intrapleural	30 June 2013	NA
Sterile talc	Powder	5 g/100 mL	Intrapleural	15 December 2003	NA
Steritalc 2 g	Powder	2 g/50 mL	Intrapleural	1 November 2017	NA
Steritalc 3 g	Powder	3 g/10 mL	Intrapleural	1 November 2017	NA
Steritalc 4 g	Powder	4 g/50 mL	Intrapleural	1 August 2017	NA

NA, not applicable.
Data from DrugBank Online (Knox et al., 2024).

Table 1.8 Characteristics of selected over-the-counter products containing mainly talc

Product name	Dosage form	Strength	Route	Marketing start	Marketing end
Baby	Powder	100 g/100 g	Topical	17 July 2014	NA
Budpak Baby	Powder	0.9 g/1 g	Topical	7 July 2014	18 December 2015
Dusting powder	Powder	99 g/100 g	Topical	1 February 2012	26 October 2017
Health Smart Baby	Powder	1 g/1 g	Topical	19 December 2012	NA
Natures Choice Baby	Powder	99 g/100 g	Topical	7 June 2016	NA
Pan Aromas Baby	Powder	1 g/1 g	Topical	19 December 2012	NA
Soft Skin Baby Powder	Powder	1 g/1 g	Topical	27 March 2007	17 October 2017

NA, not applicable.
Data from DrugBank Online (Knox et al., 2024).

samples; this sample comprised a mixture of talc, phlogopite mica, and quartz. Of the 21 samples, 10 samples contained measurable amounts of tremolite asbestos and anthophyllite asbestos, with concentrations ranging from 0.1% to 35%. Two of the samples contained trace amounts of chrysotile asbestos. Quartz was also detected in eight of the samples (concentration range, 1.6–35.1%). Four samples contained significantly higher concentrations of cobalt, chromium, and nickel than those found in the other samples.

As part of the previous evaluation of talc by the *IARC Monographs* in 2006 (IARC, 2010), the work published by Flick (2005) on formulations from the Cosmetics and Toiletries Database was used to determine that there was a total of 249 products containing talc or talcum in the USA. The beauty aids category had the highest number of products (n = 184), and included products such as aerosol talc products, face masks, foundations, body oils, make-up bases, concealers, blushes, body powders, rouge, make-up, compact powders, eye shadows, dusting powders, eyebrow pencils, pressed powder products, face powders, mascaras, liquid talc products, and powder cleansers (IARC, 2010).

For many years, the US FDA collected information from manufacturers on the use of individual ingredients in cosmetics as part of its Voluntary Cosmetic Registration Program (VCRP) (US FDA, 2023d). Fiume et al. (2015) obtained data from the VCRP together with data from a survey by the Personal Care Products Council (PCPC) on the maximum reported use concentration by category in 2009. The data revealed that talc was used in 3469 cosmetic formulations at concentrations up to 100% and that it was used in almost every category of cosmetic product (see Table 1.10). In 2012, the PCPC carried out another survey to assess the

Table 1.9 Characteristics of selected over-the-counter products containing talc and other ingredients

Product name	Ingredients	Dosage form	Route	Marketing start	Marketing end
AHC Premium Intense Contour Balm	Talc (2.05 g/50 mL) + adenosine (0.02 g/50 mL) + aluminium tristearate (0.04 g/50 mL) + aluminium hydroxide (0.45 g/50 mL) + arbutin (1 g/50 mL) + methicone (20 CST) (1.3 g/50 mL) + octinoxate (1.5 g/50 mL) + titanium dioxide (3.96 g/50 mL) + zinc oxide (0.96 g/50 mL)	Cream	Topical	15 January 2014	22 November 2017
Caldesene	Talc (57.51 g/71 g) + zinc oxide (10.65 g/71 g)	Powder	Topical	9 July 2009	31 August 2017
Careline Perfect Care BB	Talc (2.5 g/100 g) + allantoin (0.2 g/100 g) + caffeine (0.2 g/100 g) + octinoxate (4 g/100 g) + titanium dioxide (5 g/100 g)	Cream	Topical	17 September 2015	1 September 2019
Careline Perfect Care BB	Talc (2.5 g/100 g) + allantoin (0.2 g/100 g) + caffeine (0.2 g/100 g) + octinoxate (4 g/100 g) + titanium dioxide (2.5 g/100 g)	Cream	Topical	17 September 2015	1 September 2019
Face It Hd Perfect BB SPF30 Pa 01	Talc (0.684 mL/100 mL) + betaine (2 mL/100 mL) + octinoxate (6 mL/100 mL) + titanium dioxide (6.36 mL/100 mL) + zinc oxide (2.88 mL/100 mL)	Cream	Topical	23 August 2011	NA
Face It Hd Perfect BB SPF30 Pa 02	Talc (0.684 mL/100 mL) + betaine (2 mL/100 mL) + octinoxate (6 mL/100 mL) + titanium dioxide (6.36 mL/100 mL) + zinc oxide (2.88 mL/100 mL)	Cream	Topical	23 August 2011	NA
Foot and body powder	Talc (90.8 kg/91.7 kg) + zinc undecylenate (908 g/91.7 kg)	Powder	Topical	31 December 1970	1 August 2003
Foot spray with powder	Talc (18%) + undecylenic acid (0.35%)	Aerosol	Topical	31 December 1970	1 August 2003
Fresh scent protective powder	Talc (115 g/142 g) + zinc oxide (21.3 g/142 g)	Powder	Topical	1 September 2016	4 April 2018
Fresh scent protective powder	Talc (115 g/142 g) + zinc oxide (21.3 g/142 g)	Powder	Topical	11 January 2017	4 April 2018
OHUI Sun Science Sun Block EX plus Beige	Talc (55.493 g/100 g) + arbutin (2 g/100 g) + *Atractylodes lancea* root oil (0.1 g/100 g) + octinoxate (7.2 g/100 g) + titanium dioxide (2.59 956 g/100 g) + zinc oxide (5.76 g/100 g)	Powder	Topical	25 May 2011	NA
Protective cream	Talc (5.5%) + kaolin (11%) + zinc oxide (11%)	Cream	Topical	31 December 1991	7 August 1998
Spai-Sons Fine Talcum	Talc (81 g/100 g) + zinc oxide (5 g/100 g)	Powder	Topical	30 June 2012	NA

NA, not applicable.
Combined with data from DrugBank Online (Knox et al., 2024).

Table 1.10 Number of talc-containing cosmetic products and maximum talc concentrations, USA, in 2012

Cosmetic product	No. of products	Maximum concentration in product (%)
Totals	3469	0.0005–100
Duration of use		
Leave-on	3287	0.002–100
Rinse-off	163	0.0005–70
Diluted for (bath) use	19	0.001–88
Presented in complete US FDA, VCRP format		
Baby shampoos	NR	7
Baby lotions, oils, powders, and creams	9	99
Bath oils, tablets, and salts	18	1–88
Bubble baths	NR	0.4–2
Bath capsules	1	NR
Other bath preparations	NR	0.001
Eyebrow pencil	47	0.01–79
Eyeliner	122	0.1–90
Eye shadow	1292	20–100
Eye lotion	13	2
Mascara	83	1–50
Other eye make-up preparations	65	2–6
Perfumes	2	2
Fragrance powders (dusting and talcum)	115	15–99
Sachets	3	9
Other fragrance preparations	10	3–9
Hair conditioner	1	0.4
Rinses	NR	0.05
Shampoos	NR	0.04
Tonics, dressings, and other hair-grooming aids	2	10
Other hair preparations	2	NR
Hair dyes and colours	NR	0.4–13
Other hair colouring preparations	2	6
Blushers	331	48–94
Face powders	552	20–100
Foundations	211	12–76 (not spray) 1–6 (aerosol spray)
Leg and body paints	3	2 (aerosol spray)
Lipstick	55	3–74
Make-up bases	44	36 (not spray) 35 (aerosol spray)
Rouges	12	NR
Make-up fixatives	11	10
Other make-up preparations	105	0.8–85
Basecoats and undercoats	5	1–7
Cuticle softeners	1	0.004–18
Nail creams and lotions	NR	2
Nail polish and enamel	7	0.002–11
Other manicuring preparations	1	35

Table 1.10 (continued)

Cosmetic product	No. of products	Maximum concentration in product (%)
Dentifrices	1	NR
Other oral hygiene products	NR	11
Bath soaps and detergents	55	0.001–70
Deodorant (underarm)	18	6–85 (not spray) 1–30 (aerosol spray)
Other personal cleanliness products	30	0.03–20
Aftershave lotion	1	14
Men – talcum	4	96
Shaving cream	1	NR
Shaving soap (cakes, sticks, etc.)	NR	0.04
Other shaving preparations	2	NR
Cleansing	37	0.0005–0.005
Depilatories	4	NR
Face and neck creams, lotions, and powders (excl. shaving)	36	40 (not spray) 0.4 (spray)
Body and hand creams, lotions, and powders (excl. shaving)	22	96 (not spray) 0.3 (spray)
Foot powders and sprays	10	0.9–97
Moisturizing creams, lotions, and powders	54	3–5
Night creams, lotions, and powders	7	3
Paste masks (mud packs)	28	0.2–18
Skin fresheners	2	0.002–0.2
Other skin care preparations	26	0.03–20
Suntan gels, creams, and liquids	2	15–41
Indoor tanning preparations	4	74
Other suntan preparations	NR	3
Summary information – by exposure type		
Eye area	1622	0.01–100
Incidental ingestion	56	3–74
Incidental inhalation – spray	31[b]	0.3–35%[c]
Incidental inhalation – powder	680	2–100
Dermal contact	3309	0.0005–100
Deodorants (underarm)	18	2–75
Hair – non-colouring	5	0.04–10
Hair – colouring	2	0.4–13
Nail	13	0.002–35
Mucous membrane	160	0.001–88
Baby products	9	7–99

excl., exclusive; NR, not reported; US FDA, United States Food and Drug Administration; VCRP, Voluntary Cosmetic Registration Program.
[a] The sum of all exposure types may not be equal to the sum of total uses.
[b] It is not known whether or not the product is a spray.
[c] In 2012, a survey was completed to assess the use of talc in spray products in which companies were asked whether or not they used talc in spray products, and if so, what was the maximum use concentrate of talc in the spray product and in products that are not sprays in the same US FDA product category.
From Fiume et al. (2015).

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frequency and use concentration of talc in spray products and reported that the highest reported talc concentration in spray products was 35% in a make-up base aerosol (Fiume et al., 2015). Fiume et al. also reported that talc can be present at 100% in face powders, 99% in baby powders, up to 35% in aerosol make-up bases (47), and up to 30% in aerosol deodorants. Talc is not used at high concentrations in spray or aerosol products because it is likely to clog the container nozzle (Fiume et al., 2015). In March 2023, the US FDA stopped accepting submissions to the VCRP and announced the development of a new system of registrations mandated by the Modernization of Cosmetics Regulation Act of 2022 (MoCRA) (US FDA, 2023e).

Stoiber et al. (2020) reported that the Skin Deep database of the Environmental Working Group identified more than 2000 personal care products sold between 2018 and 2020 that contained talc, 57% of these being powder products.

A review of cosmetic and pharmaceutical talc in Spain by Delgado et al. (2020) reported that in the 1980s there were no samples on the Spanish market with a talc purity as low as that at the present time (60%). Dolomite is currently present in large quantities in some talcum powders (Delgado et al., 2020).

Wudke et al. (2024) carried out a detailed analysis of a single unopened bottle of commonly available baby powder, manufactured in 1985. Analysis by XRD of three replicate samples identified talc as the main mineral phase present, with chlorite and serpentine also present, and no other significant impurities identified. The authors reported that the presence of serpentine identified by XRD could also indicate the presence of chrysotile, although no chrysotile was detected. Repeat analysis (n = 10) of pressed powders (n = 5) via hand-held XRF yielded SiO_2 contents of 57.40–58.28 wt% and MgO contents of 29.90–30.79 wt%. The analysis also indicated the presence of chromium, nickel, copper, and zinc. In addition, replicate analysis (n = 2) of three samples via high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) detected four trace metals present at > 10 ppm: vanadium, cobalt, chromium, and nickel. Across all sample runs (n = 6), average concentrations of these metals were: vanadium, 10.6 ppm (± 0.5 ppm at 2σ); cobalt, 55.0 ppm (± 4.3 ppm at 2σ); chromium, 400.9 ppm (± 11.4 ppm at 2σ); and nickel, 1395.9 ppm (± 105 ppm at 2σ) (Wudke et al., 2024).

(vi) Asbestos contamination of talc-based personal care products

The presence or suspected presence of asbestos minerals in talc has complicated the assessment of the health effects of exposure to pure uncontaminated talc. The link between talc and asbestos-contaminated talc was first recognized in 1898 (Dana, 1898).

Lewin (1972) was commissioned by the US FDA to determine the mineral content of 102 standard commercial products containing talc. The samples were analysed by XRD, with the LOD quoted as 1–2%. Where potential asbestos minerals were detected by XRD, the fibrous nature of these minerals was confirmed by optical microscopy. For 59 products, there were no detectable amounts of any potential asbestos minerals. Of the other products, 20 of the samples were reported to contain "small but detectable percentages" of tremolite asbestos (2–5%); nine had small percentages of tremolite asbestos and chrysotile (2–5%), seven had small percentages of chrysotile (2–5%), and seven had substantial percentages of one or both tremolite asbestos and chrysotile (9–27%). [The Working Group noted that this was the interpretation of the authors in 1972 and that the Working Group does not consider 2–5% to be a small amount of asbestos.]

A review by Bird et al. (2021) described the establishment of the system for testing consumer talc products for the presence of asbestos. In 1976,

the Cosmetic, Toiletry and Fragrance Association (CTFA), which represented the personal care products industry, and the US FDA introduced a voluntary specification for "stringent safety and quality control measures designed to ensure the absence of asbestos fibres from consumer talc products" (Zazenski et al., 1995). As part of these measures, the CTFA developed a test method for the determination of the asbestos content of talc, known as the J4-1 method (CTFA Method J4-1: asbestiform amphibole minerals in cosmetic talc; CTFA, 1976). [The CTFA is now known as the PCPC and has asserted that talc has been asbestos-free since these measures were introduced in 1976.]

However, Bird et al. (2021) reviewed recent evidence and concluded that talc is not and never was asbestos-free. They also concluded that, in addition to being unenforceable, the 1976 CTFA J4-1 specification was defective since it permitted the presence of chrysotile and fibrous talc and only detected amphibole asbestos at levels > 0.5%.

A significant contributing factor to the problem of asbestos contamination of talc in general and cosmetic and personal care products in particular has been the methodology specified by various jurisdictions or trade associations and their respective LODs. For example, the PCPC (CTFA Method J4-1; CTFA, 1976) and the Cosmetic, Toiletry and Perfumery Association Limited (CTPA) in the UK have both specified an XRD-based method, followed by optical microscopy should asbestos be detected by XRD. The CTPA updated its method in 2019 to include more modern electron microscopy techniques (CTPA, 2019). Table 1.11 gives the LODs for selected published methods and scientific studies for the determination of the presence of asbestos in talc. The earlier methods and studies relied primarily on XRD and had a typical LOD of around 0.5–1.0% (Schelz, 1974; Rohl et al., 1976; Bird et al., 2021). [The opinion of the Working Group was that this method is not sufficiently sensitive and that 0.5% asbestos might still be biologically relevant.] However, more recent studies using more sensitive TEM have reported LODs in the order of 0.000 002–0.0001% (Fitzgerald et al., 2019; and US FDA, 2023a, b, c). [The Working Group noted that this method is state-of-the-art and sufficiently sensitive.]

An evaluation of so-called "high-grade" talc products using a centrifuge separation method followed by optical microscopy was reported by Blount (1991). High-grade talc from five deposits in Montana, three in Vermont, and one each in North Carolina and Alabama, USA, together with talc products sourced from outside the USA, but available on the US market, were included in the study. Talcs from other US districts were also considered but were excluded because the grade was less stringent than the others. The analytical method employed included pre-analysis removal of heavy particles unlikely to contain asbestos. This was achieved by centrifugation in a heavy liquid (cadmium borotungstate) and removal of the heavy particles with a micropipette. The high-grade talc was found to be uniformly low in amphibole mineral content. In six of the samples, no "regulatory fibres" were detected, whereas in the others between < 10 and 341 fibres/mg were detected. [It should be noted that the US FDA had equated 0.1% with 1000 particles/mg, and this referred to percentage by count and not percentage by weight (wt%).] Eight samples were reported to contain amphibole mineral "cleavage or prismatic pieces". This study defined amphibole mineral particles with aspect ratios of < 6:1 to be "cleavage or prismatic pieces" and not asbestos. [The Working Group was not aware of this < 6:1 criterion for differentiating between asbestos and non-asbestos amphibole minerals. No validation data were presented for this method and therefore its efficacy is not known.]

A study of the fibrous mineral and asbestos content of nationally and internationally available talc powders was undertaken in Italy in the 1980s (Paoletti et al., 1984). Samples of talc powders used as excipients in pharmaceutical

Table 1.11 Limits of detection for asbestos in talc

Year	Method	Organization	Title or study	Technique							Reference
				PLM	SEM	TEM	XRD	FTIR	DTA	Fluorescence microscopy	
1971	J4-1	CTFA	Asbestiform amphibole minerals in talc				0.5%[a]				Bird et al. (2021)
1974			The detection of chrysotile asbestos at low levels in talc by DTA						1%		Schelz (1974)
1976	J4-1	CTFA	Asbestiform amphibole minerals in talc				0.5%[a]				CTFA (1976)
1976			Consumer talcums and powders: mineral and chemical characterization			NR	0.1–2.0%				Rohl et al. (1976)
1977			The detection and identification of asbestos and asbestiform minerals in talc; Harold D Stanley			0.10%	0.2–0.5%				NBS (1977)
1993	EPA/600/R-93/16	US EPA	Test method – method for the determination of asbestos in bulk building materials	1%							US EPA (1993)
1995	PLM of asbestos, bulk ID-195	OSHA		1%?							OSHA (1995)
2011	Talc Revision Bulletin Official 1 August 2011	United States Pharmacopeial Convention		NR			NR	NR			United States Pharmacopoeial Convention (2011)
2014			Quantitative analysis of trace level asbestos in pharmaceutical talc by powder XRD				0.3–0.8%				Hu et al. (2014)
2016	198.6 ELAP	New York State Environmental Laboratory Approval Program	PLM method for identifying and quantitating asbestos in non-friable organically bound bulk samples	1%?							New York State Department of Health (2024)

Table 1.11 (continued)

Year	Method	Organization	Title or study	Technique							Reference
				PLM	SEM	TEM	XRD	FTIR	DTA	Fluorescence microscopy	
2016	198.4	New York State Environmental Laboratory Approval Program	TEM method for identifying and quantitating asbestos in non-friable organically bound bulk samples			NR					New York State Department of Health (2024)
2019			Asbestos in commercial Indian talc			< 0.00001% by weight					Fitzgerald et al. (2019)
2020			Quantitative analysis of asbestos-containing materials using various test methods				1%				Yang et al. (2020)
2023	Asbestos in talc		Detection of fine asbestos fibres using fluorescently labelled asbestos-binding proteins in talc							0.01–1.0% by weight[b]	Nishimura et al. (2023)
2023	US FDA		Analytical report for: testing of official samples of talc containing cosmetics for asbestiform fibres Contract No.: 75F40122P000335 Assignment DFPG# 23-19, Batch No. 04032023 (Batch #1) AMA COC No. 646090			0.00001 to 0.000002%					US FDA (2023a)

CTFA, Cosmetic, Toiletry and Fragrance Association Inc.; DTA, differential thermal analysis; FTIR, Fourier transform infrared spectroscopy; NR, not reported; OSHA, Occupational Safety and Health Administration; PLM, polarized light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy; US EPA, United States Environmental Protection Agency; US FDA, United States Food and Drug Administration XRD, X-ray diffraction.

[a] Amphibole only, CTFA asserted that chrysotile is not present in talc.

[b] Fibre diameter, 0.06 µm.

and cosmetic preparations were found to contain fibrous minerals, in some cases at up to 30% of total particles, although not all fibres were identified as asbestos. Asbestos was found in about half of the talc powders tested, chrysotile was present in five samples, and tremolite and anthophyllite were present in the other samples. The amount of asbestos ranged from < 1% up to about 90% in the different samples of the fibrous fraction and from < 0.3% up to about 22% of the total sample. The presence of fibrous talc was not reported. About 75% of the observed asbestos fibres were thinner than 0.4 µm, i.e. below the detection level of light microscopy, the most common technique applied until the 1980s to evaluate the presence of asbestos (Paoletti et al., 1984).

In 2014, three unaffiliated US testing laboratories analysed a specific brand of cosmetic talcum powder from more than 50 containers of different sizes and colours, produced over a 50-year time span. The aim was to determine the presence of asbestos, assess the releasability of asbestos, and assess potential exposure during simulated product application experiments (Gordon et al., 2014). All laboratories used either TEM or a combination of TEM and optical microscopy. [The Working Group noted that TEM is sufficiently sensitive to detect asbestos.] All three laboratories confirmed the presence of asbestiform anthophyllite and asbestiform tremolite, in multiple tests, in the talcum powder products (Gordon et al., 2014). Using TEM, asbestos was detected in all 50 samples tested; this included the detection and identification of thin asbestos fibres, < 0.2 µm. The results indicated airborne asbestos concentrations of about 1.9 asbestos fibres per cubic centimetre of air (fibres/mL) for the fibre releasability tests, and 20 fibres/mL for the 5-minute "puffer" simulated-product application test (Gordon et al., 2014). [The Working Group noted that, because of the limitations of many of the analytical methods employed, the reported results of asbestos assessment of talc powder samples using inadequate methods could have been false negatives. For more details, see Section 1.3.]

In a study in Spain, the mineral and pharmacopoeia quality of seven cosmetic–pharmaceutical talcum powders from different commercial brands, on sale in pharmacies in 2020, was investigated. Four samples met the required conditions to be classified as of both "cosmetic quality" and "pharmacopoeia quality". The remaining three samples were classified as of "industrial quality". Although these were free from fibrous minerals, the high carbonate content, specifically dolomite (close to 40%) and calcite (about 10%), had an impact on the purity of talc to the point that the material no longer satisfied many of the composition tests of the European Pharmacopoeia (Delgado et al., 2020). The authors concluded that, when comparing these results with those for samples sold in the 1980s, the fibrous mineral components were no longer present. [It was not specified what these fibres were.] In the past, a significant number of samples showed evidence of amphiboles; the purity of talc in samples of cosmetic quality has improved from 94% to 96%.

The US FDA has commissioned several studies using TEM and PLM to investigate cosmetic- and pharmaceutical-grade talc (US FDA, 2024a). One study conducted between September 2009 and September 2010 found no evidence of asbestos fibres in 27 samples of raw-grade talc (average LOD, 0.021 ppm or 0.0000021%) and 34 samples of cosmetic products containing talc (average LOD, 0.044 ppm or 0.000004%). [The Working Group noted that these LODs are appropriate for this type of analysis.] However, because of the limited number of samples that were tested, the authors did not conclude that all or most talc or talc-containing cosmetic products marketed in the USA were likely to be free of asbestos contamination.

The US FDA has reported that on 18 October 2019, one producer voluntarily recalled one lot of baby powder after a sample

tested positive for asbestos. The US FDA advised consumers not to use this specific lot of the product. The sampling took place during the ongoing US FDA survey testing talc-containing cosmetics for asbestos (US FDA, 2019). Follow-up studies on the analysis by TEM and PLM of about 50 cosmetic products containing talc were commissioned in 2020, 2021, 2022, and 2023. For the 2020 study, asbestos fibres were detected in 9 of the 52 products tested. No asbestos fibres were detected in any of the products tested in 2021–2023 (US FDA, 2024b).

In a study published in 2020, 21 talc-based cosmetic products purchased in retail stores in San Francisco, California, and Washington, District of Columbia, USA, and from an online retailer were analysed by TEM to investigate the presence of asbestos. Of the products tested, 3 out of 21 (two eye shadow palettes and one toy make-up kit) contained tremolite asbestos; actinolite asbestos was also detected in one of the eye shadow palettes. One of the contaminated products was expressly marketed for use by children. Asbestos concentrations ranged from 1.5 to 4.6 ppm (Stoiber et al., 2020).

Two batches of cosmetic talcum powder products that were widely used in 2015 in India and south-eastern Asia (some manufactured in the USA) were examined using PLM and TEM techniques to detect the presence of asbestos. Tremolite asbestos was detected in one of five talcum powder samples reported in the first batch of samples and in six of the eight samples in the second batch (Fitzgerald et al., 2019). The type and sources of talc in these products was not known.

[The Working Group noted that most industry analyses to detect asbestos in talc products used methods with an insufficiently low LOD (Section 1.3). Even among studies using these methods, there were numerous reports of asbestos detection in talcum powder. However, the Working Group noted that, because of the high LOD, asbestos may have been present in more products at amounts that were lower than the LOD but that might be relevant for health outcomes. Only more recently have state-of-the-art methods been employed that could rule out contamination with more confidence.]

(vii) Plastics

Talc is commonly added to polypropylene to give improved stiffness and dimensional stability in automotive parts, household appliances, food packaging films and white goods. For these applications, advanced milling technology is used to obtain the finest talc without diminishing the reinforcing power of its lamellar structure. This gives the best compromise between rigidity and impact strength. In polypropylene, talc of –325 mesh (about 44 μm) is used at levels of 15–40% to increase the stiffness, increase heat stability, and reduce shrinkage of homopolymer and copolymer injection-moulding grades (McCarthy, 2013).

In linear low-density polyethylene (LLDPE), talc prevents blocking, which is the adhesion of two adjacent layers of polymer film. For low-density polyethylene film, talc of 500 mesh (about 28 μm) is used at 0.5–1.5% to roughen the surface and reduce the tack of the film so that it does not adhere to itself (McCarthy, 2013).

Micronized talc (median particle size, 1–2 μm) is capable of promoting crystal growth in semi-crystalline polymers such as nylon and polypropylene. At levels of 0.2%–2% it is used to reduce cycle times in the injection moulding and thermos-forming of large parts (McCarthy, 2013). Polypropylene is one of the most extensively produced polymers. Talc has been found to be an especially efficient filler, enhancing the mechanical properties and macromolecular orientation of compounds and increasing the performance of reinforced polymeric matrices. At concentrations of > 3 wt%, talc acts as a nucleating agent, reducing spherulite size and shortening processing time (Fillon et al., 1994). At higher concentrations (10–40 wt%), it acts as a reinforcing agent, increasing tensile strength and

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stiffness, but reducing strain-at-break and impact strength (Maiti and Sharma, 1992). However, the surface activity, particle size, surface area and surface functional groups of talc all affect its reinforcement effectiveness (Sinha Ray et al., 2002; McLauchlin and Thomas, 2009).

Several studies have investigated the impact of the addition of talc as a filler on the properties of polypropylene plastics and plastic composites (e.g. Ammar et al., 2017; Huang et al., 2020; Phutfak and Larpkasemsuk, 2021). The addition of talc at up to 30% increased wear resistance, toughness, or combustibility.

(viii) Rubber

Ethylene–propylene rubber blended with talc is a so-called reinforced polypropylene compound and is widely used in a variety of automotive materials. The addition of talc at about 20% and up to a maximum of 25% by weight results in higher fluidity and excellent rigidity and impact resistance when compared with talc-free blends. Talc particle size is also important, with typical particle diameters of 3.8–16.6 µm being reported by Obata et al. (2001).

The viscosity of rubber compounds is reduced by the addition of talc. This facilitates the production of moulded rubber components. Talc also improves the process of pressurized extrusion of rubber. Sealants and gaskets have better compression resistance with the addition of talc. When used in electrical cables, talc acts as an effective insulator (Eurotalc, 2024). [The Working Group noted that there are very few data available on these uses of talc.]

(ix) Other uses

The smoothness of talc is exploited in products like crayons and colouring pencils, which must be robust but also softer than the paper. Talc is the principal ingredient in putties, where it improves adhesion and the ability of the putty to be sanded to a smooth finish (Eurotalc, 2024). The US Consumer Product Safety Commission reported the presence of trace amounts of asbestos in crayons. Larger amounts of a "transitional" fibre, known to be occasionally present in talc, were also reported (US Consumer Product Safety Commission, 2000). [The Working Group noted that no further details on the asbestos type or the "transitional fibres" were reported.]

The detection and quantification of talc on latex condoms was reported by Douglas et al. (1998). The surface powder washed from six commercial lots or batches of latex condoms was analysed by SEM and EDS. This method was used to analyse condoms and talc/starch mixtures. The limit of sensitivity of the method was determined by analysis of standard mixtures. Talc was readily identified in a talc/starch mixture of 0.7% talc, but not in a 0.1% mixture. The researchers concluded that, from the limited survey conducted, condoms produced and tested at that time did not contain talc (Douglas et al., 1998).

1.4.2 Occupational exposure

(a) Industrial hygiene monitoring

Exposure to talc dust has been documented during mining and milling, and in various downstream industries that use talc, such as rubber and paper production. Section 1.3 provides a more detailed review of sampling and analytical techniques for bulk materials and airborne particles. Briefly, samples were historically collected using liquid impinger samplers followed by particle counting analysis using light microscopy, which yielded concentrations measured in units of millions of particles per cubic foot of air (mppcf). Since the 1970s, exposures have generally been measured using respirable cyclone samplers and gravimetric determination of the mass of dust sampled. Neither of these sampling techniques were capable of discriminating talc particles from non-talc particles, and sample analysis was not specific for talc.

(i) Mining and milling

Liquid impinger particle count sampling

Table S1.12 summarizes historical impinger-sampling results from talc mines and mills (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646). [The Working Group noted that details of the measurements, such as sampling duration and method (e.g. static/stationary or personal sampling), were often lacking in historical reports, which limited the Working Group's interpretation of the data.] Section 1.2 gives details of the different types of talc in mines around the world.

Most historical impinger-sampling data identified in the literature were from the industrial talc deposit in the Gouverneur District in the state of New York, USA. [The Working Group noted that depending on the study, mine and mill sites were sometimes referred to as being located in New York, St Lawrence County, or northern New York; however, for clarity, only the descriptor Gouverneur District deposit is used herein.] Talc in the Gouverneur District deposit contains anthophyllite and tremolite asbestos, and the presence of chrysotile asbestos is possible (see Table 1.1). Dreessen (1933) stated that respirable dust levels at a mine and mill in Gouverneur District were 1440, 52, and 4 mppcf for drillers, millers, and "other" workers, respectively, although no details were given on the type of size-selective sampler used for measurements. Siegal et al. (1943) reported dust measurements for Gouverneur District deposit in three underground mines and five mills (an identical article was also published as Greenburg, 1947). At mines A, B, and C, dust levels ranged from 6 mppcf (mucker) to 5000 mppcf (driller), 24 mppcf (mucker) to 760 mppcf (stoping), and 16–300 mppcf (drillers), respectively. Average dust levels at the mills ranged from 46 mppcf (jaw crusher at mills 1–3) to 163 mppcf (bagging paper).

Kleinfeld and colleagues (Kleinfeld et al., 1955) published a series of follow-up studies in the cohort reported by Siegal et al. (1943), which included dust measurements from 1941 and 1954 (the same exposure data was republished by Messite et al., 1959). The authors noted that, since the study by Siegal et al. (1943), several engineering modifications had been implemented at the mine and mill, including changing from dry to wet drilling, enclosure of elevator and chutes, installation of automatic bagging machines, implementation of a convey for cart loading, installation of local exhaust ventilation for some processes, and discontinuation of blow rooms. Average dust levels were lower for all jobs at the mine and mill in 1954 than in 1941. Kleinfeld et al. (1964) compared lung function among 43 millers, 30 of whom processed fibrous talc from the Gouverneur District deposit (average dust level, 19.5 mppcf) and 13 of whom processed granular talc from the Lewis County, New York deposit (average dust level, 17.9 mppcf).

Kleinfeld et al. (1967) extended the follow-up of their cohort and updated available impinger-sampling data from 1955 through 1965 to assess the efficacy of controls implemented in these workplaces. At the mines, average dust levels decreased by a factor of 164 (from 818 mppcf to 5 mppcf) for drilling and by a factor of 24 (from 120 mppcf to 5 mppcf) for mucking between 1945 and 1965. At the mills, dust levels decreased by up to a factor of 10 (from 278 mppcf to 27 mppcf for separators) between 1945 and 1965. Kleinfeld et al. (1974) published an update for this cohort that included dust measurement data from before 1965 and up to 1972. Data from before 1965 were a republication of those reported by Kleinfeld et al. (1967). Data from 1966 to 1969 appeared to be averages of those reported by Kleinfeld et al. (1973). A comparison of the data from 1966 to 1969 with that from 1972 showed that average dust levels decreased for drilling and mucking at the mine and for milling at the mill,

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but were similar or higher for bagging, crushing, and loading bags onto railroad cars and trucks.

In another study, Kleinfeld et al. (1973) evaluated respiratory health and exposures among 39 miners and millers in a study that, according to their 1974 publication, was conducted at a different facility from that in their previous studies. Dust levels were reported for the period 1954–1970. At the mine, dust levels remained approximately the same (drilling), increased (dragline loading, primary crushing), or decreased (mucking, hoist loading) over time. At the mill, dust levels remained approximately the same (secondary crushing, Wheeler mill, loading bags) or decreased (Hardinge mill, bagging, palletizing) over time.

Two studies were conducted at the same mine and mill complex for which it was claimed that, despite coming from the Gouverneur District deposit, the talc did not contain tremolite and anthophyllite asbestos minerals (Brown et al., 1979; Dement and Zumwalde, 1979). [The Working Group noted that Kleinfeld et al. (1973) reported that talc from this mine contained tremolite and anthophyllite asbestos, and mineralogical data presented in Table 1.1 confirmed their conclusion.] The underground mine was reported to be ventilated. Inside the mine, ore was wet crushed then moved to the surface. At the mill, the talc was ground, bagged, and stored, and local exhaust ventilation was present at several points in the process. On the basis of the impinger-sampling data reported by Dement and Zumwalde (1979), the average personal 8-hour time-weighted average (TWA) exposure at the mine was 10.5 mppcf and at the mill it was 2.9 mppcf. As part of a comparison of this data, the authors republished the historical (1954–1970) measurements from Kleinfeld et al. (1973), as well as results from Mining Enforcement and Safety Administration (MESA) reports (1972–1975) and results from a NIOSH survey (1975). [The Working Group noted that it was unclear from the text whether these measurements were all collected at the same mine and mill.] In a later report by NIOSH, a breakdown of the impinger dust monitoring data by job was provided (NIOSH, 1980). At the mine, personal 8-hour TWA exposures ranged from 0.7 mppcf (driller) to 15.8 mppcf (mucker), and at the mill exposures ranged from 0.5 mppcf (labourer) to 3.6 mppcf (packer).

Dreessen and DallaValle (1935) reported impinger-sampling results for jobs at a mine and two mills in the Chatsworth district in Georgia, USA. The talc deposit in this district contains actinolite and anthophyllite asbestos (see Table 1.1). In the mine, average dust levels ranged from 32 mppcf (mucker) to 855 mppcf (driller). At the mills, waste talc from sorting and cutting of raw talc was used to make marking pencils for the steel and construction industries. Dust levels ranged from 17.1 mppcf (pencil packaging) to 1672 mppcf (packerman).

Rubino et al. (1979) reported that the average historical dust concentration among millers of high-purity talc (no asbestos present, see Table 1.1) in Val Chisone, Piedmont, Italy, over a 22-year period (dates not given) was 11 mppcf. Wergeland et al. (1990) surveyed the mortality experience of miners and millers of talc in Norway. This talc contains anthophyllite and tremolite asbestos (see Table 1.1). In a follow-up of this cohort to 2011 (Wergeland et al., 2017), the authors reported that historical sampling data from 1960 to 1965 in the mill had been found, and levels were 28.2, 150–200, 26, and 1.3–393.3 mppcf for the bagging room, sieving room, crushing operation, and unspecified jobs, respectively.

Inspection of the historical impinger-sampling results presented in Table S1.12 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646) indicated that before about 1950, maximum dust concentrations in workplaces were often hundreds to thousands of million particles per cubic foot

(e.g. Siegal et al., 1943), whereas after 1950, levels rarely exceed a few hundred million particles per cubic foot. [The Working Group noted that a consistent pattern in exposure levels between mine and mill workplaces was not observed.] Several studies reported higher exposures at mines than at mills (Dreessen, 1933; Siegal et al., 1943; Dement and Zumwalde, 1979), whereas others reported similar or higher exposures at mills than at mines (Dreessen and DallaValle, 1935; Kleinfeld et al., 1955, 1967, 1973, 1974). [The Working Group noted that direct comparison of exposure levels by job is complicated by study-specific differences in job descriptions.] In general, exposures at mines were highest for drillers, muckers, and crushers, whereas exposures at mills were highest for packers and separators.

Respirable mass sampling

Table S1.13 summarizes the results of personal breathing zone, respirable dust sampling in talc mines and mills (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646). Boundy et al. (1979) measured seasonal variations in exposures to high-purity talc at six mines and four mills in Vermont, USA. It is probable that the Vermont talc deposit contains actinolite and tremolite asbestos, and it is possible that it contains anthophyllite and chrysotile asbestos (see Table 1.1). [Selevan et al. (1979) stated in a NIOSH report that there was no asbestos found in the analysis of mill and mine airborne dust and dust samples using XRD and analytical electron microscopy. The Working Group noted that this method could be sufficiently sensitive to detect asbestos contamination. The authors stated that the deposit at one closed mine was reported to contain tremolite (unspecified as to asbestos content) and that, although asbestos exposure of the miners was possible, exposure of the millers was unlikely because the miners avoided or discarded the tremolite.] Among the three underground mines, exposures ranged from 0.5 to 1.5 mg/m^3 in the summer and from 0.5 to 0.9 mg/m^3 in the winter. At the two walk-in mines, exposures were 1.2–1.7 mg/m^3 but in the open-pit mine they were higher at 5.1 mg/m^3. Among mills, talc exposures were approximately similar (range, 0.5–2.9 mg/m^3) across seasons and work shifts. The authors described the mills as large "barn-like" structures with air drafts that could explain the similar results.

Dement and Zumwalde (1979) reported the results of sampling of personal respirable dust from Gouverneur District industrial talc mines and mills [the talc contained tremolite and anthophyllite asbestos]. The average 8-hour TWA exposure at a mine was 0.86 mg/m^3 (range, 0.23–1.29 mg/m^3) and at a mill it was also 0.86 mg/m^3 (range, 0.25–2.95 mg/m^3). In an epidemiological study on this workforce published in the same year by NIOSH, the authors reported almost identical 8-hour TWA exposure concentrations for the mine (0.23–1.20 mg/m^3) and mill (0.25–2.96 mg/m^3) but referred to the values as means (Gamble et al., 1979). Subsequently, NIOSH published a report that provided job-level respirable dust exposure values at Gouverneur District industrial talc mines and mills from the summary data provided previously (NIOSH, 1980). At the mine, personal 8-hour TWA exposures ranged from 0.23 mg/m^3 (cageman) to 1.29 mg/m^3 (scrapper man), and at the mill exposures ranged from 0.25 mg/m^3 (pack foreman, bulk loader) to 2.96 mg/m^3 (millwright helper). Oestenstad et al. (2002) evaluated respirable dust exposures at two Gouverneur District industrial talc mines and a mill in order to support a worker mortality study (see Honda et al., 2002). Personal exposures to respirable dust were measured in the summer and winter of 1991. The average respirable dust exposure was 0.47 mg/m^3 for all samples of different sites, jobs, and seasons combined. For all jobs monitored at all sites, the average respirable dust concentration was lowest

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for maintenance workers at mine 2 (0.06 mg/m³) and highest for underground workers at mine 1 (0.73 mg/m³) and crushing workers at mine 2 (0.83 mg/m³).

Greife (1980) monitored respirable dust exposures at seven mines and eight mills in Montana (cosmetic talc), Texas (industrial talc), and North Carolina (cosmetic talc), USA. [The Working Group noted that the mineral districts of these mines and mills were not provided in the report. From Table 1.1, the presence of tremolite was probable at some, but not all, mines in Montana. In Texas, there were two districts. In one, tremolite was present; in the other, tremolite and chrysotile were present, and the presence of actinolite and anthophyllite was probable. In North Carolina, there were two districts. In one, anthophyllite was present and the presence of tremolite was probable; and in the other, the presence of tremolite was possible. Among all mine and mill sites in Montana, the arithmetic mean respirable dust concentration was [1.21 mg/m³] (geometric mean, GM, 0.86 mg/m³). GM concentrations were 0.66 mg/m³ (mines only) and 1.1 mg/m³ (mills only). By job, geometric mean exposure levels ranged from 0.1 mg/m³ (boiler operator, driller) to 6.3 mg/m³ (welder). For all sites in Texas, the arithmetic mean respirable dust concentration was [2.64 mg/m³] (GM, 1.08 mg/m³). By job, GM exposure levels ranged from 0.1 mg/m³ (miner) to 38.4 mg/m³ (mill operator). In North Carolina, among mine and mill sites, the arithmetic mean respirable dust concentration was [0.28 mg/m³] (GM, 0.21 mg/m³). By job, GM exposure levels ranged from 0.1 mg/m³ (driller, hoist operator) to 1.2 mg/m³ (cutter, packer).

Leophonte and Didier (1990) evaluated the respiratory health of millers at a site in France. Talc that was free of asbestos (see Table 1.1) was extracted from an open-pit mine in the Pyrenees mountains and transported via cable car to the mill. According to Leophonte and Didier (1990), in 1984, the average respirable dust concentration was 4 mg/m³ for milling and 5 mg/m³ for packaging. In 1988, the average respirable dust concentration was 1 mg/m³ for milling and 3 mg/m³ for packaging. Wild et al. (2002) reported that measured respirable dust concentrations ranged from 0.21 to 134 mg/m³ at a mine in France and from 6.5 to 19.6 mg/m³ in mines in Austria. In the follow-up study by Wild et al. (2008), based on newer exposure data, respirable dust concentrations were generally lower than historical measurements. The geometric mean respirable dust concentrations were 0.37 mg/m³ (compared with 0.67 mg/m³) and 0.80 mg/m³ (compared with 1.95 mg/m³) at the French mine and mill, respectively. At the Austrian mines and mills, respirable dust concentrations decreased by a factor of approximately two over time.

Teikari et al. (2003) compared the relative performance of eight aerosol-sampling techniques during a granulating process in a talc plant. [The Working Group inferred that, on the basis of the author affiliations and funding support for this project, the mill was located in Finland. If the talc were from Finland, the presence of tremolite is probable (see Table 1.1).] No details were given on the duration of sampling or numbers of samples. A sampling device was used to measure the inhalable aerosol fraction, and a modified version of the sampling device was used to measure the thoracic and respirable aerosol fractions. The measured concentrations decreased as the particle size fraction decreased: inhalable (3.6–6.5 mg/m³), thoracic (2.0–2.9 mg/m³), and respirable (0.4–0.6 mg/m³), respectively.

The cohort reported by Rubino et al. (1979) of high-purity talc miners and millers in Val Chisone, Italy (asbestos-free talc, see Table 1.1) was followed up by Coggiola et al. (2003), Pira et al. (2017), and Ciocan et al. (2022). Coggiola et al. (2003) reported that the average respirable dust concentration in the mine was 1.1 mg/m³ [they also reported a concentration of 1.0 mg/m³ for "talc alone", but the Working Group noted that it was unclear how this value was determined].

Romano et al. (2011) evaluated talc miners in this region and reported exposure data for the period 2004–2010. [The Working Group estimated the 8-hour TWA dust exposure by dividing the yearly cumulative exposure by 200 working days per year.] For talc miners, the average dust exposure was [1.9] mg/m^3, and for grinding and bagging plant workers the average was [0.8] mg/m^3. [The Working Group estimated respirable dust concentrations for the period 2007–2014 from figures in Pira et al. (2017); at the mine, concentrations ranged from 0.2 to 1.6 mg/m^3 and at the mill from 0.3 to 0.9 mg/m^3.]

Rossner et al. (2020) obtained respirable dust sampling data for workers in Vermont talc mines and mills from private company records (1976, 1978–1980, and 1999/2003) and Mine Safety and Health Administration (MSHA) inspection records (1978–1980, 1981–1989, and 1990–1998). It is probable that Vermont talc contains actinolite and tremolite asbestos, and it is possible it contains anthophyllite and chrysotile asbestos (see Table 1.1). The authors reported data for seven sites in Windsor County, USA: the Hammondsville underground mine, Ludlow surface and open-pit mines, West Windsor mill (which services the Hammondsville and Ludlow mines), West Windsor office (administration associated with the West Windsor mill), Columbia mill (which services Ludlow mines only), Columbia shipping centre (associated with Columbia mill), and the Gassetts Mill (an older dry processing plant). Overall, approximately 700 samples of respirable dust were collected for 44 job categories at the seven sites over an approximately 30-year period. The authors stated that, because of differences in sampling strategies, the company and MSHA data were reported separately. On the basis of company data, average exposure levels decreased from 1.38 mg/m^3 (1976) to 0.09 mg/m^3 (1999/2003) for all mines. For all mills, the decrease in average exposure levels was less pronounced, i.e. from 1.13 mg/m^3 (1976) to 0.83 mg/m^3 (1999/2003). Using MSHA data, a similar decrease in exposure levels was observed for all mines (1.27 mg/m^3 in 1978–1980, to 0.68 mg/m^3 in 1990–1998). For all mills, MSHA data showed similar average exposure levels from 1978–1980 (2.83 mg/m^3) to 1981–1989 (3.32 mg/m^3) and then a decrease in 1990–1998 (0.62 mg/m^3).

The evaluation of data presented in Table S1.13 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646) suggested a general pattern of decreasing average exposures to respirable dust at talc mines and mills over time. In the 1970s, average exposures at mines and mills ranged from approximately 1 mg/m^3 (Rossner et al., 2020) to 34.6 mg/m^3 (Wild et al., 2002). In the 1980s, average exposures at talc mills were approximately 0.8 mg/m^3 (Wild et al., 2008) to 1 mg/m^3 (Leophonte and Didier, 1990). In the 1990s, average exposures at most mines and mills were approximately 0.3–2.0 mg/m^3 (Wild et al., 2008). By the 2000s, average exposures at mines and mills ranged from 0.09 mg/m^3 (Rossner et al., 2020) to 1.6 mg/m^3 (Pira et al., 2017). Type of workplace did not appear to be related to exposure level. Average respirable dust levels at mines ranged from 0.09 mg/m^3 (Rossner et al., 2020) to 5.1 mg/m^3 (Boundy et al., 1979), which is similar to levels at mills, where average levels ranged from 0.25 mg/m^3 to 2.96 mg/m^3 (Gamble et al., 1979). Job-level exposures tended to have much more variability than did facility-level averages. A job-level comparison of respirable dust exposures across studies is problematic, because different investigators classified jobs differently and/or used different names. Greife (1980) reported exposure levels for the same job at three different mills; exposure were lower for drillers and maintenance jobs than for mill operator and bagger jobs. [The Working Group noted that the majority of data on occupational exposures during talc mining and milling were from Europe and North America; however, as noted in Section 1.2, currently, the largest talc

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producers in the world are China, India, and Brazil, for which there were no data.]

(ii) Downstream industries

Table 1.14 summarizes the results of studies that reported exposure to industrial talc in downstream industries. [The Working Group noted that in most of these studies no information was provided on the source or characteristics of talc that would permit an appraisal of whether it might contain asbestos.] Fine et al. (1976) measured personal exposures to respirable mass among rubber workers at two plants in the USA. At plant A, exposures ranged from 0.60 mg/m^3 (splicer) to 1.41 mg/m^3 (curemen) in the truck and bus inner-tube process. At plant B, exposures ranged from 0.51 mg/m^3 (hose extruding) to 3.55 mg/m^3 (rubber band area). Governa et al. (1987) monitored exposures to respirable dust for workers at a rubber-tyre manufacturing facility in Italy. They reported mean respirable dust exposures of 1.90, 2.20, and 2.85 mg/m^3 for compounding, Banbury mixing, and milling operations, respectively. Neghab et al. (2007) evaluated respiratory morbidity among 97 talc workers and 110 unexposed employees (controls) engaged in rubber tube production in the Islamic Republic of Iran. Personal breathing zone samples for total and respirable dust were collected in four process areas (extruder, flap bladder, curing, and inspection). The average inhalable and respirable dust concentrations (all process areas) were 41.8 ± 23.52 mg/m^3 and 19.8 ± 8.04 mg/m^3, respectively. [The Working Group noted that the quantities of talc used in most downstream industries are likely to be lower than the amounts processed in mines and mills. Additionally, there may be multiple sources of dust in these workplaces. For example, processes in rubber-product manufacturing require accelerators, activators, antioxidants, fillers, and other ingredients (Governa et al., 1987). Since dust sampling is not specific for talc, in these situations the proportion of talc in the samples may be less than the total mass reported.]

Industrial talc is used in the paper industry as an additive to impart whiteness to paper. Exposure to talc is more likely to occur during processing of raw materials and paper production processes. Gautam et al. (1979) evaluated exposure to several agents at three paper mills in India. Sampling was described as drawing air through a filter using a calibrated sampling pump and determining the collected mass gravimetrically, which suggests that it was total dust monitoring. Samples were collected for "handling of talc bags" and "near the talc mixer" in a talc mixing plant. [The Working Group noted that the methods did not specify whether these were personal breathing zone or static air samples, although the latter description implied static sampling for the talc mixer.] For handling of talc bags, levels ranged from 614 mg/m^3 (factory III) to 2640 mg/m^3 (factory II). Near the talc mixer, levels ranged from 1064 mg/m^3 (factory III) to 2757 mg/m^3 (factory II). [The Working Group noted that these workers were handling talc directly, and it is likely that the proportion of talc in dust was relatively high.] Sahle et al. (1990) monitored personal dust exposures in a soft paper factory in Sweden. They reported that the concentration of total dust for a worker batching talc was 8.2 mg/m^3.

NIOSH conducted a series of Health Hazard Evaluations (HHEs) at downstream facilities that use talc. The evaluation reported in NIOSH (1978) was conducted at a company that made asphalt roofing shingles. "Non-asbestiform talc" was used in the production process to prevent shingles from sticking together. Personal total dust exposure concentrations ranged from 0.5 mg/m^3 to 28.8 mg/m^3, and personal respirable dust exposure levels ranged from 0.5 mg/m^3 to 1.2 mg/m^3. [The Working Group noted that the proportion of talc in these samples was probably low because there were many other dusts sources present, including pigments, limestone, and

Table 1.14 Exposures to dust in downstream industries using talc (personal sampling)

Country (industry) Period	Site	Job	Sampling type	Fraction of aerosol	No. of samples	Arithmetic mean ± SD (range) (values in mg/m³)	Comment	Reference
USA (rubber) NR	Plant A	Splicer	NR	Resp.	7	0.60 ± 0.49	Truck/bus inner tubes	Fine et al. (1976)
		Cureman	NR	Resp.	6	1.41 ± 0.87	Truck/bus inner tubes	
		Tuber operator	NR	Resp.	3	0.47 ± 0.19		
		Booker	NR	Resp.	3	0.74 ± 0.68		
		Splicer	NR	Resp.	6	0.82 ± 0.44	Farm service inner tubes	
		Cureman	NR	Resp.	2	0.91 ± 0.41	Farm service inner tubes	
	Plant B	Rubber band	NR	Resp.	6	3.55 ± 2.88		
		Gum engraving	NR	Resp.	6	0.64 ± 0.16		
		Hose extruding	NR	Resp.	4	0.51 ± 0.15		
		Curing	NR	Resp.	3	1.29 ± 0.45	Heavy duty flaps	
		Dust room	NR	Resp.	2	0.59 ± 0.10		
India (paper) 1976–1977	Mixing plant	Handling bags	NR	Total	NR	1540	Factory I	Gautam et al. (1979)
		Near mixer	NR	Total	NR	2224		
		Handling bags	NR	Total	NR	2640	Factory II	
		Near mixer	NR	Total	NR	2757		
		Handling bags	NR	Total	NR	614	Factory III	
		Near mixer	NR	Total	NR	1064		
USA (asphalt shingles) 1977	Production plant	Coater, press, and slate men	FS	Resp.	3	NR (0.5–1.2)	No local ventilation	NIOSH (1978)
		Dry felt, saturator, coater, press, granule, slate, lead, and cutter, conveyor men; machine operator	FS	Total	18	NR (0.5–28.8)	No local ventilation	

Table 1.14 (continued)

Country (industry) Period	Site	Job	Sampling type	Fraction of aerosol	No. of samples	Arithmetic mean ± SD (range) (values in mg/m³)	Comment	Reference
USA (flooring) 1978	Production plant	Resin scale operator, scrap loader, pigment scale operator, utility man, and mixer operator	FS	Total	14	NR (0.3–9.3)		NIOSH (1979)
USA (rubber thread) 1979–1980	Production plant	Tape packing, slitting, strip cutting, wrapping, bale cutter, calendar inspector and operator	FS	Resp.	35	NR (ND–1.2)		NIOSH (1982)
USA (baby powder) 1980–1981	Mixing room	Mixer A	$TWA_{8\,h}$	Resp.	1	1845	No local ventilation	NIOSH (1981)
		Mixer B	$TWA_{8\,h}$	Resp.	1	22.13	No local ventilation	
		Area sample	FS	Resp.	1	3.40	To right of mixer	
		Area sample	FS	Resp.	1	5.45	Top of staircase	
		Mixer A	$TWA_{8\,h}$	Resp.	1	2.18	Local ventilation	
		Mixer B	$TWA_{8\,h}$	Resp.	1	40.57	Local ventilation	
USA (ceramics) 1984	Casting shop	NR	$TWA_{8\,h}$	Resp.	38	2.69 ± 2.73	Dusting/cleaning moulds	NIOSH (1988)
		Area samples	FS	Total	11	1.04 ± 0.49	Dusting/cleaning moulds	
Italy (rubber) 1979	Plant	Compounding	NR	Resp.	NR	1.90		Governa et al. (1987)
		Banbury mixing	NR	Resp.	NR	2.20		
		Milling	NR	Resp.	NR	2.85		
Sweden (paper) NR	NR	Batching talc	FS	Total	1	NR (0.2–2.8)	Production	Sahle et al. (1990)

Table 1.14 (continued)

Country (industry) Period	Site	Job	Sampling type	Fraction of aerosol	No. of samples	Arithmetic mean ± SD (range) (values in mg/m³)	Comment	Reference
Islamic Republic of Iran (rubber) NR	Plant	NR	NR	Inhalable	NR	41.8 ± 23.52	Four process areas	Neghab et al. (2007)
		–	NR	Resp.	NR	19.8 ± 8.04	Four process areas	
USA (metal furniture) 2007	Powder painting	Painters	NR	Resp.	8	ND		NIOSH (2007a)

FS, full-shift (e.g. 4–8 hour) sample; ND, not determined; NR, not reported; Resp., respirable aerosol fraction; SD, standard deviation; Total, total dust; $TWA_{8\,h}$, 8-hour time-weighted average; USA, United States of America.

plasticizers.] The evaluation reported in NIOSH (1979) was conducted at a company that made asbestos-containing flooring. Talc was used at the factory, although no details were given on how much was used or where it was used in the production process. Personal total mass exposures ranged from 0.3 mg/m^3 to 9.3 mg/m^3. [The Working Group noted that the proportion of talc in these samples was probably low because there were many other dusts sources present, including mica, limestone, and felt.] NIOSH also conducted an HHE at a company that made rubber thread for golf balls (NIOSH, 1982). Talc was used to prevent rubber sheets from sticking together, and respirable mass concentrations ranged from not detected to 1.2 mg/m^3 (tape packing machines) Analysis of nine bulk samples determined that the talc content was 20–100%, and it did not contain asbestos. [The Working Group noted that, on the basis of the bulk analyses, it is likely that the proportion of talc in dust was relatively high.] NIOSH conducted an HHE at a pharmaceutical company that mixed cosmetic talc with fragrances to produce baby powder (NIOSH, 1981). One survey was conducted in 1980, and personal 8-hour TWA respirable dust exposures were 1845 mg/m^3 (mixer A) and 22.13 mg/m^3 (mixer B). [The Working Group noted that workers directly handled talc, so it is likely that the proportion of talc in dust was relatively high.] It was reported that employees wore respirators, although they were incorrectly fitted with organic gas filters, and seals had signs of damage. After this initial visit, the company installed local exhaust ventilation in the mixing room. A second survey was conducted in 1981, and personal 8-hour TWA respirable dust exposures were 2.18 mg/m^3 (mixer A) and 40.57 mg/m^3 (mixer B). NIOSH conducted a survey at a vitreous china factory that made ceramic toilets, water tanks, and sinks (NIOSH, 1988). In the casting room, a casting slurry was poured into moulds that were dusted with talc using a talc-filled cloth bag to prevent sticking to the mould. After casting, moulds were cleaned with compressed air for reuse. [The Working Group noted that the authors reported that the talc was from Montana and was silica- and fibre-free, indicating cosmetic talc, although analysis of a talc used in the past at this facility confirmed that the talc was of fibrous nature.] The average personal 8-hour TWA exposure to respirable dust (predominantly nonfibrous talc dust) was 2.69 ± 2.73 mg/m^3. The average static (area) air concentration of respirable dust (primarily talc) was 1.04 ± 0.49 mg/m^3. Finally, NIOSH conducted an HHE at a metal furniture manufacturing facility that used talc-containing paints (NIOSH, 2007a). All personal respirable mass samples were below the analytical LOD.

A comparison of the data in Table S1.13 (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646) and Table 1.14 shows that, compared with the mining and milling industries, there were much fewer exposure data available for downstream industries, especially those involving the manufacture of consumer products. [The Working Group noted that average personal respirable dust exposures in downstream industries ranged from not detected to 1845 mg/m^3. The latter value was for an unventilated process. More typical was that personal respirable dust exposures did not exceed 90 mg/m^3. Some investigators performed total dust sampling and reported that levels ranged from 8.2 mg/m^3 to 2640 mg/m^3. The highest total dust exposures were at a paper mill in India. The maximum dust concentration levels in downstream industries were similar, with the highest levels reported for mining and milling. Most average respirable mass levels were consistent with average exposures at mines and mills in the 1970s (see Section 1.4.2(i)).]

(b) Biomonitoring

Some investigators have analysed particles in bronchoalveolar lavage fluid of workers using electron microscopy and element-specific detectors (e.g. EDX). An abundance of talc particles in fluid from people with occupational exposure to talc was taken to be a biomarker of exposure (de Vuyst et al., 1987; Dumortier et al., 1989; Corhay et al., 1995). However, this parameter was not validated for exposure assessment, because of missing information on the retention of inhaled talc as well as on the clearance rate of deposited talc (see also Section 4.1).

1.4.3 Exposure of the general population

(a) Introduction

Talc is present in many products likely to be used by the general population (see Section 1.4.1(e)). However, there are very few published data on personal exposures to talc while using these products, and the few data that are available do not always identify the type or source of the talc. The limited data that are available are mainly from epidemiological studies.

(b) Use of talc for feminine hygiene

Exposure to body powder containing mineral talc has been estimated in several studies. In the absence of substantive published exposure data, the use of body powder for feminine hygiene can be estimated from the prevalence reported for controls in case–control studies on the association between use of cosmetic talc for feminine hygiene and risk for ovarian or endometrial cancer (see Table 1.15). In a study published in 2020, data were pooled from four large US cohorts, making it one of the largest studies of its type in this area (O'Brien et al., 2020).

In the four cohorts considered by O'Brien et al., exposure to talc was estimated by questionnaire (for details on assessments using questionnaires, see Section 1.6.1). Participants in the Nurses' Health Study (referred to hereafter as NHS-I) were asked whether they "ever commonly used talcum, baby powder or deodorizing powder" on their perineal area, with the following options provided: no, < 1 per week, 1–6 times/week, daily. In the subsequent Nurses' Health Study II (NHS-II), women were asked to report use only if it was at least weekly and if so for how long (< 1 year, 1 to < 10 years, 10 to < 20 years, 20 to < 30 years and ≥ 30 years. For the Sister Study, questions were specifically focused on talcum powder use and application to "a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area" in the last year or at ages 10–13 years. For the fourth study, the Women's Health Initiative Observational Study (WHI-OS), participants were asked whether they had ever used powder on their "private parts (genital areas)" and if so for how long (< 1 year, 1–4 years, 5–9 years, 10–19 years, or ≥ 20 years). Similar questions were asked for sanitary pads and diaphragms. There were no quantitative exposure data available for any of these studies. In the pooled study, "frequent use" was defined as the use of powder in the genital area at least once per week, and "long-term" use was generally described as use of powder in the genital area for ≥ 20 years. The data covered long-term exposures of approximately 20 years and frequency of use of once per week in the genital area. The pooled sample included 252 745 women with a median age at baseline of 57 years. Reported ever use ranged between 15% and 53% in these studies (Table 1.15).

By their nature, these studies rely on self-reporting; the reliability of "recalled exposure" has been the focus of a separate study (O'Brien et al., 2023). Here, the consistency of retrospective data on douching and genital use of talc from the US-based Sister Study (Sandler et al., 2017) was reviewed at two time points. At enrolment (2003–2009), participants were asked to report usage in the previous year and at ages 10–13 years. At the follow-up questionnaire

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Table 1.15 Prevalence of perineal use of talc or body powder, according to epidemiological studies

Location	Cohort size	No. of controls	Prevalence of ever use of talc/body powder (%)	Type of perineal use of powder by women	Reference
Case–control studies					
Massachusetts, USA		215	28%	Exposure to talc by dusting or on sanitary napkin	Cramer et al. (1982)
Washington DC, USA		171	2%	Body talc	Hartge et al. (1983)
California, USA		539	46%	Use of talcum powder	Whittemore et al. (1988)
United Kingdom		451	61%	Use of talc	Booth et al. (1989)
Washington, USA		158	40%	Exposure to powder (cornstarch, baby powder, talc, deodorizing powder); detailed information on type of powder used	Harlow and Weiss (1989)
Massachusetts, USA		239	39%	Exposure to baby powder, deodorizing or scented powder	Harlow et al. (1992)
Beijing, China		224	2%	Dusting powder	Chen et al. (1992)
Maryland, USA		46	19%	Genital bath talc (also asked use on napkins or diaphragm)	Rosenblatt et al. (1992)
Athens, Greece		193	4%	Local application of talc	Tzonou et al. (1993)
Australia		860	52%	Use of talc around abdomen/perineum	Purdie et al. (1995)
Israel		408	6%	Use of talc moderately/a lot (never/seldom use 94%)	Shushan et al. (1996)
Toronto, Canada		564	36%	Regular application of talc	Chang and Risch (1997)
Washington, USA		422	39%	Any lifetime dusting with cornstarch, talcum powder, baby or scented powder, and deodorizing spray	Cook et al. (1997)
Australia		855	40–41%	Use of talc	Green et al. (1997)
New York, USA		50	26%	Use of talc	Eltabbakh et al. (1998)
Montreal, Canada		170	5%	Use of talc	Godard et al. (1998)
New England, USA		523	18%	Use of talc, baby or deodorizing powders or cornstarch	Cramer et al. (1999)
New York, USA		693	35%	Use of talc (on genital or thigh area and sanitary napkins)	Wong et al. (1999)
Delaware Valley, USA		1367	42%	Use of talc (on genital/rectal area, sanitary napkins, underwear, diaphragm/cervical cap, male partner user)	Ness et al. (2000)

Table 1.15 (continued)

Location	Cohort size	No. of controls	Prevalence of ever use of talc/body powder (%)	Type of perineal use of powder by women	Reference
Norway		121	44%	Ever use in personal hygiene	Langseth and Kjaerheim (2004)
California, USA		1122	37%	Use of talcum powder	Mills et al. (2004)
Australia		1478	45%	Use of talc	Jordan et al. (2007)
Australia		1509	43%	Perineal/underwear/napkins/diaphragms	Merritt et al. (2008)
North Carolina, USA		667[a]	[40%]	Use of talc	Moorman et al. (2009)
Washington state, USA		1313	12%	Regular use after bath during ≥ 1 year	Rosenblatt et al. (2011)
Pennsylvania, Ohio, New York State, USA		1802	21%	Using dusting powder or deodorizing spray	Kurta et al. (2012)
USA, Canada		9859	25%	Any type of powder including cornstarch	Terry et al. (2013)
USA		2391	29–44% by race	Use of talc	Wu et al. (2015)
Eastern Massachusetts and New Hampshire, USA		2100	26%	Dusting of genital area with main commercial brand product or other powder	Cramer et al. (2016)
11 states, USA		745	53%	Genital and non-genital use of body powder	Schildkraut et al. (2016)
Eastern Massachusetts and New Hampshire, USA		2100	20–32% by age group	Use of talc	Gabriel et al. (2019)
USA		390	19–58% by race	Any type of powder including cornstarch	Davis et al. (2021)
USA, Australia		13 592	~10%	Use of talc	Phung et al. (2022)
Cohort studies					
USA (NHS-I)	66 028		40%	Use of talc, baby powder, deodorizing powder	Karageorgi et al. (2010)
USA (WHI)	61 576		53%	Powder or sanitary napkin/pad; on diaphragm	Houghton et al. (2014)
USA (NHS-II)	61 261		26%	Talc dusting of genital area	O'Brien et al. (2020)

Table 1.15 (continued)

Location	Cohort size	No. of controls	Prevalence of ever use of talc/body powder (%)	Type of perineal use of powder by women	Reference
USA (Sister Study)	36 202		27% initial; 32% follow-up	Talc powder or spray on a sanitary napkin, underwear, diaphragm, cervical cap or directly to vaginal area	O'Brien et al. (2023)
USA (Sister Study)	45 465		15–36% by race	Talcum powder to sanitary napkin, underwear, diaphragm, cervical cap, or directly to vaginal area; ages 10–13 years	Goldberg et al. (2024)

AACES, African-American Cancer Epidemiology Study; DC, District of Columbia; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; USA, United States of America; WHI, Women's Health Initiative.

[a] Number of controls without missing data on talc use.

(2017–2019), they were asked about their use of douche or genital application of talc over their lifetimes. A total of 36 202 women responded, of whom 27% reported ever using genital application of talc. For the follow-up, 32% reported ever using genital application of talc. Good consistency was noted across the two questionnaires, with 87% giving the same response for genital use of talc, and the kappa was moderate at 0.62. The researchers concluded that ever use of feminine hygiene products was recalled with good consistency, but this varied with time period and by case status, since the women who had developed ovarian cancer comprised the only group to increase their reporting.

In a case–control study published in 2016, Cramer et al. (2016) also looked at the association between talc use and ovarian cancer between 1992 and 2008. Participants were enrolled in three phases (1992–1997, 1998–2002, and 2003–2008). In total, 3957 women living in eastern Massachusetts and New Hampshire, USA, diagnosed with ovarian cancer and aged 18–80 years were identified through tumour boards and registries. Control participants (n = 2100) were identified using similar criteria, except that they had not been diagnosed with ovarian cancer. Exposure to talc was estimated by personal interview. Participants were asked whether they "regularly" or "at least monthly" applied powder to the rectal or genital area, sanitary napkins or tampons, underwear, or areas other than the genital area. In addition, information on the type of powder used, age started, and number of applications per month was obtained. This was used to estimate lifetime exposures by multiplying the frequency of applications per month by the number of months used. This in turn was divided by 360 (based on daily use of 30 per month) to give an estimate of "talc-years". Where known, the type of powder used was identified as "cornstarch only", by name for the most common brands of powder for babies or shower use, or "other brands". The most commonly reported powders were products of the major brand. Estimated exposure data in "talc-years" were presented as "percent ever used on genitals" in categories by decade of birth and age at diagnosis or interview (see Fig. 1.4). In controls, ever use was lowest (< 5%) among women questioned at age > 30 years who were born after 1971, and highest (> 35%) among women questioned at age 60–69 years and born between 1941 and 1950.

Harlow and Weiss conducted a case–control study on the influence of perineal exposure to talc on the development of ovarian tumours (Harlow and Weiss, 1989). The researchers conducted in-person interviews of 116 female residents of western Washington state, USA, who had been diagnosed between 1980 and 1985 with serous and mucinous borderline ovarian tumours. Participants were questioned on their reproductive, sexual, and medical histories, and perineal exposure to talc. A sample of 158 control women from the same area were also interviewed. The types, but not brand names, of powders they had used for perineal application after bathing, on sanitary napkins, and for diaphragm storage, before diagnosis (or similar dates for the controls) were recorded. Powder types were classified as either one of three talc-containing powders (baby powder, deodorizing powder, or unspecified talcum or dusting powders) or as cornstarch (see Table 1.15). However, exposure for each powder type was reported only as "any use" or "no use". No quantitative data were reported for the actual duration or amount of exposure experienced, nor was the specific type of talc reported. However, the authors concluded that, although from 1975 the purity of US cosmetic talc was required to be ≥ 90% talc, many cosmetic talcs did not achieve this level, and contamination by asbestos could not be ruled out. The authors referred to the study by Rohl et al. (1976) carried out between 1971 and 1975 on 21 consumer talcum powders labelled as baby powders, facial powders, or body powders that were found to contain asbestos

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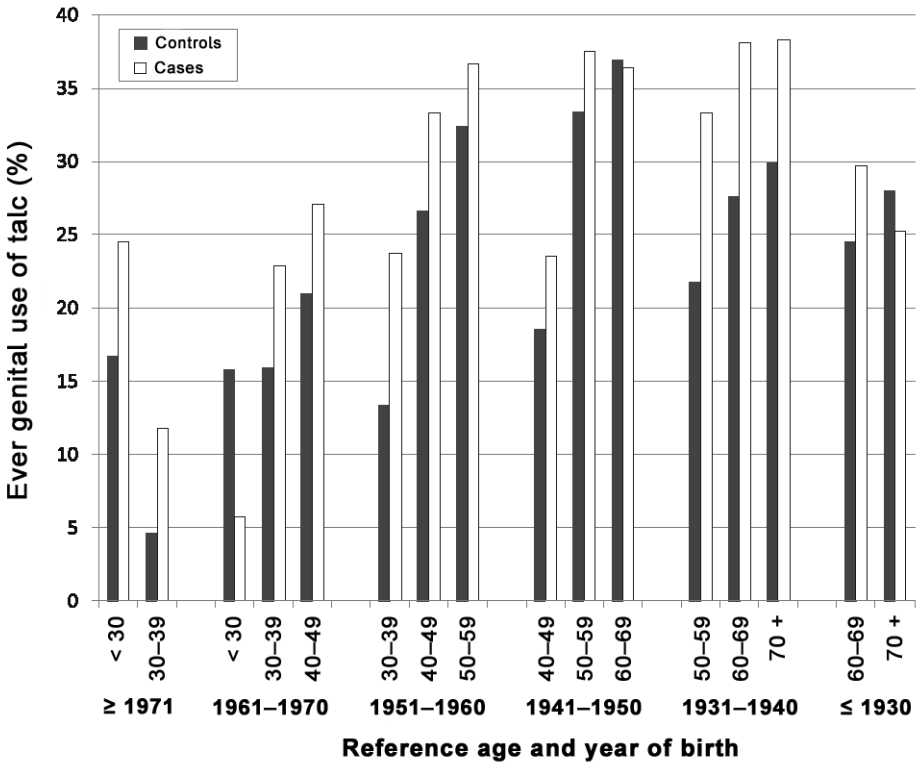
Fig. 1.4 Proportions of cases and controls who had ever used talc on the genital area as reported by Cramer et al. (2016), by decade of birth and reference age



[The Working Group noted that in this study, the questions assessed specific products, and exposure for talc products was reported specifically.] Reproduced from Cramer et al. (2016). The association between talc use and ovarian cancer: a retrospective case–control study in two US states, *Epidemiology*, Volume 27, Issue 3, pages 334–346, Copyright © 2015 Wolters Kluwer Health, Inc.

at levels ranging from 0.2% to 14%, as well as substances used specifically for deodorization.

Further information on the presence of talc at pelvic sites distant from the perineum, after talc use, can be found in Section 4.1.1(a)(iii). [Talc in tissues has been measured as a proof of exposure; however, this is not an established biomonitoring method.]

(c) Other uses of cosmetic talc

There are very few published quantitative exposure data for other uses of talc. Where limited data were available, this was often as part of a pilot study. One such example was undertaken by Rasmussen et al. (2019) to investigate the nature of the cloud of airborne talc particles that forms in the personal breathing zone during the application of talc-containing cosmetic products. Four talc-containing cosmetic products commercially available in Canada (one face powder, one powder for babies, and two powders for adults) were selected for use in laboratory chamber experiments and exposure experiments using human participants. Direct reading instruments were used to measure concentrations of PM_4 (particles with an aerodynamic diameter of ≤ 4 μm) at different distances from the participants as they applied talc-based products. The researchers concluded that, although the average airborne dust concentrations were measured to be about 1.0 mg/m^3, the results were strongly influenced by the type of product and method of

application, combined with physical and behavioural differences between the participants. The duration of the exposures ranged from about 1 to 10 minutes. The use of real-time measuring devices allowed the sampling of secondary dust clouds as they formed sporadically as a result of resuspension of talc from skin and other surfaces. Real-time measuring instruments also allowed the characterization of short-duration exposures to airborne talc particles.

The European Union Cosmetic Regulation (EC) No. 1223/2009 (European Commission, 2009) requires that all cosmetic products, including powders must be assessed for their safety, including all possible routes of consumer exposure. In a review of consumer exposures to talc, Steiling et al. (2018) reported that exposure is predominantly by dermal contact. However, these authors also identified the potential for inhalation exposure from cosmetic sprays and powders. A panel of international experts was created by the European trade association for the cosmetics industry, "Cosmetics Europe". A strategy was developed that allowed small and medium-sized enterprises and other organizations to provide a safety evaluation of cosmetic powder products. The review focused on exposure to or inhalation of solids and the setting of safe exposure levels for cosmetic powder products. Prediction models for best estimates of inhalation exposure were developed from simulation exercises or real-time measurements, or from market experience on how the products were introduced and applied. The expert panel referred specifically to habitual human behaviour data published on talc powders in consumer products to estimate typical exposure scenarios. Estimated exposure to consumer powder products was found to be significantly lower than the TWA limit for occupational exposure to respirable talc particles. As a rough estimate and for orientation, the panel compared the 8-hour TWA limit with a typical 1.23-minute exposure to a cosmetic talc-based product for which the respirable airborne fraction in the breathing zone was estimated to be 2.03 mg/m^3. The calculated concentration for the respirable fraction of 0.0052 mg/m^3 was significantly lower than the occupational TWA limit; for example, the American Conference of Governmental and Industrial Hygienists (ACGIH) defined a threshold limit value – time-weighted average (TLV-TWA) for respirable talc particles of 2 mg/m^3. Cosmetic powders did not generate significant levels of inhalable or respirable particles. However, there is still a risk of unintended inhalation exposure in addition to dermal and oral exposure. The expert panel concluded that unintended inhalation exposure during the application of cosmetic powders would be very low or negligible (Steiling et al., 2018).

In a study in Mexico, researchers investigated the use of cosmetics (cleansers, moisturizers, and talc) in infants and children (aged 1 month to 12 years) of low socioeconomic background, with and without skin disease (Palacios-Lopez et al., 1998). On behalf of these children, mothers answered questions on name, sex, age, dermatological diagnoses (if any), and routinely used type of soap, talc, body oil, cream, shampoo, and body lotion. The questionnaire was completed by 200 mothers for 58 girls and 42 boys. The use of talc was more frequent for healthy infants (21%) than for infants with skin disease (12%). The use of talc in the diaper area for both healthy infants and those with skin disease (32%) was reported as being lower than for infants in the USA (69%) (Brouillette and Weber, 1978). Although rare, aspiration of talc has been reported in children, mainly related to the use of baby powder (Mukhopadhyay and Katzenstein, 2007) (see also Section 4.1.1(a)(iii)).

(d) Pharmaceutical products

There was one study on the relation between prescribed talc powder and stomach cancer in Taiwan, China (Chang et al., 2019) (see also Section 2.7.3). There had been an earlier report

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of an association between talc ingestion and stomach cancer in the 1970s, but earlier studies on talc-treated rice in Japan were complicated by possible contamination of the talc by asbestos (Merliss, 1971b). As a result, Chang and colleagues focused specifically on exposure to asbestos-free talc. In the population-based sample of 605 652 participants, there were 21 575 (3.4%) who were exposed to Chinese herbal products containing talc, based on a nationwide claims database.

In Chinese herbal medicine, talc is used as an antipyretic (reduces fever) and diuretic (reduces body fluid build-up) agent (Chang et al., 2019).

(e) Food and drinking-water

The use of silicate-based food additives (E552–553) is authorized in 28 food categories, including FC 0, which means that such additives are permitted in all categories of food except food for infants and young children. Thus, there is potential dietary exposure resulting from the use of talc as a food additive. In a report by EFSA, dietary exposure to talc from its use as a food additive was calculated for different exposure scenarios (EFSA, 2018a). Dietary exposure to silicates (E552–553, mainly talc) was up to 31 mg/kg bw per day at the mean level in children and up to 46 mg/kg bw per day at the high (95th percentile, P95) level in the elderly. [The Working Group noted that potential exposure of the general population to talc in food additives is not exactly clear from the information available since such additives also contain other silicates.]

The addition of talc to wheat flour is prohibited in China (Chinese Standards, 2016). The US FDA considered talc as Generally Recognized as Save (GRAS) (US FDA, 2024). The adulteration of wheat flour with illegal additives has been reported in several recent studies in China. [The Working Group noted that there were few data on the legal and illicit use of talc in food; however, substantial exposure to talc via food may occur in some instances.]

In addition, in an evaluation made by Health Canada in 2021, it was concluded that dietary exposure from the use of talc as a component in the manufacture of some food packaging materials is expected to be negligible, and dietary exposure is not expected from its use as a component in the manufacture of incidental additives (Health Canada, 2021). Talc is insoluble in water and is expected to settle out during water treatment. Therefore, exposure of the general population via drinking-water is not expected (Health Canada, 2021).

(f) Other exposures

A study of risk factors associated with diaper dermatitis in children aged < 24 months in Thailand investigated the link between the use of baby talcum powder and increased risk of dermatitis. Sukhneewat et al. (2019) conducted a cross-sectional study of 1153 participants, using questionnaires. The contextual information for exposure to talc indicated that 37.1% of the participants reported topical application of baby talcum powder to the diaper area. This was the first reported study on diaper dermatitis in Thailand, and the findings were similar to those of other studies conducted in Asia (Prasad et al., 2003), North America, and Europe (Scheinfeld, 2005; Thaman and Eichenfield, 2014). However, the authors did not elaborate on the composition of the baby talcum powder. [The Working Group noted that although the use of baby powder containing talc seemed to be widespread, there were few quantitative data on the prevalence of this use and the exact composition of the products involved. The Working Group noted that the person applying baby powder to an infant might also be exposed to talc; however, this is poorly documented.]

There have been several reports of cases in which the injection of talc-containing drugs of abuse has resulted in the development of "talcosis". The intravenous injection of crushed pharmaceutical tablets (typically containing

insoluble binding agents, such as talc, microcrystalline cellulose, and crospovidone) was reported, with exposures in some cases estimated to have been daily for 15–20 years. These insoluble binding agents may become irreversibly trapped in the lungs and produce angiocentric foreign body granulomatous inflammation. Some examples have been reported by Ranib et al. (2021), Baylor et al. (2013), and Scheel et al. (2012). In all three studies, the mineral talc was detected during the analysis of lung biopsy tissue. Further case reports of talc found in retina and lung tissue, together with systematic distribution of talc by intravenous injection, are described in Section 4.1.1(a)(ii).

Medical gloves and condoms are regulated as Class II medical devices in Canada under the Medical Devices Regulations and may both be sources of talc exposure if talc is present as a dry lubricant. [The Working Group noted that although exposure of the general population via use of these products can be expected, no quantitative estimates of exposure were available to the Working Group.]

1.5 Regulations and guidelines

1.5.1 Occupational exposure

Occupational exposure limits (OELs) for talc are usually expressed as the 8-hour TWA concentration of respirable or total inhalable dust per cubic metre of air sampled. OELs and guidelines for talc not containing asbestos fibres are presented in Table 1.16. When current OELs are compared with those described in the previous evaluation of talc by the *IARC Monographs* in 2006 (Volume 93; IARC, 2010), there has been very little change in the last two decades. The OEL has reduced in only three of the countries listed, namely Finland (reduced from 5 mg/m^3 to 2 mg/m^3 for total inhalable dust and 1 mg/m^3 for respirable dust), the Netherlands (reduced from 1 mg/m^3 to 0.25 mg/m^3), and Denmark (reduced from 0.3 fibres/cm^3 to 0.003 fibres/cm^3 for talc containing fibres). The OEL in South Africa appears to have increased from 1 mg/m^3 to 4 mg/m^3 for respirable dust. [The Working Group noted that in many countries where there is not a specific OEL for talc, the OEL for general dust is used.]

Drechsel et al. (2018) reviewed the close interrelationship between talc and the amphibole mineral tremolite (both asbestiform and nonfibrous analogues) and give a detailed commentary on the development of US OELs for talc and associated minerals, including asbestos. Their review also considered the way that different US agencies defined and characterized varieties of talc and asbestos, particularly amphibole minerals, and the characterization of health risks associated with exposures to these minerals.

The first set of published OELs for talc, including a limit of 20 mppcf in air, was published in 1946 by the National Conference of Governmental Industrial Hygienists (NCGIH), later renamed the American Conference of Governmental Industrial Hygienists (ACGIH), in the USA. These OELs were later adopted by regulatory agencies such as the Department of Labour under the Walsh–Healey Public Contracts Act in the 1950s and the Occupational Safety and Health Administration (OSHA) in 1971. In its first set of OELs established in 1971, OSHA largely adopted the 1968 ACGIH TLVs. However, the OELs enforced by OSHA were referred to as "permissible exposure levels" (PELs). Initially, the standards adopted by OSHA in May 1971 included a PEL for talc (not containing asbestos) of 20 mppcf. However, in 1971 a distinction was made between talc (non-asbestiform) and talc (fibrous). [The Working Group inferred that talc (fibrous) in this context meant talc containing asbestos.] For the latter, TLV for asbestos was adopted, and this has remained the case. Between 1989 and 1992, the PEL for talc changed to 2 mg/m^3, and then reverted to 20 mppcf in 1992 and was still in place in 2024. The TLV for talc

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Table 1.16 Occupational exposure limits for talc

Country or region	Concentration (mg/m³)		Talc containing fibres (fibres/cm³)	Type of OEL	Remarks
	Respirable dust	Total inhalable dust			
Australia[a]	2.5			TWA	
Austria[a]	2			TWA	
Belgium[a]	2			TWA	Asbestos-free
Bulgaria[b]	3			TWA	
Canada – Ontario[a]	2[c]		2[d]	TWA	
Canada – Quebec[a]	2		1	TWA	
China[a]	1	3		TWA	
Czechia[b]	2			TWA	
Denmark[a]	0.3			TWA	
	0.6			STEL	
Finland			0.5	TWA	
		2		STEL, particles	
Greece[b]	2			TWA	
Hungary[b]	2			TWA	
Ireland	0.8[b]	10[a]		TWA	
Italy[b]	2			TWA	
Japan	0.5[a]	2[a]		TWA	
	1[e]	4[e]		TWA not containing fibres	
Latvia[a]		4		TWA	No information on whether respirable or inhalable dust
Lithuania[b]	1			TWA	
Luxembourg[b]	2			TWA	
Netherlands[b]	0.25			TWA	
New Zealand[a]	2			TWA	Containing no asbestos
Norway[a]	2	6		TWA	
Poland [a]	1	4		TWA	
Portugal[b]	2			TWA	
Republic of Korea	2				No information if respirable or inhalable dust
Romania[b]	2			TWA	
Singapore	2			TWA	No information if respirable or inhalable dust
Slovakia[b]	2			TWA	
Slovenia[b]	2			TWA	
South Africa[a]	4			TWA	For particulate matter containing no asbestos and 1% crystalline silica.
South Africa (mining)		10			
Spain[a]	2			TWA	
Sweden[a]	1	2		TWA	
Switzerland[a]	2			TWA	
United Kingdom[a]	1			TWA	

Table 1.16 (continued)

Country or region	Concentration (mg/m³)		Talc containing fibres (fibres/cm³)	Type of OEL	Remarks
	Respirable dust	Total inhalable dust			
USA					
ACGIH (TLV)	2			TWA	ACGIH: containing no asbestos and < 1% crystalline silica (ACGIH, 2024)
NIOSH [a]	2			TWA	NIOSH: containing no asbestos
OSHA[a]	20 mppcf			TWA	OSHA: mppcf × 35.3 = million particles per cubic metre = particles per cubic centimetre

ACGIH, American Conference of Governmental and Industrial Hygienists; mppcf, millions of particles per cubic foot; NIOSH, National Institute for Occupational Safety and Health; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration; STEL, short-term exposure limit; TLV, threshold limit value; TWA, 8-hour time-weighted average; USA, United States of America.

[a] Data from GESTIS International Limit Values database (IFA, 2024).

[b] Data from IMA Europe (2022).

[c] The value for this particulate matter containing no asbestos and < 1% crystalline silica.

[d] Should not exceed 2 mg/m³ respirable particulate mass.

[e] OEL (mg/m³): 4 mg/m³ (total particulate matter), 1 mg/m³ (respirable particulate matter) (The Japan Society for Occupational Health, 2024).

(fibrous) was also applied to tremolite at the same time. In 1983, ACGIH set an OEL of 2 mg/m³ for talc (not containing asbestos) (Drechsel et al., 2018).

The US Bureau of Mines (BOM) adopted the OEL published by ACGIH, i.e. 20 mppcf, and began to address the problem of the mineralogical characterization of talc and associated minerals. By the end of 1977, the BOM and its associated regulatory arms, the Mining Enforcement and Safety Administration (MESA) and the Mine Safety and Health Administration (MSHA) had concluded that "talc containing non-asbestiform minerals" was not subject to regulation under the asbestos standard. The BOM (and associated arms) OEL for talc has remained at 20 mppcf since 1971 (Drechsel et al., 2018).

1.5.2 Food and water

Talc is an authorized food additive in the European Union (identified by the reference number E553b). It is mainly used in fine powdered form as an anticaking agent to prevent clumping of other ingredients. [The Working Group noted that there was very little information available concerning permitted levels in food and water or acceptable daily intakes.] A review in 1991 by the European Scientific Committee for Food, a subgroup of EFSA, concluded that for silicon dioxide and silicates (including talc, E553b), a group acceptable daily intake (ADI) was "not specified" (Scientific Committee for Food, 1991). However, more recent evidence suggested that this assumption may not be valid and that, on the basis of the evidence currently available, there was no rationale for a group ADI for silicates (including talc, E553b) and silicon dioxide (Younes et al., 2018). As described above, silicate-based food

additives (E552–553) are authorized in 28 food categories, including FC 0, meaning that they are permitted in all categories of food except foods for infants and young children. The EFSA Panel concluded that the absorption of silicates and talc was very low, and there was no indication for genotoxicity or developmental toxicity for talc (Younes et al., 2018).

There are currently no published limits for talc in drinking-water for the European Union (European Commission, 2024a), the USA (US EPA, 2024), or the UK (Drinking-water Inspectorate, 2024).

1.5.3 Consumer products and pharmaceuticals

The USP and European Pharmacopoeia specify criteria for the use of talc in pharmaceutical preparations. These are summarized in Table 1.17.

The use of cosmetic talc in the European Union is regulated by the EU Cosmetics Regulation (No. 1223/2009; European Commission, 2009), which, like its predecessor, the EU Cosmetics Directive (76/768/EEC), requires that "a cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use" (European Commission, 2009). In the UK, talc specifications for cosmetic use are defined by the CTPA. These criteria are given in Table 1.18.

The CTPA also gives guidance on the microbial population limits for cosmetic talc, namely, no more than 100 colony forming units per gram or millilitre (cfu/g or cfu/mL) for products intended specifically for use in the eye area or for use on babies, and no more than 1000 cfu/g (or cfu/mL) for products for general use. [The Working Group noted that standards for the purity and asbestos content of cosmetic and pharmaceutical talc are set by industry associations and are not necessarily legally enforceable. However, more generally, some countries have banned the sale of products containing asbestos, although the enforcement of this varies.]

1.6 Quality of exposure assessment in key epidemiological studies of cancer and mechanistic studies in humans

1.6.1 Quality of exposure assessment in key epidemiological studies of cancer

For each key study on cancer in humans, the reviews and critiques undertaken in relation to different aspects of exposure assessment are tabulated in Tables S1.19 and S1.20 (Annex 1, Supplementary material for Section 1, available from: https://publications.iarc.who.int/646), and are summarized in the following sections.

(a) Occupational exposure assessment

The Working Group undertook a critical appraisal of the exposure assessment methods used in 19 of the studies of cancer in humans. These included 17 industry-based cohort studies: six on mining and milling workers (Fu and Zhang, 1992; Honda et al., 2002; Wild et al., 2002; Wergeland et al., 2017; Fordyce et al., 2019; Ciocan et al., 2022), five on rubber workers (Monson and Fine, 1978; Blum et al., 1979; Zhang et al., 1989; Li and Yu, 1999; Straif et al., 2000); two on the same cohort of pulp and paper workers (Langseth and Andersen, 1999; Langseth and Kjaerheim, 2004) and a large international pooled cohort of pulp and paper workers (Boffetta and Colin, 2001); and one study each on pottery workers (Thomas and Stewart, 1987), printers (Bulbulyan et al., 1999), and fibreglass workers (Chiazze et al., 1993). There were two population-based case–control studies focused on occupational exposures, one on lung cancer (Ramanakumar et al., 2008) and the other on ovarian cancer (Leung et al., 2023).

Critical to this appraisal was whether the purity of the talc was described or assessed.

Table 1.17 Acceptance criteria for pharmaceutical talc, as specified by the US Pharmacopeia and European Pharmacopoeia

Criteria	United States Pharmacopeia Formulary[a]	European Pharmacopoeia[b]
Identification/ purity	FTIR; minimum, 98%	Infrared absorption spectrophotometry
Particle size	NMT 3% of particles > 75 µm in diameter	
Determination of absence of asbestos	Analysis by either FTIR or XRD If amphibole or serpentine minerals are detected, further analysis by optical microscopy	Analysis by either FTIR or XRD If amphibole or serpentine minerals are detected, further analysis by optical microscopy
Water solubility	NMT 0.1%	NMT 0.2%
Acid-insoluble substances	NMT 0.5%	NMT 1.0%
Loss on ignition	NMT 7.0%	NMT 7.0%
Magnesium	17–19.5%	17–19.5%
Iron	NMT 0.25%	NMT 0.25%
Lead	NMT 10 ppm	NMT 10 ppm
Calcium	NMT 0.9%	NMT 0.9%
Aluminium	NMT 2.0%	NMT 2.0%
Microbiology – topical	Aerobic microbial count, NMT 100 cfu/g Moulds and yeasts, NMT 50 cfu/g	NMT 10^2 bacteria and fungi per gram
Microbiology – oral	Aerobic microbial count, NMT 1000 cfu/g Moulds and yeasts, NMT 100 cfu/g	NMT 10^3 bacteria per gram (TVC, oral administration) NMT 10^2 fungi per gram (TVC, oral administration)

cfu/g, colony forming unit per gram; FTIR, Fourier transform infrared spectroscopy; NMT, not more than; ppm, parts per million; TVC, total viable count; US, United States; XRD, X-ray diffraction.

[a] United States Pharmacopeial Convention (2011).

[b] Council of Europe (2024).

Unlike the previous evaluation of talc by the *IARC Monographs*, the present monograph is focused on talc that is not contaminated with asbestos. This is challenging because in most of the studies there was some level of contamination and a level of uncertainty. The exception was studies on mining and milling operations, for which the source of the talc was clearly defined (on the basis of the mineralogical characteristics of the talc deposits) and indicated that in, some of these operations, the talc was probably pure. It is more challenging in the secondary, or talc-user, industries where the characteristics are more rarely described. Closely related is the assessment and control for the impact of potentially confounding exposures. In mining and milling, in addition to asbestos contamination, such exposures may include crystalline silica and diesel engine exhaust (both classified by IARC as *carcinogenic to humans*, Group 1), and in other industries, such as rubber and pulp and paper, there are potential exposures to a variety of carcinogens.

In appraising the quality of the exposure assessment of occupational studies and their relevance to the present evaluation, there were several important criteria to consider. First, was exposure to talc directly assessed? Only in the population-based case–control studies was individual exposure estimated on the basis of extensive interviews of study participants combined with expert assessment (Ramanakumar et al., 2008; Leung et al., 2023). In occupational cohort studies, in particular, exposure assessment was rarely made on an individual basis. Instead, detailed work histories were used to identify

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Table 1.18 Criteria for the CTPA cosmetic talc specification[a]

Criteria	Requirement	Method
Macroscopic appearance	A powder free from visible extraneous matter	Not specified
Microscopic appearance	Cosmetic talc is composed predominantly of translucent, laminar, irregular but substantially isodiametric particles not normally exceeding 60 µm in maximum dimension	Not specified
Colour	White or "off-white"; shade criteria to be agreed between buyer and supplier	Not specified
Odour	Virtually odourless	Not specified
Texture and slip	Free from gritty particles by palpation	Not specified
Sieve test[b]	100% passes through a BSS 100 mesh sieve and 98% minimum through a BSS 200 mesh sieve	CTPA Method 1
Bulk density	Must meet buyer's requirements	
Loss on drying	Loses not more than 0.6% when dried at 105 °C to constant mass	CTPA Method 2
Loss on ignition	5% maximum	CTPA Method 3
Acid-soluble matter	6% maximum; there must be no odour of H_2S	CTPA Method 4
Iron	Must meet buyer's requirements	Not specified
Identification	By X-ray diffractometry	CTPA Method 5
Amphibole minerals	Not detected by X-ray diffraction	CTPA Method 6, or other method of equivalent accuracy and sensitivity[c]
	Not detected by polarized light and dispersion staining microscopy	CTPA Method 7, or other method of equivalent accuracy and sensitivity
Ethylene oxide residues	No residues harmful to health	CTPA Method 8

BSS, British standard sieve; CTPA, Cosmetic, Toiletry and Perfumery Association Limited.

[a] In addition to meeting the criteria of this specification, cosmetic manufacturers also usually choose to conform to the physical, chemical, and microbiological criteria of the European Pharmacopoeia (Ph. Eur.) or United States Pharmacopeia (USP).

[b] Optional. Deviations from this specification are acceptable if agreed between the customer and the supplier. Source: Guide to Cosmetic Talc; CTPA (2019).

[c] No information on limit of detection.

exposed groups, for example using job titles. An important concept to consider is that of homogeneous exposure groups, which is fundamental to occupational exposure assessment. The goal is to identify groups that are similar in probability, level, and frequency of exposure, as well as similar in exposure to other chemicals. Levels of exposures within each of the cohorts reviewed are likely to be highly variable. However, prevalence of exposure in the population can also vary greatly, ranging from very high in mining and milling operations to relatively low in in industries such as pulp and paper. Thus, when an assumption is made that an entire industry is exposed, substantial misclassification of exposure can occur. When assumptions are made regarding exposure in departments or other broad groups, the potential for substantial misclassification remains, depending on the validity of the assumption.

Another important criterion is the ability to assess whether there is an exposure–response relation. This criterion requires a complete work history, either at the facility under investigation for cohort studies or a lifetime work history for case–control studies. The quality of even the best exposure assessment methods can be affected by the completeness and detail of the work histories and whether they were collected without knowledge of the outcome. The most

basic approach is to use duration of employment as a surrogate for exposure. If exposure in the population is heterogeneous, this can also lead to substantial misclassification. In the studies of lowest quality, from the point of view of exposure assessment, talc was not assessed specifically but was simply noted as one of the potential exposures, and it was assumed that the entire population was exposed. The assumption of some level of exposure in talc mining and milling cohorts may be valid. However, it is very problematic in industries with low prevalence of exposure and where other workplace carcinogens are present, in which case duration of employment or even duration of exposure may be poor surrogates.

Better approaches to assessing exposure–response relations make use of expert assessment to assign levels of exposure. The quality of such assessments can vary greatly according to the expertise of the assessors and their knowledge of local working conditions. Ideally, exposure assessments should be based, at least in part, on measurement data. This can be challenging for talc, as is true for most other occupational exposures, because historical measurements are often not available. In addition, exposure levels in many workplaces have changed substantially over time, and it is important that these changes be taken into account. These more advanced approaches generally use a job-exposure matrix (JEM) to assign level of exposure on the basis of job (based on occupation, department, or a combination to define a homogeneous exposure group) and time period. The best cohort exposure assessments were conducted using JEMs or department-exposure matrices developed specifically for those workplaces (Straif et al., 2000; Boffetta and Colin, 2001; Honda et al., 2002; Wild et al., 2002).

[A challenge in interpreting even the best exposure assessments is that almost all measurements reported do not reflect talc levels but rather dust levels, which may include talc, asbestos, quartz, and other substances present in the environment. This means that any assessment by talc exposure level is likely to have some misclassification in the exposure categories.]

(i) Cohort studies of talc miners and millers

Honda et al. (2002) studied talc miners and millers working on the Gouverneur District deposit, upstate New York, USA, who were employed for ≥ 1 day between 1948 and 1989. Detailed work histories were collected through employer and tax records. Non-asbestiform amphibole in ore was mentioned by the authors, but there was no discussion of other contaminants or exposures at the facility. [The Working Group noted that the Gouverneur District deposit in upstate New York is known to be contaminated with both anthophyllite asbestos and tremolite asbestos, as well as crystalline silica (see Section 1.2, Table 1.1).] A total of 1322 historical measurements of exposure to dust and fibres collected using a variety of sampling and analytical methods were identified but were deemed inadequate for exposure assessment (for exposure levels, see Section 1.4.2, Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646). A JEM for respirable dust was developed through using the assessments of a panel of seven long-term employees; the exposure scale of 0–10 was calibrated to measured exposure levels from dust surveys. Exposure was estimated for each year for five work areas on the basis of similarity of tasks, processes, engineering controls (e.g. ventilation), and exposures to airborne talc (Oestenstad et al., 2002). Time periods of uniform exposure were identified to assign exposure on the basis of work area and calendar period. Inter-rater agreement was assessed and found to be poor, although there was better agreement on trends. The investigators conducted their own exposure measurement survey in 1991 and used the results to adjust and validate the historical exposure estimates (for exposure levels, see Section 1.4.2,

Table S1.14). Results were presented for miners, millers, minimal exposure, no exposure, and unknown exposure, and by length of employment, as well as by cumulative exposure (mg/m^3-days). Exposure to crystalline silica was not assessed. [The Working Group noted that this was a high-quality, quantitative exposure assessment. The major limitations were the lack of consistently gathered historical measurement data and poor inter-rater agreement. The major strengths were the investigators' efforts to assess and mitigate these limitations and the effective use of their own exposure measurement survey. However, the talc at this site is contaminated with asbestos.]

Wild et al. (2002) studied mining and milling workers employed for ≥ 1 year at one site in France using talc from the Pyrenees mountains, in 1945–1994, and at three smaller sites in Austria using talc from the Styrian Alps, in 1972–1995. In Austria, detailed work histories were abstracted from employer records, whereas in France, paper files from a previous mortality study and files from the company's occupational physician in combination with interviews with former workers were used. Exposure was assessed using work histories in combination with a JEM developed by occupational physicians on the basis of some stationary measurements available since 1954 (Leophonte and Didier, 1990) and systematic personal measurements of respirable dust available since 1986 at the French site (Wild, 2000), and more limited measurement data from the Austrian sites in 1988–1992 (for exposure levels, see Section 1.4.2(c), and Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646). Workers were assigned to one of four quantitative groups based on job and mill: no exposure, < 5 mg/m^3, 5–30 mg/m^3, and ≥ 30 mg/m^3. In a nested case–control study, cumulative exposure was assigned for the three exposed groups using 2.5 mg/m^3, 10 mg/m^3, and 40 mg/m^3 multiplied by duration in exposed jobs. The authors stated that there was no asbestos contamination "to their knowledge" and that the end-product contained < 1% quartz, although deposits in some parts of the mine could contain quartz at up to 2–3%. [The Working Group noted that no asbestos has been reported in deposits in the French Pyrenees or in the Styria deposits in Austria (see Section 1.2, Table 1.1)]. Exposure to respirable crystalline silica was assessed in a similar manner as for talc but was classified as exposed or not. In the lung cancer case–control study, results were presented by cumulative exposure (mg/m^3-years). [The Working Group noted that this was a high-quality, quantitative exposure assessment performed by an occupational physician who worked for the company. An additional strength was that exposure to crystalline silica was also assessed. The major limitation was the lack of measurement data before the late 1980s for the Austrian sites.]

Wergeland and colleagues (2017) studied Norwegian miners and millers exposed to talc described as "high-purity talc" but that contained trace amounts of both tremolite asbestos and anthophyllite asbestos, as well as quartz. Optical microscopic analysis identified levels of 0.2–0.9 fibres/mL, and electron microscopy identified tremolite asbestos, anthophyllite asbestos, and talc (Wergeland et al., 1990). [The Working Group noted that the optical microscopic analytical technique used in this study did not differentiate between talc fibres and asbestos.] Although some measurement data were reported for 1980–1982 (for exposure levels, see Section 1.4.2, Table S1.13, Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646), they were not used for the exposure assessment. Work histories from company payroll lists, union records, and a registry of silica-exposed workers were used together with individual assignment of dust exposure intensity (Wergeland et al., 1990). For talc exposure, jobs

were classified as having low, medium, or high exposure, or unexposed, using expert assessment by the local trade union leader for mine jobs and by two long-term employees for mill jobs. For specific cancers, results were presented for miners, millers, and combined, and by duration of employment. Analyses by exposure intensity were presented only for non-malignant diseases. Exposure to crystalline silica was not assessed. [The Working Group noted that this was a moderate-quality exposure assessment based on expert assessment. However, since only duration of employment, with the potential for substantial misclassification, was used for cancer outcomes, the Working Group considered that the exposure assessment was of limited quality.]

Ciocan and colleagues (2022) studied talc miners and millers employed for ≥ 1 month in Val Chisone, Italy. No asbestos fibres were detected in the bulk samples collected, according to SEM analysis. [The Working Group noted that no asbestos has been reported in the Val Chisone deposits (see Section 1.2, Table 1.1).] The authors reported exposure to quartz among the miners, but not the millers. [It was unclear why the millers would not have exposure to silica, and exposure to crystalline silica was not further assessed.] The authors also reported that levels of gases associated with diesel exhaust were below the TLVs, PAHs were close to 1 ng/m^3, and radon was < 300 Bq/m^3. Results were presented stratified by miners and millers, as well as by duration of employment, but there was no specific assessment of talc exposure. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, and duration of employment may be a poor surrogate for level of exposure. Strengths of this study were the analysis of talc samples by SEM and the evaluation of potentially confounding exposures.]

Fordyce et al. (2019) studied talc miners and millers from Vermont, USA, who had worked for ≥ 1 year between 1930 and 1983. The talc was reported to be free of asbestiform minerals and significant amounts of silica. [The Working Group noted that Vermont (Blackwall talc) may be contaminated with asbestos (actinolite, tremolite, anthophyllite, and chrysotile) and that quartz was present (see Section 1.2, Table 1.1).] Results were presented stratified by miners and millers separately, as well as by duration of employment for both studies, but there was no specific assessment of talc or crystalline silica exposure. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, and duration of employment may be a poor surrogate for level of exposure.]

Fu and Zhang (1992) report on a study of miners and millers from the Haichen talc mine in China. Workers who had been employed for ≥ 1 year as of January 1974, according to the wage list of the mine, were followed until 1988. Workers with previous employment in the chemical industry were excluded. Job histories were from company records (information extracted from Chang et al., 2017, which reported on this study within their meta-analysis). The authors stated that dust exposure history was based on health records, pneumoconiosis census records, company files, and interviews. Workers from an iron and steel company (1971–1985) were used as a comparison population. Stratified results were presented for all workers, miners, millers, those with or without pneumoconiosis (no further details provided), and by years since first employment. [The Working Group noted that this was a limited exposure assessment. The authors stated that many sources of data were consulted, and interviews were conducted, but it was unclear how these were used, and, without further details, it was not possible to assess the quality of the exposure assessment. Given that these were talc miners and millers, it may be safe to assume that they were exposed, but no levels were reported. Approximately 12% were reported to have some history of pneumoconiosis (not specified in the translation available to

the Working Group), which may indicate high levels of exposure to crystalline silica or talc. The Working Group noted that chrysotile asbestos was probably present, tremolite was possibly present, and that quartz was present in the Chinese deposits (see Section 1.2, Table 1.1).]

(ii) Cohort studies of rubber workers

Talc is generally used as an antisticking agent (detackifier) in tyre-related departments of the rubber industry.

Blum and colleagues (1979) studied rubber workers from two companies in the USA, either active or employed as of 1 January 1964; dates of employment and characteristics of the talc were not stated. Detailed work histories were used, but the source was not stated. Talc was used as an antisticking agent. The investigators stated that they were still trying to determine whether the talc from company A contained "asbestiform material". Job titles were classified into 20 groups, and three environmental scientists independently rated the groups for high, moderate, low, or no exposure to talc, PAHs, nitrosamines, and carbon black. A nested case–control study on stomach cancer was conducted using analyses by occupational title group and by high and/or moderate exposure to talc for > 2 years. [The Working Group noted that this may be a good semiquantitative assessment of exposure based on expert assessment. However, it was unclear how knowledgeable the environmental scientists were regarding the exposure conditions at the facilities being studied.]

Straif et al. (2000) studied cancer in a large cohort of factory workers in the German rubber industry, with a focus on nitrosamines. The study population was 8933 workers, from five plants, who were hired on or after 1950 and were either still employed or retired as of 1981. Individual work histories were reconstructed using employer records. The exposure assessment was conducted by external experts and industrial hygienists from the participating rubber factories. Exposures to talc, nitrosamines, asbestos, and carbon black were assessed. The authors mentioned that the talc may have been contaminated with asbestos. There were three categories for exposure to talc: (i) low: wet application and no exposure (59% of cohort); (ii) medium: moderate use as an anti-tacking material (22%); and (iii) high: use as a filler and heavy use as an anti-tacking material (13%). They were unable to assess 6% of the cohort. Two exposure categorizations were developed. In the first, high exposure included workers employed for ≥ 1 year in areas with high exposure, and the low-exposure category was assigned to workers who had been employed for < 1 year in jobs with medium or high exposure levels. In the second, the cut-point for high exposure was > 10 years and for low exposure was < 0.5 years. The remaining workers in both exposure categorizations were included in the medium exposure category. Lagging exposures by 10 years was used to account for latency. [The Working Group noted that this was a high-quality, semiquantitative exposure assessment based on expert assessment. Although talc and asbestos were assessed separately, they were combined for the multivariate analyses, and consequently it was not possible to assess an independent effect of talc. The major limitation was the lack of historical measurement data before 1979 (exposure was assessed for the period 1950–1981).]

Li and Yu (1999) studied stomach cancer in workers at a rubber-manufacturing plant in Shanghai, China. From 1973 to 1995, 36 cases of stomach cancer were identified, and a subcohort of 175 individuals (also referred to as controls by the authors), approximately 12% of the full cohort of 1598 workers, was randomly selected. The exposure assessment was not presented in detail. Work history was obtained from company records and a questionnaire. Jobs were coded into four groups: (i) tyre curing and vulcanizing; (ii) compounding, weighing, mixing, reforming, washing, and milling; (iii) inner tyre

tube production; and (iv) general service. Years of employment within these groups were examined. Talc exposure was not assessed, but the authors stated that talc dust levels were highest in the inner-tube department. There was no discussion of the characteristics of the talc used at the facility. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, and job group may be a poor surrogate for level of exposure.]

Zhang et al. (1989) assessed the risk of cancer in a cohort of rubber workers in Shanghai, China, using work histories obtained from records of a screening programme in 1972. Dates of employment and characteristics of the talc were not identified. Five job groups were analysed: curing; inner-tube of tyre; raw material handling, weighing, mixing, extruding and calendaring; component assembly and building; and general services. No assessment of talc exposure was performed, but the inner-tube workshop, one of the five subgroups examined, used talc to dust the inner tyre tube. [The Working Group noted that the exposure assessment was limited. Exposure to talc was not specifically assessed, and the talc may have been contaminated with asbestos. Job group may be a poor surrogate for level of exposure. Furthermore, it was not clear whether the grouping was based on ever performing these tasks, the longest duration, or the time when the records were developed.]

Monson and Fine (1978) investigated mortality among 13 570 unionized White male rubber workers employed by a company in Ohio, USA. The study population included all workers employed in or after 1933 and for ≥ 5 years. The company's facilities included a tyre and rubber-products plant and a smaller plant producing chemicals used by the rubber plant. A limited work history was assembled using data from both company and union records, including first employment and termination dates, and department (of more than 10) in which the individuals worked. There was no assessment of exposure to talc, or other hazardous substances. Results were presented by ever or usual department, but there was mention of talc use to "dust some types of tires" in the discussion. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, department may be a poor surrogate for level of exposure, and the work history may not be complete.]

(iii) Other industry-based cohort studies

Thomas and Stewart (1987) studied a cohort of pottery workers employed for ≥ 1 year between 1939 and 1966 at three plants owned by a company producing ceramic plumbing fixtures in the USA. Nonfibrous Montana steatite talc was used in some tasks since 1955, and "tremolitic (fibrous) talc" was used in some glazes before 1976. [The Working Group noted that fibrous talc is often contaminated with other fibrous minerals and that some Montana talc deposits may be contaminated with tremolite asbestos (see Section 1.2, Table 1.1).] Detailed work histories from personnel records were used, and each job title-department combination was classified by the study industrial hygienist, after a walk-through survey of the plants, for potential exposure to crystalline silica, and fibrous and nonfibrous talc. A JEM based on job title and department was developed for silica (none, low, or high) with workers who were highly exposed to silica being separated into those with "no talc", "nonfibrous talc", and "fibrous talc" exposure. The assessment was performed without knowledge of the vital status of study participants. Talc exposure occurred only in combination with high exposure to crystalline silica. Results were presented stratified by silica and talc exposure category and by duration of exposure to nonfibrous talc. [The Working Group noted that this was a moderate-quality, semiquantitative assessment of exposure based on expert assessment for both fibrous and nonfibrous talc, but that potential contamination by asbestos was not reported.]

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Chiazze et al. (1993) reported on a nested case–control study on malignant and non-malignant respiratory disease among a cohort of fibreglass-manufacturing workers employed for ≥ 1 year at a large plant in Ohio, USA, between 1940 and 1962. Work histories were collected through in-person and telephone interviews using a questionnaire with both participants and proxies. In addition, a historical reconstruction of engineering processes from 1938 to 1987 was performed by four company engineers, and a list of exposures associated with each process was developed. An exposure assessment committee, consisting of current and former employees who were knowledgeable regarding industrial hygiene and current and historical plant processes, developed quantitative estimates of potential exposure to talc, asbestos, formaldehyde, respirable silica, respirable fibres, asphalt fume, and total dust for each process. The committee assigned each process to one of four ranges of potential exposure specific to calendar time in order to estimate cumulative exposure. For talc, these were 0.001–0.009, 0.01–0.09, 0.1–0.99, and > 0.99 fibres/mL. [The Working Group noted that talc is generally measured as particulate in milligrams per cubic metre and that it was not clear what was being measured.] Work histories were linked to process codes, blind to case–control status. [The Working Group noted that this was a moderate-quality, semiquantitative assessment of exposure based on expert assessment. However, it was unclear how quantitative exposure estimates in fibres per millilitre were estimated without industrial hygiene records before 1970.]

Langseth and Andersen (1999) examined the incidence of cancer among 4247 women employed for ≥ 1 year between 1920 and 1993 in the pulp and paper industry in Norway. Work histories (departments, job titles and date of start and end of employment in specific work activities) were obtained from the personnel files of each mill. Talc exposure was mentioned for the paper departments, where it was used as a filler, but exposure to talc was not directly assessed, nor were department-based results presented. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, and using overall duration could result in substantial misclassification.]

Langseth and Kjaerheim (2004) conducted a nested case–control study on ovarian cancer within the same cohort, with the follow-up period extended to 1999. Forty-six cases of ovarian cancer and 179 controls were selected. Detailed work histories were used, and a questionnaire, including questions on production processes, use of specific agents, and changes over the years, was completed by industrial hygienists and senior employees at each mill. Data from Norwegian mills were extracted from PAPDEM (pulp and paper department-exposure matrix, see Kauppinen et al., 2002, below), which was created as part of an international study of pulp and paper workers coordinated by IARC. Data from the questionnaire and PAPDEM were used to assess ever versus never exposure to talc, asbestos, and total dust. [The Working Group noted that this was a high-quality, semi-quantitative assessment of exposure based on expert assessment by the international IARC-coordinated study team. The major limitation of this assessment was the use of departments, because of the lack of job title information for all mills.]

In a report that only became publicly available in 2023, Boffetta and Colin (2001) described an international study that included 103 773 pulp and paper workers employed for ≥ 1 year from 76 facilities in 15 countries and was coordinated by IARC. The exposure assessment methods were described in detail by Kauppinen et al. (2002). Briefly, more than 31 000 measurements were identified, mostly from the 1980s and 1990s, for 246 chemical agents, including talc and asbestos, from 13 of the countries. Detailed company questionnaires were collected on the use and

occurrence of chemical agents and working conditions. The assessments related to mill, department, and time period were also based on the judgement of an international group of experts with knowledge of the pulp, paper, and paper products industry. A department-exposure matrix was developed because work histories were generally limited to the department level. Both prevalence (< 5%, 5–50%, 51–95%, > 95%) and level of exposure were estimated. For talc, the levels of exposure were low (0.2–0.6 mg/m^3), medium (0.6–2 mg/m^3), and high (> 2 mg/m^3). [The Working Group noted that this was a high-quality quantitative assessment of exposure based on expert assessment by an experienced international team. The major limitation of this assessment was the use of departments because of the lack of job title information for all mills; this would result in nondifferential misclassification, with bias towards the null.]

Bulbulyan et al. (1999) studied cancer mortality among women in two printing plants in the Russian Federation. Cohort members were current female employees who had worked for ≥ 2 years as of 1978. Work histories were abstracted from personnel records, and jobs were classified into four groups: compositors, press operators, bookbinders, and other (jobs thought generally to be without hazardous exposures). Russian paper contains talc as a filler, so printing workers (press operators and particularly book binders) probably had exposure to talc, which the authors indicated may have been contaminated with asbestos. Other potential exposure to known and suspected carcinogens included lead, benzene, benzo[*a*]pyrene and other PAHs, benzidine-based dyes, and carbon black. No specific assessment of talc exposure was performed. There was no discussion of the characteristics of the talc used at the facilities outside of potential asbestos contamination. Analyses were conducted by job group. [The Working Group noted that this was a limited exposure assessment. Exposure to talc was not specifically assessed, and job group may be a poor surrogate for level of exposure.]

(iv) Occupational case–control studies

Ramanakumar et al. (2008) pooled data from two population-based case–control studies conducted in Montreal, Canada, to examine the occupational risks of lung cancer associated with occupational exposure to industrial and cosmetic talc, as well as carbon black and titanium dioxide. The two case–control studies (1979–1986 and 1996–2001) were conducted by the same group of investigators using the same exposure assessment approach. For each job in the lifetime work history, a semi-structured questionnaire was used to collect information on the company, its products, the worksite, work tasks, protective equipment, and maintenance. A team of chemists and industrial hygienists assessed and classified potential exposure to 294 substances according to their confidence that the exposure occurred (possible, probable, definite), the frequency during a normal workweek (< 5%, 5–30%, > 30%), and the relative level (low, medium, high). [The Working Group noted that this was a high-quality, semiquantitative exposure assessment of industrial and of cosmetic talc, separately.]

Leung et al. (2023) investigated the occupational risks for ovarian cancer in the PRevention of OVArian Cancer in Quebec (PROVAQ) study, a population-based case–control study conducted in Montreal, Canada (2010–2016). Lifetime occupational histories for jobs held for ≥ 6 months were collected during in-person interviews by trained interviewers, and occupations and industries were coded by an industrial hygienist. Exposure to 258 agents was assessed using the Canadian job-exposure matrix (CANJEM), which was developed in Montreal and based on the case-by-case assessments used in previous case–control studies by the same research group as Ramanakumar et al. (2008) (Siemiatycki and Lavoué, 2018). CANJEM assigns probability,

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frequency (hours per week), and concentration of exposure (low, medium, and high assigned values of 1, 5, and 25 for calculation of cumulative exposure). Ever-exposed was assigned as > 50% probability of exposure for ≥ 2 years. Results were presented for the 29 most prevalent agents (≥ 15 ever-exposed cases or 15 ever-exposed controls), including cosmetic talc, and stratified by duration of exposure, and cumulative exposure (duration × concentration/25 × frequency/40). Industrial talc was assessed separately from cosmetic talc, but results were not presented because it was not one of the prevalent exposures among women. [The Working Group noted that this was a high-quality, semiquantitative assessment.]

(b) Non-occupational studies

Since the 1980s, many non-occupational studies have evaluated associations between talc powder use and various cancer outcomes, particularly ovarian cancer, after early reports from case–control studies on an association between talc-based body powder application to the genital area and ovarian cancer risk (Cramer et al., 1982; Wentzensen and O'Brien, 2021). Most non-occupational studies evaluated application of body powder to the genital area. Several studies additionally evaluated use of powder on other areas of the body, primarily as a comparison to evaluate the specificity of genital exposure underlying the observed associations with ovarian cancer.

With one exception (Chang et al., 2019), exposure assessment in non-occupational studies was based on self-reports, either questionnaires or interviews. Independent of study type, self-reported exposure assessment was retrospective from the time of the survey or interview. Depending on the study type and age at survey or interview, retrospective exposure assessment may cover a long period in an individual's lifetime. In case–control studies, only a single exposure assessment was conducted around the time of diagnosis. In cohort studies, repeated talc exposure assessments were possible, but rarely conducted.

Some variables that are important for the exposure assessment of talc in non-occupational observational studies are listed in Table 1.21. The limitations of these studies with respect to exposure assessment are discussed in more detail below, including uncertainty about which product was used, as well as risk of exposure misclassification with respect to dose and duration.

Chang et al. (2019) investigated oral intake of talc contained in products used in traditional Chinese medicine products and the association with gastric cancer. In that study, the assessment of talc exposure was based on centralized prescription data, which are much less affected by exposure misclassification than are the retrospective self-reports in the other studies.

Type of product

A critical challenge in non-occupational studies is the lack of information about specific products used by the participants (see also Section 1.4.1(e)). Many studies included a range of terms in their exposure assessment surveys and interviews, including questions about body powder, talcum powder, deodorizing powder, and cornstarch. Few studies asked about specific brand names of body powders or other personal hygiene products. Examples of questions were whether participants "ever commonly used talcum, baby powder or deodorizing powder", whether "talcum powder was applied to a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area", or whether participants "had ever used powder on their 'private parts (genital areas)'" (O'Brien et al., 2020).

Historically, most body powder products included talc, but talc-free alternatives such as cornstarch have existed for decades (e.g. cornstarch baby powder was introduced in the USA

Table 1.21 Relevant variables for exposure assessment in non-occupational observational studies

Variable	Relevance for exposure assessment
Talc/body powder product	Information about talc content and concentration versus other ingredients of body powder, including possible asbestos contamination: observed associations may be related to other powder ingredients, lack of observed associations may be related to other powder ingredients.
Frequency and duration of use	Estimate cumulative exposure to evaluate dose–response relations.
Route of application (perineal versus non-perineal)	Estimate specificity of exposure: association with perineal application versus upper body application may indicate a specific effect of talc/body powder on the tissue at risk.
Exposure prevalence	Evaluate exposure differences across studies/populations, identify possible exposure misclassification.
Minimum use definition	May affect exposure prevalence.
Calendar period of talc use	May provide information about specific talc products that were on the market, particularly with respect to potential asbestos contamination and other ingredients such as cornstarch.
Calendar period of self-report	Self-reported exposure assessment may be affected by awareness of possible associations between talc use and cancer risk.
Age at self-report	Individuals at older age may have more difficulty remembering distant past.
Assessment in relation to disease status	Exposure assessment at time of disease may lead to differential misclassification.

in 1980). [In the following text, the Working Group uses the term "talc or body powder" to include all these products in studies that were not exclusively focusing on talc-based body powders. It can be highlighted that talc is both the most frequent and the main component of these products. Whenever studies provided more detail on the products studied, the terms "talc powder" or "body powder" were used. Please see also Table S1.20 for details on exposures assessed (Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/646).] The presence and concentration of talc can vary from brand to brand and within brands over time (Rosenblatt et al., 2011). Detailed use statistics for different powder products over time are not publicly available. Cramer et al. assessed use of specific talc products between 1992 and 2008 and reported a low (1.6%) proportion of use of products containing only cornstarch among those who reported use of body powders (Cramer et al., 2016). [This suggests that cornstarch powder use was low until relatively recently, when talc-based body powder was taken off the market in the USA.] Owing to the possible co-occurrence of talc with asbestos in talc mines, it is important to consider whether cosmetic talc products may be contaminated with asbestos (see Section 1.4.1(e)). Testing of talc products for asbestos was initiated in the 1960s and showed asbestos contamination of a subset of talc products. In the 1970s, 40% of tested products in the USA included "asbestiform minerals" (Rosner et al., 2019). Despite various attempts to regulate the purity of talc products in the USA, some talc products were found to be contaminated with asbestos fibres as recently as 2019 (see Section 1.4.1(e)). [Theoretically, identification of the specific body powder product used may allow talc-based products to be distinguished from non-talc-based products and could also help to estimate the likelihood of asbestos contamination; in practice, with few exceptions, these data were not available in non-occupational

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studies. Furthermore, talc products have not been systematically tested over time to sufficiently establish or rule out possible asbestos contamination.]

Challenges of retrospective exposure assessment

The retrospective self-assessment of body powder use and limited information on duration and dose (which is particularly difficult to estimate for powder application) pose additional challenges for exposure assessment. Different studies used different minimal exposure thresholds to define "any use" or "ever use", ranging from no minimum duration in most studies to requiring ≥ 1 year of use. Although a longer minimum duration of use can make the exposure assessment more specific for the exposed group, the effect of including short-term users as "never users" may increase or decrease the exposure contrast depending on whether there is an association with cancer risk in short-term users. A wide range of exposure prevalence was reported in different studies, ranging from 12% and 13% genital use of powder in controls and cases, respectively (Rosenblatt et al., 2011), up to 53% and 63% use of body powder in controls and cases, respectively (Schildkraut et al., 2016). [The Working Group noted that it is important to evaluate to what extent these differences represented true differences in exposure or were related to differences in exposure assessment, age of the population, or time period of the study. For example, Cramer et al. (2016) showed a decrease in reported powder use in more recent birth cohorts, see Table 1.15.] Rosenblatt et al. (1998) reported that smoking, alcohol use, and increased body mass index (BMI) were associated with higher talc use. Generally, a higher prevalence of talc and body powder use has been reported for African-American women than for White women in US-based studies (Kim et al., 2010; Wu et al., 2015; Schildkraut et al., 2016; Davis et al., 2021).

Exposure assessment in case–control studies

In case–control studies, exposure assessment is conducted at the time of diagnosis for cases and in a defined control population for non-cases. In theory, exposure assessment can capture lifetime exposure until the time of diagnosis. However, the exposure period can include several decades, and details about use over the entire lifetime may not be remembered accurately. An important concern is that recollection of prior use may differ by case–control status, with case participants being more likely to report use of talc powder than were control participants. It is possible that case participants were more likely to incorrectly report that they used talc powder. Raised awareness about a potential role of talc in ovarian cancer may have further contributed to this effect since 2009; some direct evidence came from a study conducted during that time period and in which reported use was higher after 2014, when news reports on court cases related to talc and ovarian cancer were widely publicized (Schildkraut et al., 2016; Trabert, 2016). This type of differential misclassification (also referred to as recall bias) could potentially lead to underestimation of use among controls and an increased association for the exposure. There were no studies in which self-reports were validated with a more objective metric of talc powder exposure.

Exposure assessment in cohort studies

In cohort studies, exposure assessment is typically performed before the outcome occurs and thus the results cannot be affected by differential misclassification related to disease status. However, in most cohort studies, the exposure assessment for talc or body powder was carried out a long time before the outcomes occurred and was not repeated, and in some studies participants were asked only about a limited past window of exposure (O'Brien et al., 2020). Therefore, many cohort studies may suffer from incomplete exposure assessment, which can lead to nondifferential exposure misclassification.

Furthermore, because of the broad scope of most cohort studies, the exposure assessment was often less detailed than that in case–control studies, and this may affect the ability to estimate duration and dose of talc or body powder exposure and limit the available information on specific products.

Assessment of dose and duration

There is a range of approaches to application of talc to the genital area, including direct application with the hands, application with sanitary napkins, underwear, or diaphragm, and use in conjunction with douching. None of these applications are standardized with respect to the amount of talc powder used, which may vary substantially between type of application and across individuals. In studies in which an attempt was made to estimate dose and duration, the exposure assessment usually focused on the number of applications per week multiplied by the entire exposure period to estimate "talc years" as an approximation of the total lifetime exposure to talc powder. However, the actual amount of talc powder to which participants were exposed to may vary substantially within these use categories.

(i) Non-occupational cohort studies

O'Brien et al. (2020, 2021a) conducted two studies, one on ovarian cancer and the other on uterine cancer, in the same pooled cohort, from four large US-based studies: NHS-I (enrolment, 1976), NHS-II (enrolment, 1989), the Sister Study (enrolment, 2003–2009), and WHI-OS (enrolment, 1993–1998). For all cohorts, powder use in the genital area was assessed in baseline questionnaires, but the wording of the questions varied considerably. For example, only the Sister Study was specific for talcum powder, and a broader definition of body powder was used in the other studies, which could contribute to exposure misclassification. In NHS-I, talc and body powder use was assessed in the 1982 questionnaire, which contained questions about "common" use of talcum, baby powder, or deodorizing powder to the perineal area or on sanitary napkins (Gertig et al., 2000; Karageorgi et al., 2010). Ever use (no minimum duration) and frequent use (use at least once per week) were assessed, but not duration of use. In NHS-II, talc or body powder use was assessed in the 2013 questionnaire. Ever and frequent use were defined as in the NHS-I assessment; additionally, long-term use (at least weekly for ≥ 20 years) was assessed (O'Brien et al., 2021a). In the WHI-OS, powder use was assessed in the baseline questionnaire, with questions about direct powder use and application of powder to a diaphragm or to sanitary napkins. There was no minimum duration for assessment of ever use. Frequent use was not assessed, and long-term use was defined as use for ≥ 20 years. In the Sister Study, use of talcum powder was assessed in the baseline questionnaire. Use was assessed for ages 10–13 years and in the 12 months before the baseline questionnaire was administered; use was not assessed for an extended period of time (between age 13 years and 1 year before enrolment). [This limited assessment could lead to underreporting of lifetime use; the Sister Study was at the low end of reported talc use, although similar to the contemporary NHS-II cohort.] Nothing has been reported directly from the studies about the presence of asbestiform fibres in talc products. Across all four cohort studies, the study period ranged from 1976 to 2017, and the period when study participants used talc powder probably ranged from the 1950s to the 2000s, suggesting that the products in the first half of the exposure period could have had a higher likelihood of asbestos contamination than had the products from the second half of the exposure period. To harmonize the responses, the study used ever, long-term (≥ 20 years), and frequent (≥ 1/week) use of powder in the genital area. In a secondary analysis, the ovarian cancer study focused on women without hysterectomy and tubal ligation at the time of enrolment, for whom direct

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exposure of the tissue at risk is more likely. [This is referred to as "patency" analysis, which could support an association mechanistically, under the assumption that talc products can reach the tissue at risk only when the reproductive tracts are open.]

Chang et al. (2019) conducted a study in a random sample of people in the National Health Insurance Research Database of Taiwan, China, in 2005. The exposure of interest was oral prescriptions for talc powder, in the form of Chinese herbal medicines. Although the presence of asbestos in medicinal talc has been prohibited in Taiwan since 2005, there was no information on how this was monitored and enforced. Use of talc was treated as a time-dependent variable, and cumulative talc exposure (in grams) was also evaluated. The researchers calculated cumulative exposure estimates of ≤ 6 g (9 774 552 person-years), 6–21 g (87 550 person-years) and > 21 g (47 004 person-years). [Since the exposure data were limited to prescription data, other potential sources of oral talc intake, such as over-the-counter herbal medicines or food products, could not be assessed. Furthermore, the role of other ingredients of herbal medicine products in these studies was not known. Although the study was not subject to reporting bias, the assessment of oral intake of talc was likely to be incomplete since the study captured only medications with a prescription in the insurance database].

(ii) Non-occupational population-based case–control studies

Terry et al. (2013) conducted a pooled case–control study of genital use of powder with data from the Ovarian Cancer Association Consortium (OCAC). There were six studies from the USA (Diseases of the Ovary and their Evaluation Study, DOV, cases diagnosed in 2002–2009; Hawaii Ovarian Cancer Study, HAW, cases diagnosed in 1993–2008; Hormones and Ovarian Cancer Prediction Study, HOP, cases diagnosed in 2003–2008; North Carolina Ovarian Cancer Study, NCO, cases diagnosed in 1999–2008; New England Case–Control Study of Ovarian Cancer, NEC, cases diagnosed in 1992–2008; and University of Southern California Study of Lifestyle and Women's Health, USC, cases diagnosed in 1993–1997), one study from Australia (Australian Cancer Study, AUS, cases diagnosed in 2002–2006), and one study from Canada (Southern Ontario Ovarian Cancer Study, SON, cases diagnosed in 1989–1992) that collected data on body powder use. The questions regarding genital use of powder varied greatly between studies. Harmonized variables were developed for various types of regular genital, perineal, or rectal use of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown; applied directly or indirectly), although the criteria varied from "ever use" (AUS) to "one year or longer" (DOV). None of the study questions were specific to talc or talcum powder only, and DOV and NEC did not use the words "talc" or "talcum" at all in their questionnaires. Other harmonized variables included duration and frequency of powder use, age at first powder use, use by sexual partners, and non-genital use. Lifetime number of powder applications was calculated by multiplying total months of use by frequency of use per month, for all direct and indirect genital application of powder for seven out of eight studies in which this information was collected (HOP excluded).

Phung et al. (2022) conducted a pooled ovarian cancer case–control study on "well-established" risk factors, also using data from the OCAC, that was focused on women with and without endometriosis. Seven studies from the USA: DOV, HAW, HOP, USC, and NEC (also used by Terry et al., 2013), CON (cases diagnosed in 1999–2003) and UCI (cases diagnosed in 1995–2005) (not in Terry et al., 2013) and one from Australia (AUS, also used by Terry et al., 2013) were included for the talc analyses. Assessment of exposure was not discussed in detail. Use was categorized as genital, non-genital, or never, although the

wording of the talc questions was not provided. Collection methods varied; in-person interviews were conducted for CON, DOV, HAW, HOP, NEC, and USC, and self-completed questionnaires for UCI and AUS.

Schildkraut et al. (2016) conducted a case–control study on ovarian cancer in African-American women (African-American Cancer Epidemiology Study, AACES, 2010–2015) that evaluated genital application of talc powder and other products such as cornstarch or deodorizing powders. Telephone interviews and a minimum period of 6 months of talc or body powder use were used to define ever use. The exposure prevalence in this study was one of the highest reported, with 53% users among the controls and 63% users among the cases. Importantly, the reporting of talc or body powder use among case participants with ovarian cancer increased after 2014, during a time of extensive press coverage of lawsuits related to use of talc products in patients with ovarian cancer. The results suggested that reporting of talc or powder use may change in response to news reports about concerns related to talc and ovarian cancer, possibly increasing differential misclassification.

Cramer et al. (2016) conducted a large case–control study on ovarian cancer in New England, USA, with three recruitment periods between 1992 and 2008, investigating perineal application of talc or body powder, including products like cornstarch. Personal interviews were used to explore an extensive range of risk factors for ovarian cancer and included a detailed assessment of talc or powder products, duration, and dose of use. The study reported perineal exposures to talc of 32% among cases and 27% among controls overall, and a reduction in use among more recent birth cohorts; this was one of the few studies that reported on talc exposure over time (see Fig. 1.4). [The Working Group noted that a strength of this study was the extensive exposure assessment in a large population over an extended time period. Since it is a case–control study, differential exposure misclassification cannot be excluded.]

Davis et al. (2021) conducted a pooled case–control study on genital use of powder, with data from the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium. This study included the AACES (2010–2015), the NCO (1999–2003), Los Angeles County Ovarian Cancer Study (LACOCS, 1998–2002), Cook County (Chicago) Case Study (CCCS, 1994–1998), and a nested case–control study within the WHI-OS (1994–2018). Standardized questionnaires were used for exposure assessment, either interviewer-administered or self-administered. Genital use of powder was defined as any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly, and the wording varied by study, with only three using the word "talc". Ever use and duration of genital use of powder was assessed in all studies, and frequency of use was assessed in four studies. Frequency of genital use of powder was categorized as no use, up to once per week, and more than once per week. Duration was categorized as none, < 20 years, and ≥ 20 years.

Neill et al. (2012) conducted a case–control study on endometrial cancer using data from the Australian National Endometrial Cancer Study (ANECS) for cases diagnosed in 2005–2007. Information was collected using standardized telephone interviews. Participants were asked if they had ever used any sort of powder or talc in the genital area and, if yes, how old they were when they first used talc, how often (average use over a year, daily, a few times per week, a few times per month, and less often), and how many years (never, 1–20, 21–40, 41–60, and 61–80 years). The questions were repeated for talc use on the upper body (including under arms, and on chest or abdomen).

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(c) Asbestos contamination of talc

The major cross-cutting issue, which has an impact on both the occupational and non-occupational studies in humans, was the known and potential contamination of talc with asbestos. Many talc deposits that have been mined to produce both cosmetic and industrial talc are contaminated with asbestos, although to varying degrees. However, high-purity talc deposits exist, and asbestos-free synthetic talc can also be produced. Without knowing the source of the talc used in a workplace or in a consumer product, there is the potential risk of asbestos exposure. Asbestos fibres have very little mass (even a microgram may contain thousands of fibres; Berry et al., 2019; Bernstein, 2022), such that even slight contamination can potentially produce hazardous levels of exposure.

Among occupational studies, cohort studies of mining and milling workers in locations where the mineralogical nature of the talc deposit is known seem to present the best opportunity to study the independent effects of talc. Many of these mines and mills have been in operation for many decades, and some have been studied by multiple groups of investigators who have come to their own conclusions regarding the purity of the talc used in their study. The Working Group has also examined mineralogical evidence for potential asbestos contamination in talc deposits around the world (Section 1.2, Table 1.1). The Working Group's assessments did not always agree with those of the authors. For example, when studying the Vermont miners, Fordyce et al. (2019) reported the talc to be "free of asbestiform minerals", which was supported by previous reports by researchers from NIOSH (Selevan et al., 1979). However, the Working Group noted that Vermont (Blackwall talc) may be contaminated with asbestos (actinolite, tremolite, anthophyllite, and chrysotile). In fact, the conclusions of both the Working Group and the authors may be correct because of the following points.

Contamination can vary within a deposit, and where the deposit sample is collected may not be representative of the area being mined, which may also change over time. Measuring airborne asbestos in a work environment is the best way to assess worker exposure, but the LODs vary greatly. If more sensitive methods, such as TEM, are not used, contamination may not be detected. Lastly, terminology may vary (see Section 1.1 for details). "Asbestiform" has a very specific meaning in mineralogy, referring to the fibrous habit (form), which is similar to that of asbestos. However, asbestiform or fibrous talc is not asbestos. Many minerals can have an asbestiform habit, but only six minerals are classified as asbestos when in their fibrous form: serpentine (chrysotile) and the amphibole minerals (amosite (cummingtonite-grunerite), crocidolite (riebeckite), tremolite, actinolite, and anthophyllite).

The uncertainty about possible contamination of talc with asbestos and other carcinogenic agents also applied to the non-occupational studies summarized in the present monograph. This was particularly important for studies evaluating talc use and risk of gynaecological cancers. The source of talc in cosmetic and body powder products was not specified in any study and, consequently, the risk of contamination cannot be assessed on the basis of the talc provenance. The voluntary industry standards included proposed methods to assess contamination of cosmetic talc products and body powder, which are, however, not sufficiently sensitive to exclude non-trivial contamination (≤ 0.5%) and have not been consistently applied (see Section 1.3 and 1.4.1(e)). Testing of talc products in the USA over past decades has shown that a variable range of products were contaminated with asbestos at levels above the industry threshold as recently as 2019, and testing of products with more sensitive methods that can detect lower-level contamination has not been widely conducted. Thus, there were no epidemiological studies on talc powder

use that could exclude the possibility that the talc powders assessed were contaminated with asbestos. The extent of the contamination is not known. Although it has been theorized that talc products on the market up to the 1970s had a higher risk of asbestos contamination, according to the limited characterization of such products that was carried out, it was not clear whether levels of contamination had truly changed in a meaningful manner over time.

1.6.2 Quality of exposure assessment in key mechanistic studies

Exposure assessment literature

The Working Group undertook a critical appraisal of the exposure assessment methods used in 14 mechanistic studies in exposed humans, including one case–control study (Yang, 2019), two case series (Attanoos and Gibbs, 2004; Froudarakis et al., 2007), and 11 case reports. Of these, three studies involved medical exposure (Attanoos and Gibbs, 2004; Froudarakis et al., 2007; Vandemoortele et al., 2014), four involved occupational exposure (Gysbrechts et al., 1998; Nath et al., 2014; Kobayashi et al., 2019; Yang, 2019), six involved use of talc-based body powder (Creery et al., 1957; van Huisstede et al., 2010; Shakoor et al., 2011; Jasuja et al., 2017; Verlynde et al., 2018; Cho et al., 2021), and one was on exposure through intravenous drug use (Griffith et al., 2012).

(i) Occupational exposures

Yang (2019) studied the effectiveness of biomarkers for identifying pneumoconiosis among stone-craft workers in a case–control study nested within a screening programme in Hualien, Taiwan, China. The analysis included 48 cases of pneumoconiosis and 90 controls who were screened in 2013–2014. The focus of the study was on stone-craft workers exposed to asbestos-contaminated minerals. These workers produced jade artefacts, building materials, decorations, sculptures, vases, and urns. A face-to-face interview was conducted to assess exposure, including the types of stone they worked with. The questionnaire was developed using surveys conducted by occupational physicians and industrial hygienists and pretested using senior workers, and included occupational histories, number of years worked with different types of stone, and tasks performed. Of the participants, 90% of cases and 68% of controls processed asbestos-contaminated materials, including nephrite, antigorite, and talc. Results were not presented for talc-exposed workers, and no results specifically related to talc exposure were presented. [The Working Group noted that this was a limited exposure assessment concerning talc. Although the questionnaire appeared to be carefully developed, it was not clear whether there were specific questions regarding talc. Asbestos-contaminated minerals were the focus, and the prevalence and level of exposure to talc was not provided.]

(ii) Mechanistic studies focused on other exposures

The quality of the exposure assessment was evaluated for six studies that provided some mechanistic evidence, including three studies on pleural talc exposure and one study on exposure related to breast implants. Critical components of the assessment included the source and concentration of talc, which was specified only in some studies. Several of the studies summarized in the present section had only a limited exposure assessment.

Froudarakis et al. (2007) measured peripheral blood lymphocyte counts after pleural talc application. Depending on the clinical indication, either 2 g or 4 g of sterile asbestos-free talc was injected into the pleural space. [Given that talc was applied as part of a medical procedure, with a defined asbestos-free talc source and highly standardized application, this study provided a very accurate exposure assessment.]

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Attanoos and Gibbs (2004) conducted a postmortem study in individuals with malignant pleural mesothelioma to evaluate responses to different treatment procedures, including intrapleural talc application. The authors conducted morphological and immunohistochemical evaluation of the mesothelioma tissues and X-ray spectrometry for mineral fibre analysis. Information on treatment type was abstracted from medical records; no information on talc type, dose, or risk of contamination was provided. [The Working Group noted that, although the study was conducted in a clinical setting with presumably standardized procedures, the lack of information on type and quantity of talc products used resulted in a poor exposure assessment.]

(iii) Review of case reports

As part of the present evaluation, the Working Group considered case reports of presumed talc-induced disease. Eleven of these case reports were reviewed for the quality of their exposure assessment. Three involved occupational exposure (Gysbrechts et al., 1998; Nath et al., 2014; Kobayashi et al., 2019), six involved non-occupational exposure to cosmetic talc in baby or body powder (Creery et al., 1957; van Huisstede et al., 2010; Shakoor et al., 2011; Jasuja et al., 2017; Verlynde et al., 2018; Cho et al., 2021), one through talc pleurodesis (Vandemoortele et al., 2014), and one through intravenous drug use (Griffith et al., 2012). The exposure assessment for most studies was based primarily on a history collected from patients in a health-care setting. The exceptions were the studies by Nath et al. (2014), in which the patient developed breathlessness at work and was dead on arrival at the hospital; Creery et al. (1957), where the patient was an infant; Vandemoortele et al. (2014), where three patients in France who had received talc pleurodesis were followed up 20 years later; and Griffith et al. (2012), where exposure was assumed on the basis of the disease characteristics, which corresponded to unrecognized intravascular talcosis, and a history of intravenous drug use in six of nine patients in the USA.

The three occupational case studies were of patients with pulmonary talcosis. Interestingly, the most extensive exposure assessment was by Nath et al. (2014), where the patient in India was diagnosed with talcosis after death. The exposure assessment included a site visit to the workplace, interview with former co-workers, and laboratory analysis of the source of exposure, which flour used to make samosas. The worker had spent 5 years working 10–12 hours per day with three other workers in very dusty conditions with no ventilation. Gysbrechts et al. (1998) identified talc exposure > 40 years previously in a patient during a follow-up history after diagnosis in the UK. The patient had worked from age 14 to 18 years in a factory making rubber hoses and had operated a machine injecting talc; there were no dust controls, and workers were covered in white dust. Kobayashi et al. (2019) identified exposure in a confectionery company in Japan where the patient had made candies containing talc for > 20 years.

Five of the non-occupational studies were of patients with pulmonary talcosis or granulomatosis. Cho et al. (2021) described a patient in the USA who had applied "excessive" talcum face powder during the 2 years before diagnosis. Jasuja et al. (2017) described a patient in the USA who applied "copious amounts of baby powder to his bed-bound wife twice daily" during the year before his diagnosis. Shakoor et al. (2011) described a patient aged 24 years in Pakistan who "admitted to sniffing cosmetic talcum powder" for 4 months when she was aged 14 years, 10 years before diagnosis. van Huisstede et al. (2010) described a patient aged 36 years in the Netherlands who, since her childhood, had applied "large amounts" of cosmetic talcum powder twice daily after bathing. Verlynde et al. (2018) described a patient aged 31 years in Belgium who had applied "abundant cosmetic

talcum powder" to soften her skin daily over several years. In an older case report from the UK, Creery et al. (1957) described a talc granuloma of the umbilicus in an infant who had "a standard proprietary talcum baby-powder" applied to the umbilicus. However, whether the powder was applied in a health-care setting or elsewhere and the source of information were not stated.

The exposure assessment for seven of these studies was based solely on a history collected from the patients (Gysbrechts et al., 1998; van Huisstede et al., 2010; Shakoor et al., 2011; Jasuja et al., 2017; Verlynde et al., 2018; Kobayashi et al., 2019; Cho et al., 2021). Although not always stated, histories were presumably taken by a diagnosing or attending physician. [Few physicians receive any training in identifying exposures during a work history interview and, even for a person with such training, identifying specific exposures may be difficult. However, with knowledge of talc-induced disease, very targeted questions could be used to uncover useful details. Although self-reported exposure collected with knowledge of disease may be considered limitations, they are generally inherent in case reports.]

All assessments were qualitative in nature, and measured levels of exposure were not available. Nevertheless, "high" levels of exposure can sometimes be inferred on the basis of the description of workplace conditions (Gysbrechts et al., 1998; Nath et al., 2014) or the adjectives used, such as "abundant" (van Huisstede et al., 2010; Verlynde et al., 2018) and "copious amounts" (Jasuja et al., 2017).

In case reports, the characteristics of the talc (e.g. asbestos contaminants, fibrous versus nonfibrous) were rarely reported. Although some studies reported analysis of tissue samples (e.g. Gysbrechts et al., 1998; van Huisstede et al., 2010; Kobayashi et al., 2019), these were generally done to confirm the diagnosis, and it was unclear whether this reliably represented the talc characteristics. For recent studies on cosmetic talc exposure, it may be possible to predict the purity of the talc on the basis of the years during which exposure occurred. For example, if the patient described by Cho et al. (2021) was diagnosed in 2020, then her exposure to cosmetic talc would have been between 2018 and 2020, and if the patient described by Jasuja et al. (2017) was diagnosed in 2016, his exposure would have been in 2015–2016.

2. Cancer in Humans

Introduction

Talc has been evaluated by the *IARC Monographs* programme in two previous volumes. In Volume 93, "inhaled talc not containing asbestos or asbestiform fibres" was classified in Group 3, on the basis of *inadequate* evidence in humans (IARC, 2010). Perineal use of talc-based body powder was classified in Group 2B, on the basis of *limited* evidence for ovarian cancer in humans. In 2009 during the evaluation of asbestos, the Working Group concluded that "talc containing asbestos" was included within the classification of asbestos in Group 1, *carcinogenic to humans*; there was *sufficient* evidence in humans that asbestos causes cancers of the lung, larynx, mesothelium, and ovary (IARC, 2012a).

The Working Group for Volume 136 decided that the agent evaluated in the present monograph would be "talc", acknowledging however that it was often not possible in the studies in humans to determine whether or not the talc was contaminated with asbestos. The one exception was for the talc mining and milling industry, where information was available to the Working Group on the presence or absence of asbestos in the talc or for each mine.

A systematic search was done in the PubMed database to identify relevant studies (NCBI, 2024b; as described in the General Remarks). The search terms, and the lists of retrieved studies are

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available from: https://hawcproject.iarc.who.int/assessment/703/.

Cohort, nested case–control, and case–control studies were included. Case reports, ecological studies, or studies without cancer end-points were not considered further. Results reporting on "all cancer types combined" were not considered to be informative for the evaluation, since the determination of human carcinogenicity is done at the level of cancer site or tissue, and hence were not discussed further.

Associations between talc exposure and human cancer have been investigated in two main groups of epidemiological studies. The first group of studies included occupational cohort studies on talc mining and milling. These studies were further stratified by whether or not the mined talc ore was contaminated with asbestos. Other cohort studies were in the following downstream industries that are known to use talc in parts of their process: the rubber industry, the pulp and paper industry, and the pottery, ceramic, cement, and fibreglass industries. Some of these studies also had nested case–control designs. There were also two publications from a population-based case–control study in Canada in which associations between several cancers and occupational exposure to talc, as one of a large number of occupational exposures, were investigated.

The second group of studies investigated cancer and the use of talc-based powder for perineal and other personal use. This group comprised cohort studies and case–control studies; either registry-based or hospital-based. The cancers of prime interest were those of the ovary, corpus uteri, and cervix. Three of the four cohort studies were published after *IARC Monographs* Volume 93, whereas most of the case–control studies were published before. One of these case–control studies also investigated occupational exposure to talc. Few studies in humans investigated cancer and the medical use of talc, such as in pleurodesis, or the use of talc in traditional Chinese medicine.

The Working Group conducted a quantitative bias analysis and meta-analysis to assess the impact of information bias from exposure misclassification in the studies investigating perineal use of talc and ovarian cancer because of concern that exposure misclassification could affect the validity of the study findings. These analyses are detailed in Annex 2 (Quantitative bias analysis for exposure misclassification for the effects of ever versus never talc use on ovarian cancer, available from: https://publications.iarc.who.int/646).

This section starts with a description of each of the cohort and case–control studies, ordered by type of exposure (occupational exposure, perineal use, medical use) and then chronologically (Section 2.1). The results, including those from any informative meta-analyses, are then presented by cancer type (Sections 2.2–2.6). The Working Group also conducted two meta-analyses for lung and stomach cancer, which are reported in Sections 2.3.3 and 2.4.

2.1 Description of the studies

Studies are ordered chronologically in Table 2.1 (according to the first publication year for studies with repeated follow-up), without regard to the type of exposure setting for the study. Case–control studies that are described in the present section (Section 2.1) are reported chronologically in Table 2.2 for cancers of the ovary and other female reproductive organs, Table 2.3 for cancers of the lung and respiratory tract, Table 2.4 for cancers of the digestive system, Table 2.5 for cancers of all other solid organs, and Table 2.6 for lymphohaematopoietic cancers.

2.1.1 Cohort studies in talc miners

See Table 2.1.

Table 2.1 Description of cohort studies (including nested case–control studies) on exposure to talc and cancer

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Honda et al. (2002) USA Enrolment, 1948–1989/follow-up, 1950–1989 Cohort	809 White men who worked at a talc mining and milling facility in the Gouverneur District of upstate New York for ≥ 1 day between 1948 and 1989, whose vital status was known in 1950 onwards; study was restricted to White men because of the low prevalence of other race/ethnicities. Exposure assessment method: Detailed work histories from personnel and tax records for talc miners and millers used with a respirable dust JEM developed using assessments by long-term employees and both current and historic exposure measurements. Details found in: Oestenstad et al. (2002).	Lung, mortality Mesothelioma, mortality Larynx, mortality Digestive organs and peritoneum, mortality Stomach, mortality Colon and rectum, mortality Lymphatic and haematopoietic, mortality	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.6	*Exposure assessment critique*: This was a high-quality exposure assessment using a combination of expert assessment and measurement data. Key strengths were the investigators efforts to assess and mitigate lack of consistency in historical measurement data and poor inter-rater agreement, and the effective use of their own exposure measurement survey. Key limitations were the lack of consistently gathered historical measurement data and poor inter-rater agreement; and that the talc at this site is contaminated with asbestos (see Section 1.2, Table 1.1). *Other strengths*: The SMRs compare mortality with local rates rather than national rates, which is probably more relevant. A further strength was the internal comparisons based on Poisson regression. *Other limitations*: The reference population was rather small; mortality rates might therefore be unstable and consequently the confidence intervals for the SMRs might be wide. No smoking data were available. Only lung cancer was described in detail.
Finkelstein (2012) USA 1990–2007 Cohort	Included 567 members of the Honda et al. (2002) cohort who were alive at the end of follow-up in 1989. The cohort was followed from 1990 (end of follow-up by Honda et al.) through 2007 for mesothelioma incidence. The author did not have access to the original data and made the conservative assumption that all 567 were alive at the end of 2007.	Mesothelioma, incidence	Reported in Table 2.3	*Strengths*: The author was careful to use conservative (overestimated) estimates of the number of person-years so that the expected number of mesotheliomas was probably also overestimated. *Limitations*: The number of incident mesotheliomas was probably underestimated since no systematic follow-up of the cohort was attempted. It was unclear how the author ascertained that the identified mesothelioma cases were actually part of the cohort followed up by Honda et al., based solely on the published paper.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Monson and Fine (1978) Akron (OH), USA Enrolment, early 1940s to 1 July 1971/follow-up, 1940 through 30 June 1976 (mortality) and 1964–1974 (diagnoses) Cohort	13 570 White men, members of local union and employed (≥ 5 yr) before 1 July 1971 in Akron in rubber or tyre manufacture. Follow-up (1940–1976) through death certificates (any cancer listed in the death certificate, even those not listed as underlying cause of death). For the period 1964–1974, incident cancers were identified through the tumour registry of four Akron-based hospitals. Exposure assessment method: A limited work history was assembled using data from both company and union records.	Lung	Reported in Table 2.3	*Exposure assessment critique*: This was a limited exposure assessment. Key limitations were that exposure to talc was not specifically assessed; department may be a poor surrogate for level of exposure; and the work history may not be complete. *Other strengths*: Large size of the cohort and the large numbers of deaths and nonfatal cancers, especially for gastrointestinal tumours and lung cancer. *Other limitations*: Ascertainment of nonfatal cancers was known to be incomplete. The use of national cancer death rates would not account for geographical variation across the country. *Other comments*: The paper by Monson and Fine (1978) included 13 570 people instead of 13 571 (in Monson and Nakano, 1976), stating that for that one person there was an "error in the data". This is the latest update of the Peters et al. (1976) cohort.
		Stomach	Reported in Table 2.4	
		Intestine	Reported in Table 2.4	
		Pancreas	Reported in Table 2.4	
		Urinary bladder	Reported in Table 2.5	
		Prostate	Reported in Table 2.5	
		Brain	Reported in Table 2.5	
		Lymphatic	Reported in Table 2.6	
		Leukaemia	Reported in Table 2.6	
Ciocan et al. (2022a) Val Chisone, north Italy Enrolment, 1946–1995/follow-up, through 31 January 2020 Cohort	1749 (1184 miners, 565 millers); men employed for ≥ 1 mo in the talc mine or mill in Val Chisone between 1946 and 1995. Exposure assessment method: Detailed work histories from personnel records for talc miners and millers used to assess duration only. Air measurement results published by Pira et al. (2017).	Lung, mortality	Reported in Table 2.3	*Exposure assessment critique*: This was a limited exposure assessment. Key strengths were the analysis of talc samples by electronic microscopy and the evaluation of potential confounding exposures. The Working Group noted that no asbestos has been reported in the Val Chisone deposits (see Section 1.2, Table 1.1). Key limitations were that exposure to talc was not specifically assessed; and that duration of employment may be a poor surrogate for level of exposure. *Other strengths*: Long follow-up. *Other limitations*: Analysis of duration of employment was not performed separately by department (miners or millers). Analysis by year of first employment mentioned in the methods but results not reported.
		Larynx, mortality	Reported in Table 2.3	
		Pleura, mortality	Reported in Table 2.3	
		Oral/pharyngeal combined, mortality	Reported in Table 2.4	
		Oesophagus, mortality	Reported in Table 2.4	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Ciocan et al. (2022a) (cont.)		Stomach, mortality	Reported in Table 2.4	
		Colon and rectum, mortality	Reported in Table 2.4	
		Liver and bile ducts (ICD-9 155), mortality	Reported in Table 2.4	
		Pancreas, mortality	Reported in Table 2.4	
		Peritoneum, mortality	Reported in Table 2.4	
		Kidney, mortality	Reported in Table 2.5	
		Urinary bladder, mortality	Reported in Table 2.5	
		Prostate, mortality	Reported in Table 2.5	
		Brain and other CNS (ICD-9, 191–192), mortality	Reported in Table 2.5	
		Lymphoma (type not specified; ICD-9, 200–202), mortality	Reported in Table 2.6	
		Multiple myeloma, mortality	Reported in Table 2.6	
		Leukaemia, mortality	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Blum et al. (1979) USA 1964–1973 Nested case–control	Source cohort: about 17 000 workers (active or retirees) aged 40–84 yr as of 1 January 1964, working in two rubber processing plants in the USA. Cases: 100 workers from two rubber plants whose death certificate indicated stomach cancer (as underlying cause of death or anywhere on the death certificate). Controls: 400 controls selected from the same worker cohort and matched for age (± 3 yr), race, sex, and company; 50% of controls were additionally matched on total duration of employment in the industry, but this was found to be similar for cases and controls. Exposure assessment method: Detailed work histories for rubber workers. Three environmental scientists independently rated 100 occupational titles for possible exposure to PAHs, nitrosamines, carbon black and talc.	Stomach, mortality	Reported in Table 2.4	*Exposure assessment critique*: Key strengths were that this was a good semiquantitative assessment of exposure based on expert assessment. Key limitations were that it was unclear how knowledgeable the environmental scientists were regarding the exposure conditions at the facilities being studied; in addition, the exposure assessment was categorical rather than quantitative and was not based on hygiene surveys; and asbestos contamination of the talc cannot be excluded. *Other strengths*: The nested case–control design within the cohort, with the use of internal matched controls. *Other limitations*: Case–control analysis was poorly described, controls were not selected using density sampling, and the analysis used Mantel–Haenszel OR) to account for the matching variables rather than conditional logistic regression. Differing results between the two plants for stomach cancer deaths and talc exposure could not be explained by the authors.
Fordyce et al. (2019) Vermont, USA Enrolment, 1940–1969 (initial), 1930–1983 (expanded)/follow-up, 1940–2012 Cohort	427; all White male Vermont talc workers who had worked ≥ 1 yr in 1940–1969 (initial enrolment) or 1930–1940 or 1970–1983 (expanded enrolment). These correspond to all talc workers who participated in the Vermont Health Department radiograph programme (workers were offered annual chest radiographs from 1930 to 1983). Exposure assessment method: Work histories from talc miners and millers used to assess duration of employment.	Lung, mortality Mesothelioma, mortality Larynx, mortality Oral/pharyngeal combined, mortality	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4	*Exposure assessment critique*: This was a limited exposure assessment. Key limitations were that exposure to talc was not specifically assessed; and that duration of employment may be a poor surrogate for level of exposure. The Working Group noted that Vermont (Blackwall talc) may be contaminated with asbestos (actinolite, tremolite, anthophyllite, and chrysotile) and that quartz was present (see Section 1.2, Table 1.1). *Other strengths*: Long follow-up. *Other limitations*: Small study size. Potential bias because of the HWE since comparison was with the US population. Lack of control for smoking. Lack of exposure–response or latency analysis.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Fordyce et al. (2019) (cont.)		Oesophagus, mortality	Reported in Table 2.4	
		Stomach, mortality	Reported in Table 2.4	
		Colon, mortality	Reported in Table 2.4	
		Rectum, mortality	Reported in Table 2.4	
		Liver and bile ducts, mortality	Reported in Table 2.4	
		Pancreas, mortality	Reported in Table 2.4	
		Kidney, mortality	Reported in Table 2.5	
		Urinary bladder, mortality	Reported in Table 2.5	
		Prostate, mortality	Reported in Table 2.5	
		CNS, mortality	Reported in Table 2.5	
		Breast, mortality	Reported in Table 2.5	
		NHL (ICD-10, C82, C83.0–C84.9, C85.1–C85.9), mortality	Reported in Table 2.6	
		Leukaemia and aleukaemia (ICD-10 C91–C95), mortality	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Wild et al. (2002) France, Austria Enrolment, 1945–1994 (French cohort) or 1972–1995 (Austrian cohort)/follow-up, through 1996 (French cohort), or 1995 (Austrian cohort) Cohort and nested-case–control (for lung cancer only)	Cohort: 1612 (1070 French, 542 Austrian); male workers employed continuously for ≥ 1 yr during 1945–1994 in a talc mine in the French Pyrenees (French cohort) or 1972–1995 in mine or mills in the Styrian Alps or in the Head office in Graz (Austrian cohort). For the French cohort, cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. A nested case–control study of lung cancer compared estimated talc exposure for 30 cases of lung cancer with 87 controls selected using incidence density sampling and matching on calendar period. Exposure assessment method: Detailed work histories from personnel records for talc miners and millers. Exposure was assessed using a JEM developed by occupational physicians on the basis of personal measurements collected at the mill during 1986–1987 and at the mine during 1988–1989. See also Wild et al. (1995)	Lung, mortality Mesothelioma, mortality Stomach, mortality	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4	*Exposure assessment critique*: This was a good-quality exposure assessment performed by an occupational physicians who worked for the companies. Key strengths were the use of measurement-based JEMs and that no asbestos has been reported in the deposits in the French Pyrenees and in the Styria deposits in Austria (see Section 1.2, Table 1.1). A key limitation was the lack of measurement data before 1986. *Other strengths*: Use of a nested case–control study limits potential for bias caused by the HWE or other factors. Able to control for smoking and quartz exposure. *Other limitations*: Small sample size, particularly for mesothelioma (0 cases).
Thomas and Stewart (1987) USA Enrolment, 1939–1966/follow-up, 1940 through 1 January 1981 Cohort	2055 White men employed for ≥ 1 yr (1939–1966) at three plants of a single US company producing ceramic plumbing fixtures. Exposure assessment method: Detailed work histories from personnel records. Each job was classified on potential for exposure to talc.	Lung, mortality Mesothelioma, mortality Digestive cancers (ICD-8, 150–159), mortality Lymphatic and haematopoietic (ICD-8, 200–209), mortality	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.6	*Exposure assessment critique*: Key strengths were that this was a moderate quality, semiquantitative assessment of exposure based on expert assessment for both fibrous and nonfibrous talc. A key limitation was that potential contamination by asbestos was not stated, but the Working Group noted that fibrous talc is often contaminated with other fibrous minerals and that some Montana talc deposits may be contaminated with tremolite asbestos (see Section 1.2, Table 1.1). *Other strengths*: Large sample size; silica exposure was also assessed; almost complete follow-up. *Other limitations*: The main exposure in this industry was silica. Talc exposure occurred only in workers with high silica exposure.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Negri et al. (1989) Italy 1946–1981 Cohort	6629; all men who worked for ≥ 1 yr between 1946 and 1981 in a rubber tyre factory in the Turin district; 9% who could not be traced were excluded from the cohort. Cohort of rubber tyre workers compared with general population. Exposure assessment method: Subgroup analyses were performed by period of employment, age at first exposure, duration of exposure and period since last exposure. No analyses based on talc exposure were performed.	Lung, mortality	Reported in Table 2.3	*Strengths*: The large size of the cohort and the access to historical employment records. *Limitations*: There was 9% loss to follow-up and no analyses were based on talc exposure. No data on potential confounding were available. Asbestos exposure was considered likely and would possibly explain the excess of pleural cancer.
		Pleura, mortality	Reported in Table 2.3	
		Larynx, mortality	Reported in Table 2.3	
		Oesophagus, mortality	Reported in Table 2.4	
		Stomach, mortality	Reported in Table 2.4	
		Liver, mortality	Reported in Table 2.4	
		Pancreas, mortality	Reported in Table 2.4	
		Kidney and other urinary organs, mortality	Reported in Table 2.5	
		Urinary bladder, mortality	Reported in Table 2.5	
		Brain, mortality	Reported in Table 2.5	
		Lymphoma (type not specified), mortality	Reported in Table 2.6	
		Leukaemia, mortality	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Wergeland et al. (2017) Norway Enrolment 1944–1972 (miners), 1935–1972 (millers)/ follow-up, 1953–2011 (incidence and mortality) Cohort	390 (94 miners, 296 millers); men employed in the mine for ≥ 1 yr (1944–1972) or in the mill for ≥ 2 yr (1935–1972). Exposure assessment method: Work histories from company payroll lists, union records, and a registry of silica-exposed workers were used, with individual assignment of dust exposure intensity. Jobs were classified as low, medium, high, or unexposed by local trade union leader for mine jobs and two long-time employees for mill jobs. See also Wergeland et al. (1990).	Lung, incidence and mortality Mesothelioma, incidence Pleura, incidence Stomach, incidence Colon and rectum, incidence Kidney, incidence Urinary bladder, incidence Prostate, incidence	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.5 Reported in Table 2.5 Reported in Table 2.5	*Exposure assessment critique*: Key strengths were that this was a moderate quality exposure assessment based on expert assessment. A key limitation was that only duration of employment, with the potential for substantial misclassification, was used for cancer outcomes. The talc contained trace amounts of tremolite and anthophyllite (asbestos) and quartz. *Other strengths*: Use of cancer incidence data. *Other limitations*: Small study size; lack of control for smoking and the HWE. The cancer incidence analysis counted multiple cancers in the same individual. For example, one worker had four colon cancer diagnoses, three occurring more than a decade after the first.
Ierardi et al. (2022) Austria, France, Italy, Norway, USA Enrolment/follow-up varies by study Cohort	4178; pooled analysis of five cohorts of talc miners and millers. Included cohorts are Italian miners and millers described in Ciocan et al. (2022a); Norwegian miners and millers described in Wergeland et al. (2017); French and Austrian miners and millers described in Wild et al. (2002); and US miners and millers described in Fordyce et al. (2019).	Mesothelioma, mortality	Reported in Table 2.3	*Limitations*: Number of expected deaths in this cohort may have been overestimated because of high rates of mesothelioma in areas with asbestos exposure, particularly in Italy, but also noted that the impact was likely to be irrelevant.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Zhang et al. (1989) Shanghai, China Enrolment, 1972/follow-up, 1 December 1972 to 30 November 1984 Cohort	1624 (957 men and 667 women); male and female rubber workers working at a rubber plant in the Xuhui district of Shanghai who entered a screening programme for coronary heart disease in 1972. Exposure assessment method: Work histories collected by a coronary heart disease screening programme.	Lung, mortality	Reported in Table 2.3	*Exposure assessment critique*: This was a limited exposure assessment. Key limitations were that exposure to talc was not specifically assessed; the talc may have been contaminated with asbestos; and job group may have been a poor surrogate for level of exposure. Furthermore, it was not clear whether the grouping was based on ever performing these tasks, the longest duration, or the time when the records were developed. *Other strengths*: Subgroup analyses based on work history and accounting for smoking history in the analyses. *Other limitations*: The possibility of selection bias because of limited eligibility for inclusion in the cohort; the small size of the cohort; short period of follow-up; high loss to follow-up for the men.
Fu and Zhang (1992) Haichen talc mine, China Enrolment, January 1974/follow-up, 1974–1988 Cohort	1357 male workers on the wage employee list in January 1974 with ≥ 1 yr of work history, followed until 1988. Workers with a work history in the chemical industry were excluded. For SMR estimation, age-standardized mortality was calculated relative to a cohort of workers in the iron and steel industry. Exposure assessment method: Job histories were from company records. [information based on Chang et al., 2017]	Lung, mortality Oesophagus, mortality Stomach, mortality Colon, mortality Liver and bile ducts, mortality	Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.4	*Exposure assessment critique*: This was a limited exposure assessment. A key limitation was that the authors stated that many sources of data were used but it was unclear how these were used. Without further details, it was not possible to assess the quality of the exposure assessment. Given that these were talc miners and millers, it may be safe to assume they were exposed, but no levels were reported. Approximately 12% were reported to have some history of pneumoconiosis, which may indicate high levels of exposure to crystalline silica or talc. Chrysotile asbestos was probably present, tremolite possibly present, and quartz was present in the Chinese deposits (see Section 1.2, Table 1.1). *Other strengths*: Used another working population as the referent. *Other limitations*: Uncertain whether ascertainment of cause of death from the home was reliable and that this may have resulted in disease misclassification. Despite availability of smoking data, smoking or exposure to other respiratory carcinogens were not controlled for in the analysis.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Nie et al. (1992) China Enrolment, 1972–1974/follow-up, through 1989 Cohort	12 218 (8654 men, 3564 women); registered employees with > 1 yr of employment between 1972 and 1974, in seven porcelain factories	Lung, mortality Stomach, mortality Liver, mortality	Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4	*Limitations*: No follow-up of workers who left the factories. Person-years < 1 yr were not excluded, therefore introducing immortal time bias slightly downwards. Mortality from pneumoconiosis (often complicated by tuberculosis) was highly increased in the two groups exposed to dust and/or talc, suggesting substantial confounding by silica exposure.
Chiazze et al. (1993) USA 1940–1982 Nested case–control	Source cohort: Production and maintenance workers employed at the Owens-Corning Fiberglass Newark plant for ≥ 1 yr between 1940 and 1962, followed until 1982 (Enterline et al., 1987). Cases: 144 cases died from a malignant respiratory disease. In the source cohort study, vital status had been determined through the US Social Security Administration and other sources; death certificates had been requested from state health departments and the underlying cause of death was coded according to the ICD revision in effect at the time of death (Enterline et al., 1987). Controls: 260; included cohort members who had not died from malignant or non-malignant respiratory disease, but also excluded those who died from suicide or homicide. Controls matched (2:1) on year of birth and survival at the end of follow-up/death. Exposure assessment method: Work histories collected through in-person and telephone interviews using a questionnaire designed for both subject and proxies. Assessment based on historical reconstruction of processes by engineers and expert assessment by current and former employees knowledgeable in industrial hygiene	Lung, mortality	Reported in Table 2.3	*Exposure assessment critique*: Key strengths were that this was a moderate quality, semiquantitative assessment of exposure based on expert assessment. A key limitation was that it was not clear how quantitative exposure estimates in fibres/mL were estimated without industrial hygiene records before 1970. *Other strengths*: Extensive work performed to reconstruct workplace exposure to several agents. Cumulative exposure calculated. *Other limitations*: No information on type of talc used was provided. Cumulative asbestos contamination was assessed but not adjusted for in the analysis.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Bulbulyan et al. (1999) Russian Federation 1979–1993 Cohort	3473 women employed at one of two printing plants as of 31 December 1978, with a minimum of 2 yr of employment. Exposure assessment method: Work histories were abstracted from personnel records, and jobs were classified into four groups. There was no discussion of the characteristics of the talc used at the facilities outside of potential asbestos contamination. Analyses were conducted by job group.	Uterine cervix, mortality	Reported in Table 2.2	*Exposure assessment critique*: This was a limited exposure assessment. Key limitations were that exposure to talc was not specifically assessed and although book binders and press operators may be exposed, job group may be a poor surrogate for level of exposure; and that asbestos co-exposure occurred. *Other strengths*: Rather large cohort. A single job for 94% of the population. Few lost to follow-up (1.5%). *Other limitations*: The cohort was defined cross-sectionally (all current employees as of 31 December 1978). The exposure was defined by the primary process of employment.
		Uterine corpus, mortality	Reported in Table 2.2	
		Ovary, mortality	Reported in Table 2.2	
		Lung, mortality	Reported in Table 2.3	
		Mesothelioma (peritoneal), mortality	Reported in Table 2.3	
		Oesophagus, mortality	Reported in Table 2.4	
		Stomach, mortality	Reported in Table 2.4	
		Colon, mortality	Reported in Table 2.4	
		Rectum, mortality	Reported in Table 2.4	
		Liver and bile ducts, mortality	Reported in Table 2.4	
		Pancreas, mortality	Reported in Table 2.4	
		Kidney, mortality	Reported in Table 2.5	
		Urinary bladder, mortality	Reported in Table 2.5	
		Breast, mortality	Reported in Table 2.5	
		Brain, mortality	Reported in Table 2.5	
		Leukaemia: (ICD-9 191–192), mortality	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Li and Yu (2002) Shanghai, China Enrolment, 1973/follow-up, 1973–1997 Cohort	1598 (934 men, 664 women); employees of a rubber factory. Outcome ascertained through death certificates.	Lung, mortality Oesophagus, mortality Liver, mortality Urinary bladder, mortality	Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4 Reported in Table 2.5	*Exposure assessment critique*: A key limitation was that the exposure was defined by the primary process of employment. No quantitative assessment of talc exposure. Unclear overlap with Zhang et al. (1989).
Li and Yu (1999) China 1973–1995 Case–cohort	Cohort size was 1598 (934 men, 664 women); workers with ≥ 1 yr of employment in a rubber manufacturing plant in Shanghai, China, between 1973 and 1995. Analyses used the case–cohort study design. Cases included 36 deaths from stomach cancer (32 men and 4 women) observed in the cohort. A subcohort (comparison cohort, randomly sampled) of 188 workers, randomly selected from the larger cohort, included 13 stomach cancer cases so the final comparison cohort comprised 175 workers. Exposure assessment method: Work histories were obtained from company records and a questionnaire.	Stomach, mortality	Reported in Table 2.4	*Exposure assessment critique*: This was a limited exposure assessment. Key limitations were that exposure to talc was not specifically assessed; and although the highest levels of talc dust were highest in the inner-tube department, duration in this department may be a poor surrogate for exposure. *Other strengths*: An internal subcohort and subgroup analyses by work group, including tube production involving talc exposure. *Other limitations*: Small numbers of participants; limitations in the selection of the subcohort; no inclusion of confounding variables in the analysis. *Other comments*: Potential and unclear overlap with Zhang et al. (1989).
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	Cohort of 4247 women who worked for ≥ 1 yr between 1920 and 1993 in a pulp and paper mill in Norway. Women who died before 1953 were excluded from the study (unclear if those were included in the population size reported in the article). Exposure assessment method: Work history (departments, job titles, and date of start and end of employment in specific work activities) obtained from the mill personnel files.	Uterine cervix, incidence Ovary, incidence Lung, incidence Pleura, incidence Stomach, incidence Colon, incidence	Reported in Table 2.2 Reported in Table 2.2 Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4 Reported in Table 2.4	*Exposure assessment critique*: This was a very limited exposure assessment. Key limitations were that talc was not assessed, and overall duration of employment was a very poor surrogate for exposure to talc. Talc is known to be used as a filler in the paper. *Other strengths*: Large study with > 4000 women and a long follow-up with > 100 000 person-years. Use of incidence data. *Other limitations*: About 8% of the women could not be followed up because they changed their name. About one third of the person-years corresponded to women with > 3 yr of employment.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Langseth and Andersen (1999) (cont.)		Rectum, incidence	Reported in Table 2.4	
		Kidney, incidence	Reported in Table 2.5	
		Urinary bladder, incidence	Reported in Table 2.5	
		Breast, incidence	Reported in Table 2.5	
		HL (Hodgkin lymphoma), incidence	Reported in Table 2.6	
		NHL, incidence	Reported in Table 2.6	
		MM (multiple myeloma), incidence	Reported in Table 2.6	
		Leukaemia, incidence	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Langseth and Kjaerheim (2004) Norway Enrolment, 1920–1993/follow-up, 1953–1999 Nested case–control	Source cohort: 4247 women who worked for ≥ 1 yr between 1920 and 1993 in a pulp and paper mill in Norway. Cases: 46 cases of epithelial ovarian cancer selected from the Norwegian pulp and paper cohort, identified through the Cancer Registry of Norway. Controls: 179; four controls per case drawn by incidence density sampling. Matched on birth year. Controls were free of ovarian cancer and had intact ovaries. Exposure assessment method: Detailed work histories from company. Industrial hygienists and senior employees at each mill identified production processes, use of specific agents, and changes over the years and data from PAPDEM (IARC pulp and paper department-exposure matrix) used to assess exposure. Non-occupational talc and potential confounding factors were assessed through interviews of cases and controls.	Ovary (epithelial), incidence	Reported in Table 2.2	*Exposure assessment critique*: Key strengths were that this was a good semiquantitative assessment of exposure based on expert assessment of detailed work histories by the international IARC study team, including expertise by industrial hygienists and senior employees in each mill. See Boffetta and Colin (2001). A key limitation was that only ever versus never talc exposure was analysed. Use of departments because of the lack of job title information for all mills. *Other strengths*: Relatively large number of cases. The controls were selected by incidence density sampling within the industrial cohort, which limits most of the possible biases. Relatively high response rates for interviews (cases, 76%; controls, 66%). *Other limitations*: The proportion of self-respondents was much lower among cases than among controls.
Straif et al. (2000) Germany Enrolment, 1950–1981/follow-up, 1981–1991 Cohort	8933; all male German blue collar workers hired during or after 1950 in five rubber plants and who had worked for ≥ 1 yr. They needed to be still alive and actively employed or retired on 1 January 1981. Exposure assessment method: Detailed work histories from company records and exposure assessment conducted by external experts and industrial hygienists from the participating factories.	Lung, mortality Mesothelioma, mortality Larynx, mortality Stomach, mortality	Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.3 Reported in Table 2.4	*Exposure assessment critique*: This was a high-quality, semiquantitative exposure assessment. Key strengths were the use of expert assessment and the retrospective exposure assessment for three other agents (nitrosamines, carbon black, asbestos) in addition to talc. A key limitation was the lack of historical measurement data before 1979 (exposure was assessed 1950–1981). *Other strengths*: Large cohort size; almost complete ascertainment of cause of death. *Other limitations*: Small numbers for some subgroup analyses and lack of data on smoking and other potentially confounding exposures, such as PAHs. Although talc and asbestos were assessed separately, they were combined for the multivariate analyses, making it not possible to assess the independent effect of talc.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Boffetta and Colin (2001) (publicly available since 2023) 15 countries Enrolment, varies/follow-up, between 1943 and 1985 through the mid-1990s (mortality and incidence) Cohort	103 773 workers employed for ≥ 1 yr in pulp and paper companies with complete data. Exposure assessment method: Work histories based on department and exposure was assessed using a JEM based on expert assessment, measurement data, and company questionnaires. Exposure assessment methods were described in detail by Kauppinen et al. (2002).	Uterine cervix, mortality	Reported in Table 2.2	*Exposure assessment critique*: This was a high-quality quantitative assessment of exposure. Key strengths were the basis in expert assessment by an experienced international team and that asbestos co-exposure was measured in this industry. A key limitation was the use of departments because of the lack of job title information for all companies, which would result in nondifferential misclassification, with bias towards the null. The type (provenance) of talc was not mentioned. *Other strengths*: A large international cohort.
		Uterine corpus, mortality	Reported in Table 2.2	
		Ovary, mortality and incidence	Reported in Table 2.2	
		Lung, mortality and incidence	Reported in Table 2.3	
		Pleura, mortality	Reported in Table 2.3	
		Other respiratory organs (ICD-9, 164–165), mortality	Reported in Table 2.3	
		Larynx, mortality	Reported in Table 2.3	
		Oral/pharyngeal combined, mortality	Reported in Table 2.4	
		Oesophagus, mortality	Reported in Table 2.4	
		Stomach, mortality	Reported in Table 2.4	
		Colon, mortality	Reported in Table 2.4	
		Rectum, mortality	Reported in Table 2.4	
		Liver, mortality	Reported in Table 2.4	
		Gallbladder, mortality	Reported in Table 2.4	
		Pancreas, mortality	Reported in Table 2.4	
		Kidney, mortality	Reported in Table 2.5	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Urinary bladder, mortality	Reported in Table 2.5	
		Prostate, mortality	Reported in Table 2.5	
		Testis, mortality	Reported in Table 2.5	
		Brain, mortality	Reported in Table 2.5	
		Thyroid, mortality	Reported in Table 2.5	
		Breast, mortality	Reported in Table 2.5	
		Lymphatic and haematopoietic, mortality	Reported in Table 2.6	
		NHL, mortality	Reported in Table 2.6	
		Hodgkin lymphoma, mortality	Reported in Table 2.6	
		Multiple myeloma, mortality	Reported in Table 2.6	
		Leukaemia: and aleukaemia, mortality	Reported in Table 2.6	
		Leukaemia (lymphoid), mortality	Reported in Table 2.6	
		Leukaemia (myeloid), mortality	Reported in Table 2.6	

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Gertig et al. (2000) NHS-I, USA Enrolment, 1976/ follow-up, 1982 through 1 June 1996 Cohort	78 630; participants were 121 700 married registered nurses enrolled in 1976, aged 30–55 yr, from 11 US states. Baseline questionnaire was administered in 1982. 307 cases of epithelial ovarian cancer (including borderline cases) diagnosed through 1 June 1996 were included. Cancer ascertainment: self-reported in follow-up questionnaires (emailed every 2 yr) and confirmed through pathology reports. Exposure assessment method: The prevalence of ever perineal use of talc in 1982 was assessed through self-administered questionnaire. The questionnaire asked, "have you ever commonly used talcum, baby powder or deodorizing powder to apply to perineal (private) area?" Responses were no, daily, 1–6 times/wk, or less than once/wk.	Ovary (epithelial), incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was the prospective design, which avoids differential misclassification. Key limitations were nondifferential exposure misclassification and limited assessment time points (one-time assessment does not allow for the assessment of lifetime or cumulative exposure to talc). Asbestos contamination cannot be excluded, particularly in earlier time periods. *Other strengths*: The prospective design reduced the potential for selection bias. Good control for confounders. *Other limitations*: Married female nurses represented a somewhat higher socioeconomic status compared with the general population and were also less likely to be nulliparous.
Karageorgi et al. (2010) NHS-I, USA Enrolment, 1976/ follow-up, 1982–2004 Cohort	66 028 women aged 30–55 yr in the prospective NHS-I cohort were included; 599 cases of endometrial cancer diagnosed between 1982 and 2004 and confirmed by medical record review as invasive type I endometrioid adenocarcinoma were included. Exposure assessment method: Use of perineal use of talcum powder or use on sanitary napkins was obtained in 1982. Frequency of use was obtained; 1982 self-administered questionnaire, "Have you ever commonly used talcum, baby powder, or deodorizing powder (a) to apply to perineal (private) area? No, daily, 1–6 times/wk, or less than once/wk or (b) to apply on sanitary napkins? No, Yes".	Endometrium, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that the prospective design avoids differential exposure misclassification. Key limitations were nondifferential exposure misclassification; exposure was obtained at only one time point and may not reflect total exposure; duration of use was not obtained; and asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Large prospective study with 599 diagnosed cases of confirmed endometrial cancer minimized survival bias. Adjustment for multiple potential confounders.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Crawford et al. (2012) WHI-OS, USA Enrolment, 1993–1998/ follow-up, through 12 September 2005 Cohort	48 526; prospective WHI-OS participants from 24 states in the USA. Postmenopausal women aged 50–79 yr were included. After exclusions for history of cancer, other than non-melanoma skin cancer, or hysterectomy at baseline, 48 526 were included and 447 cases of endometrial cancer were identified. Exposure assessment: Baseline self-administered questionnaire (between 1993 and 1998): "Have you ever used powder on your private parts (genital area)?" Women who answered yes were asked to specify duration of use: < 1 yr, 1–4 yr, 5–9 yr, 10–19 yr, or ≥ 20 yr. The second question was "Did you ever use a diaphragm (a birth control device that fits over the opening of your womb)?" Women who answered yes were asked "Did you ever use powder on your diaphragm?" and, if yes, were asked to specify duration of use with the same categories. No information on duration of diaphragm use was collected. Finally, women were asked "Did you ever use powder on a sanitary napkin or pad?"	Endometrium, incidence	Reported in Table 2.2.	*Exposure assessment critique*: A key strength was that the prospective design avoided differential exposure misclassification. Key limitations were nondifferential exposure misclassification; limited assessment time points; type of powder used was not obtained; and that asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Large prospective study. Adjusted for potential confounders. Avoided survival bias. *Other comments*: 52% of the population reported ever use of powder on a diaphragm, sanitary napkin or pad (perineal use).

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Houghton et al. (2014) WHI-OS, USA Enrolment, 1993–1998/ follow-up, through 17 September 2012 Cohort	61 576 postmenopausal women aged 50–79 yr were included. After exclusions for history of cancer other than non-melanoma skin cancer, bilateral oophorectomy, or an unknown number of ovaries at baseline, 61 576 participants were included, and 429 adjudicated incident ovarian cancers (including borderline) were identified. Exposure assessment method: Baseline self-administered questionnaire (between 1993 and 1998): "Have you ever used powder on your private parts (genital area)?" Women who answered yes were asked to specify duration of use: < 1 yr, 1–4 yr, 5–9 yr, 10–19 yr, or ≥ 20 yr. The second question was "Did you ever use a diaphragm (a birth control device that fits over the opening of your womb)?" Women who answered yes were asked "Did you ever use powder on your diaphragm?" and, if yes, were asked to specify duration of use with the same categories. No information on duration of diaphragm use was collected. Finally, women were asked "Did you ever use powder on a sanitary napkin or pad?"	Ovary, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that prospective design avoided differential exposure misclassification. Key limitations were nondifferential exposure misclassification and limited assessment time points; and that asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Large prospective study with many ovarian cancer diagnoses during follow-up. Prospective design minimized survival bias. Adjustment for multiple potential confounders. *Other limitations*: Sample size was limited for histological subtype-specific analyses. *Other comments*: Both invasive and borderline cases were included. Large proportion of exposed participants (52.3%).

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Gonzalez et al. (2016) USA Enrolment, 2003–2009/follow-up, through July 2014 Cohort	41 654; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Excluded participants with bilateral oophorectomies or ovarian cancer before enrolment. 154 incident ovarian cancers observed (135 ovary, 7 cancers of the fallopian tubes, 4 of the peritoneum, 8 of uncertain origin). Exposure assessment method: Self-administered questionnaire about personal care products used in the 12 mo before enrolment, which included questions about frequency of douching and about genital use of talc in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once/month, used 1–3 times/month, 1–5 times/week, or > 5 times/week.	Ovary, fallopian tubes, peritoneum, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that prospective design avoided differential exposure misclassification. Key limitations were that powder use was assessed only once, in the year before enrolment, and prevalence may have been artificially low (~14% of non-cases, 12% of cases); nondifferential exposure misclassification; limited assessment time points; asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Large prospective study avoids survival bias. Adjusted for confounding. *Other limitations*: Small number of ovarian cancer case diagnoses (n = 154) makes the study underpowered. Did not assess histological subtype-specific associations.
O'Brien et al. (2019) USA Enrolment, 2003–2009/follow-up, through September 2016 Cohort	33 609; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Excluded participants with hysterectomies or uterine cancer before enrolment. 271 incident invasive uterine cancers observed. Exposure assessment method: Frequency and ever perineal use of talc in last 12 mo and at age 10–13 yr. Self-administered questionnaire about personal care products used in the 12 mo before enrolment, and between ages 10 and 13 yr, which included questions about frequency of douching and about genital use of talc in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once/month, used 1–3 times/month, 1–5 times/wk, or > 5 times/wk	Uterine corpus, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that the prospective design avoided differential exposure misclassification. Key limitations were that use was assessed only in the year before enrolment and at age 10–13 yr leading to nondifferential exposure misclassification; and that asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Large prospective study. Adjustment for multiple potential confounders. Avoided survival bias. *Other limitations*: 76% of reported cases were confirmed (88% of self-reported cases confirmed).

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
O'Brien et al. (2021b) USA Enrolment, 2003–2009/follow-up, through September 2017 Cohort	48 509; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Participants with cervical cancer before enrolment (n = 523) were excluded from analyses of incident cervical cancer; 31 incident cervical cancers observed (16 confirmed out of 26 self-reported with medical documentation and 15 self-reported without documentation and assumed to be true cases). Exposure assessment method: Talc use was determined at two time points, at age 10–13 yr and use 12 mo before enrolment	Uterine cervix, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that the large prospective study avoided differential exposure misclassification. A key limitation was that no distinctions were made between types of powder used. Exposure to talc was assessed only at baseline. *Other strengths*: Low potential for survival bias; analyses were adjusted for many potential confounders. *Other limitations*: The study included very few new confirmed cases that were prospectively identified (n = 16); there was the possibility of residual confounding, since they were measured only at baseline.
Chang et al. (2019) Taiwan, China Enrolment, 2005/follow-up, 1997–2013 Cohort	605 652; the study uses data from the Longitudinal Health Insurance Database established in 2005, which includes claims data from 1 million beneficiaries randomly sampled from the National Health Insurance Research Database of Taiwan, China (includes 99.6% of Taiwanese people) which includes a drug prescription file. Patients aged < 20 yr in 1997, with a diagnosis of cancer in 1997, or with gastric ulcer, duodenal ulcer, peptic ulcer, gastritis, duodenitis, *H. pylori*, in or before 1997 were excluded. Exposure assessment method: Prescription data for talcum powder in Chinese herbal products; time-dependent analysis of use, cumulative exposure in grams [the Working Group assumed this came from prescription information]	Stomach, incidence	Reported in Table 2.4	*Exposure assessment critique*: Key strengths were that prospective assessment avoided differential exposure misclassification; asbestos contamination not likely, strict controls are in place for pharmaceuticals talc in Taiwan, authors mentioned data of measured 100 talc particles and found no asbestos; however, there were no data on asbestos contamination prior to 2005. Personal talc use was not obtained, which would lead to underestimation of total talc exposure but was unlikely to be correlated with medical talc exposure. Key limitations were that it was not clear if there were other sources of ingested talc; the role of herbal ingredients of products was not clear; cannot rule out asbestos contamination of the talc before 2005. *Other strengths*: Large study and many stomach cancers. *Other limitations*: Possible residual confounding because of diet and other lifestyle factors. As only those who were alive in 2005 were followed, those with incident stomach cancer who had died before 2005 were not included and survival bias had a slight impact on the results.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
O'Brien et al. (2020) USA (pooling four cohorts) NHS-I (1976; 1982–2016), NHS-II (1989; 2013–2017), SIS (2003–2009; 2003–2017), WHI-OS (1993–1998; 1993–2017) Cohort	257 044 (NHS-I, 81 869; NHS-II, 61 261; SIS, 40 647; WHI-OS, 73 267); NHS-I includes registered nurses in 1976; NHS-II includes registered nurses in 1989. Powder use queried in 1982 for NHS-I and 2013 for NHS-II. SIS includes breast cancer-free women with a sister or half-sister diagnosed with breast cancer. WHI-OS participants were postmenopausal women residing near one of the 40 recruiting clinical centres. Women with a history of ovarian cancer or known bilateral oophorectomy before baseline were excluded. Incident cases included both invasive and borderline diagnoses. Exposure assessment method: Self-administered questionnaires and telephone/interviewer assisted questionnaires; duration and frequency.	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that prospective assessment avoided differential exposure misclassification. Key limitations were nondifferential exposure misclassification because of limited assessment time points; may have included non-talc products; no assessment of lifetime cumulative talc exposure, and limited data on dose and duration. Asbestos contamination cannot be excluded, particularly in the earlier time period. *Other strengths*: Very large study pooling samples from four large cohorts (2168 ovarian cancer cases). Prospective design reduced the potential for survival biases. *Other limitations*: The study population, which was highly educated and mostly White, reduced generalizability. *Other comments*: Frequency of use was 38% overall.
O'Brien et al. (2021a) USA (pooling four cohorts) NHS-I (1976; 1982–2016), NHS-II (1989; 2013–2017), SIS (2003–2009; 2003–2018), WHI-OS (1993–1998; 1993–2019) Cohort	209 185 (NHS-I, 67 724; NHS-II, 53 589; SIS, 33 837; WHI-OS, 54 035); NHS-I includes registered nurses in 1976, NHS-II includes registered nurses in 1989 who voluntarily enrolled in the study. Powder used queried in 1982 for NHS-I and 2013 for NHS-II. SIS includes breast cancer-free women with a sister or half-sister diagnosed with breast cancer. WHI-OS were postmenopausal women residing near one of the 40 recruiting clinical centres. Women with a history of uterine cancer or known hysterectomy before baseline were excluded. Exposure assessment method: Self-administered questionnaires and telephone/interviewer assisted questionnaires; duration and frequency.	Uterine corpus, incidence	Reported in Table 2.2	*Exposure assessment critique*: A key strength was that prospective assessment avoided differential exposure misclassification. Key limitations were nondifferential exposure misclassification because single assessment time points (only baseline data were obtained and changes over time were not accounted for); also, may include non-talc products. *Other strengths*: A large, prospective cohort included many uterine cancers (n = 3162). Four prospective cohorts were pooled. Prospective design avoided survivor bias. Younger and older cohort could be evaluated for exposure that might reflect asbestos or lack of asbestos. Analyses were adjusted for several potential confounders. Patency analysis (i.e. restricting to participant without hysterectomy, tubal ligation). *Other limitations*: Not all cases were medically confirmed.

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Results table	Comments
Goldberg et al. (2024) USA Enrolment, 2009–2009/ follow-up, through 30 September 2019 Cohort	45 465 (4049 Black, 2104 Latina, 39 312 White); Prospective SIS cohort of women 35–74 yr in the USA or Puerto Rico without breast cancer, but with a sister (or half-sister) with a breast cancer diagnosis. Women missing data on race/ethnicity or use of personal care products were excluded. Exposure assessment method: See other SIS paper (O'Brien et al., 2019, above). Only information on exposure at age 10–13 yr was used in this analysis.	Breast, incidence	Reported in Table 2.5	*Exposure assessment critique*: See O'Brien et al. (2019) *Other strengths*: See O'Brien et al. (2019). A latent class approach captured real life exposure patterns; associations with single product analyses of talc were also evaluated. *Other limitations*: See O'Brien et al. (2019).
O'Brien et al. (2024) USA Enrolment, 2003–2009/follow-up, through September 2021 Cohort	49 806; SIS prospective cohort of women aged 35–74 yr who had a full or half-sister previously diagnosed with breast cancer, but who did not have breast cancer themselves at enrolment. Analyses of ovarian cancer excluded women with pre-baseline ovarian cancer or prior bilateral oophorectomies. Analyses of uterine cancer excluded women with pre-baseline uterine cancer or prior hysterectomies. Exposure assessment method: Self-administered questionnaire about personal care products used in the 12 mo before enrolment, and between ages 10–13 yr, which included questions about frequency of douching and about genital use of talc in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once/month, used 1–3 times/month, 1–5 times/wk, or > 5 times/wk; additional questionnaire administered between 2017 and 2019 that evaluated lifetime exposure.	Ovary, incidence Uterine corpus, incidence Breast, incidence	Reported in Table 2.2 Reported in Table 2.2 Reported in Table 2.5	*Exposure assessment critique*: A key strength was that quantitative bias assessment examined various assumptions about exposure and impact on nondifferential exposure misclassification. Limitations: For some cases, exposure was collected after case occurrence, introducing concern about possible differential exposure misclassification. Asbestos contamination cannot be excluded, particularly in earlier period.

CNS, central nervous system; *H. pylori, Helicobacter pylori;* HWE, healthy-worker effect; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; JEM, job-exposure matrix; mo, month(s); NHL, non-Hodgkin lymphoma; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; OH, Ohio; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons; PAPDEM, pulp and paper department-exposure matrix; SIS, Sister Study; SMR, standardized mortality ratio; US, United States; USA, United States of America; WHI-OS, Women's Health Initiative Observational Study; vs, versus; wk, week(s); yr, year(s).

(a) Talc miners, New York State, USA

Mortality in a population of talc miners and millers from the Gouverneur District of northern New York State, USA, has been reported repeatedly in several studies using essentially the same population database (Kleinfeld et al., 1967, 1974; Brown and Wagoner, 1980, in Dement et al., 1980; Stille and Tabershaw, 1982; NIOSH, 1990, in Gamble, 1993). [The Working Group considered the study by Honda et al. (2002) to be the most informative, and it was the most recent available update of the cohort for cancers of the lung, larynx, lymphohaematopoietic tissue, stomach, and colon.] In the same cohort, Stille and Tabershaw (1982) reported on intermediate follow-up until 1978, describing mortality for some cancer sites not reported by Honda et al. (2002) (pancreas, liver, oesophagus, kidney, lymphosarcoma, leukaemia, Hodgkin disease), but for which there were only 1 or 2 cases of each type. [The Working Group considered that these case numbers were too small to be meaningful, and this paper was not further considered. The Working Group also considered the study by Finkelstein (2012), for mesothelioma follow-up.]

Honda et al. (2002) presented the most recently published follow-up of mortality in a cohort of talc workers (millers and miners) in a talc mine and mill located in the Gouverneur District of northern New York State. The population was defined as all White men initially employed for ≥ 1 day between 1948, when the operations began, to the end of 1989. Mortality follow-up for those alive on 1 January 1950 was until 31 December 1989. Cumulative exposure to respirable dust was estimated using a JEM for all work area and calendar year combinations throughout the study period (Oestenstad et al., 2002). The estimated exposures were validated by comparison with available measured historical exposure concentrations. According to the authors, the ore mined and the dust at this facility contained a high proportion of non-asbestiform amphibole. Other sources (Van Gosen et al., 2004; IARC, 2010) stated that at least a proportion of the fibres in the dust may be asbestiform. This was confirmed by an industrial hygiene study carried out by NIOSH (Dement et al., 1980), which concluded, "These talcs were shown to contain fibrous tremolite and anthophyllite as major contaminants". [The Working Group noted that this statement implies that there was asbestos contamination but is still ambiguous, since fibrous tremolite is not necessarily asbestos.] Vital status was obtained from several sources, including company records. Cause of death was obtained from a computerized decedent database maintained by the state of New York for cohort members who died in New York and from death certificates, provided by either the company or by the respective state vital records offices, for those who died outside New York. Standardized mortality ratios (SMRs) were computed for the main causes of death using regional death rates and were adjusted for age group and calendar period, and 95% confidence intervals (CIs) were computed assuming a Poisson distribution of the observed deaths. For certain causes of death, the authors provided SMRs stratified by period of hire, years since hire, and years worked, and for five non-exclusive groups of work areas. For lung cancer and some other groups of non-malignant causes of death, the authors carried out internal Poisson regression analyses for cumulative exposure to respirable dust, years since hire, years worked, and work area (mills, mines). Rate ratios (RRs) were calculated with respect to an internal reference group and adjusted for age, years since hire or calendar period, or employment in other work areas. [The Working Group noted that no smoking data were available. Only overall mortality was described according to duration of work. The cohort might be affected by a strong healthy-worker survivor bias (HWSB), because workers with non-malignant respiratory diseases (NMRDs) would terminate work earlier, as well as a healthy-worker hire effect (HWE).]

Finkelstein (2012) identified 6 cases (one uncertain) of mesothelioma in the cohort followed by Honda et al. (2002). These cases of mesothelioma were diagnosed after 1989, the end of follow-up in the study by Honda et al. (2002). The cases were identified from death certificates and medical records for individuals employed in the New York State talc industry that were made publicly available as part of public response to a draft of NIOSH Bulletin 62 (NIOSH, 2007b; Finkelstein, 2012). The author did not have access to the original data for the cohort studied by Honda et al. and made the conservative assumption that all 567 workers alive at the end of follow-up by Honda et al. in 1989 were alive at the end of 2007. This led to an estimated total of about 10 000 person-years. The expected number of cases was estimated using rates for White men aged 65–74 years in 2001 in the USA. [The Working Group noted that although Finkelstein (2012) did not have access to the data used by Honda et al., the author was careful to use conservative estimates (i.e. overestimates) of the number of person-years and thus an overestimate of the expected number of cases. The number of cases of incident mesothelioma was probably underestimated, as no systematic follow-up of the cohort was attempted. However, it was not clear how the author ascertained that the cases posted on the NIOSH website were indeed part of the study population followed by Honda et al. (2002).]

(b) Talc miners, Val Chisone, Italy

Ciocan et al. (2022a) updated the mortality follow-up of a cohort of male talc miners and millers (previously investigated by Rubino et al., 1976, with reanalysis by Rubino et al., 1979; Coggiola et al., 2003; and Pira et al., 2017). The cohort included 1749 men employed for ≥ 1 month in a talc mine or mill in Val Chisone, in the Piedmont region, northern Italy, between 1946 and 1995; of these, 1184 miners were exposed to talc, silica, mining gases, and radon, and 565 millers were exposed only to talc and silica (as a potential contaminant of talc) (Ciocan et al., 2022a). There has been some debate about whether the talc in this mine is possibly contaminated with asbestos, but Ciocan et al. (2022a) reported that the overall evidence indicated that talc from Val Chisone is free from asbestos (see Table 4 in Ciocan et al., 2022a). [The Working Group confirmed that the ore in the mine did not contain asbestos (see Table 1.1).] Follow-up covered the period from 1 January 1946 through 31 January 2020 and was truncated at age 85 years. Expected deaths were calculated based on national reference mortality data for the period before 1970 and on regional reference mortality data for the period 1970–2020. SMRs were calculated for the whole cohort, by department (miners and millers), and by duration of employment. Tobacco smoking data obtained from two small surveys (1993 and 2010) indicated that the prevalence of current smokers was about 50% (which, according to the authors, was similar to that for men in Italy in the same period). No alcohol consumption data were available. [The Working Group noted this study lacked quantitative estimates of exposure to talc and there was no attempt to evaluate proxies of exposure (duration of exposure analysis was performed only for the whole cohort and not for miners and millers separately). Moreover, being based on comparison with the general population, the study may be biased by the HWE. Also, adjustment for potential confounders (e.g. alcohol consumption and tobacco smoking) was lacking. However, mortality from chronic obstructive pulmonary disease in the total cohort was not increased; this may indicate that smoking rates were not higher than in the reference population. Liver cirrhosis mortality was increased, suggesting potential confounding by alcohol consumption for alcohol-related cancers.]

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(c) Other talc miners

In addition to the Val Chisone (Italy) and New York (USA) miner cohorts, there were five additional cohort studies conducted among talc miners and millers: one in Vermont, USA (Fordyce et al., 2019), two in France and Austria (Wild et al., 2002), one in Norway (Wergeland et al., 1990), and one in Haichen, China (Fu and Zhang, 1992). An additional study in the Russian Federation was judged to be uninformative because the sample size and number of cases were not reported, and the statistical methods used were poorly described (Katsnelson and Mokronosova, 1979).

In an industry-funded study, Fordyce et al. (2019) updated and expanded a cohort of Vermont talc industry workers previously studied by Selevan et al. (1979). The original study included White men who were employed for ≥ 1 year between 1940 and 1969 and had received a chest radiography twice. The inclusion criteria were expanded to include all workers who were employed between 1930 and 1983. This study also extended the original follow-up of the cohort (1940–1975) through 31 December 2012.

The workers included in the study had been radiographed in annual surveys of Vermont workers employed in the "dusty trades", which were conducted by the Vermont Health Department from 1937. Workers from five different companies and three geographical regions were included. Two of the companies ceased operation in 1952 and 1960. A total of 427 workers were included in the study. Among these workers, 196 were employed only in milling, 200 were employed only in mining, 30 were employed in both the mine and the mill, with employment location being unknown for one worker.

Vital status was ascertained using records from the Social Security Administration, the National Death Index, private search firms, and other local records systems. Only 9 (2%) of the 427 workers were lost to follow-up. Death certificates were obtained from the state vital statistics offices and coded by a trained nosologist using the International Classification of Diseases (ICD) revision in effect at the time of death.

A modified life-table system (Occupational Cohort Mortality Analysis Program, OCMAP) was used to compute expected numbers of deaths, SMRs, and confidence intervals using the United States (US) population as the reference group. Results using Vermont rates were not presented because of privacy concerns, but the authors stated that the findings from analyses using Vermont mortality rates were similar to those from analyses using US rates. A special effort was made to identify cases of mesothelioma, because there was no ICD code for this cancer before 1999. All deaths that were coded in ICD categories that could have been assigned to represent mesothelioma cases were sent to a nosologist for further review. [The Working Group noted that a strength of this study was the long follow-up. Limitations included the small sample size and lack of control for confounders other than year and age, most notably smoking. No exposure–response information was presented for lung cancer. The study relied solely on comparisons with the general population.]

Wild et al. (2002) reported findings from a retrospective cohort mortality study of workers employed for ≥ 1 year in talc-producing companies in France and Austria. The authors noted that asbestos fibres had never been detected in talc deposits in these sites. However, concern was raised about potential co-exposure to quartz, especially for those working in underground mining, tunnelling, barrage building, and in milling for some of the sites included. Quartz contamination has been documented in the literature (see Table 1.1).

The French cohort included 1070 men who were employed at one site between 1 January 1945 and 31 December 1994. Follow-up of the cohort for mortality was from 1 January 1945 through 31 December 1996. Cause of death was

determined for those who died in 1968 or later by linkage with national death files. The causes of death for deaths before 1968 were determined from a previous mortality study in this cohort (Leophonte et al., 1983). The Austrian cohort included 542 men who were employed at one of four facilities between 1 January 1972 and 31 December 1995. Follow-up of the cohort was until 31 December 1995. The vital status and date and cause of death for the deceased were determined from linkage with a national mortality database. Life-table methods were used to estimate the expected number of deaths and SMRs that were standardized by age and time period. A combination of local and national mortality rates was used as the referent for the French cohort because local rates were available only since 1968. Mortality rates from the federal state of Styria were used as the referent for the Austrian cohort.

A nested case–control study of lung cancer (including 23 cases in France and 7 in Austria) was performed in which estimates of cumulative exposure were developed using an industry-specific JEM. An additional 2 deaths from lung cancer were identified in the French nested case–control study (with respect to the cohort study) either before 1968 or by review of secondary cause of death (Wild, 2000). Four semiquantitative categories (none, low, medium, and high) were created based on systematic exposure measurements at the French site between 1986 and 1987 and on less systematic measurements at the Austrian sites between 1998 and 1992. Cumulative exposure was also estimated based on the JEM. The controls were matched to the cases using incidence density sampling, in which controls were randomly selected from among individuals who were at risk at the age the case occurred and matched on 5-year calendar period. Approximately 3 controls were selected for each case (67 in France and 21 in Austria). Models were fitted with and without variables to control for smoking and quartz. [The Working Group noted that strengths of this study were the exposure–response analyses using semiquantitative categories of exposure and the use of a nested case–control design, which is less prone to the HWE and other biases than are the life-table analyses. Another strength was the ability to control for smoking and co-exposure to quartz.]

Wergeland et al. (2017) reported findings from a retrospective mortality and cancer incidence study of talc miners and millers in Norway, updating the results of an earlier study (Wergeland et al., 1990). The study included 390 men, of whom 94 worked in the mine and 296 in the mill. All workers who worked in the mines for ≥ 1 year in a talc-exposed job in 1944–1972 and all mill workers who worked for ≥ 2 years in a talc-exposed job in 1935–1972 were included in the study. The talc ore that was mined in Norway was reported to contain small amounts of asbestos (anthophyllite and tremolite) (see Table 1.1). Electronic microscopy analysis of air samples identified tremolite, anthophyllite, and talc particles that met the fibre definition of having a length-to-diameter ratio of greater than 3:1 (Wergeland et al., 1990). In the mill, approximately 90% of the talc that was processed came from the mine in Norway, and 10% from India. [The Working Group noted that no information was provided on potential asbestos contamination of the talc from India.] Follow-up of the cohort was initiated from 1 January 1953, or (for miners) the year of first employment in the mine, or (for millers) after 2 years of first employment in the mill, whichever was later. Cohort members were observed until 31 December 2011, date of death, or date of emigration, whichever came first. Information on date and cause of death was obtained from the Central Bureau of Statistics, and on cancer incidence from the Norwegian Cancer Registry. Expected numbers of deaths and incident cases were estimated using 5-year age-specific mortality and incidence rates for each year (1953–1987). SMRs (or standardized incidence ratios, SIRs) were estimated by taking the ratio of the observed and expected number

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of deaths (or incident cases). [The Working Group noted that the major limitations of this study were the small sample size, lack of control for confounding by smoking, and a HWE. The cancer incidence analysis also counted multiple cancers in the same individual. For example, one worker had four diagnoses of colon cancer, three occurring more than a decade after the first. Although all diagnosed tumours were included in both the cohort and the background population, generally only the first cancer diagnosis would be considered.]

Ierardi et al. (2022) conducted a pooled analysis of mesothelioma mortality in 4178 cosmetic-talc miners and millers from five cohorts described in four previous studies in Italy (Ciocan et al., 2022a), Norway (Wergeland et al., 2017), France and Austria (Wild et al., 2002), and Vermont, USA (Fordyce et al., 2019). This pooled analysis was an update of previous pooled analyses of these cohorts (Marsh et al., 2019; Marsh and Ierardi, 2020). Regional and/or national mortality rates were used as the reference group. [The Working Group concurred with concerns expressed by Finkelstein (2019) that the number of expected deaths in this pooled cohort may have been overestimated because of high rates of mesothelioma in areas with asbestos exposure, particularly in Italy, but also noted that the impact was likely to be minimal.]

Fu and Zhang (1992) reported findings from a cohort mortality study of miners in a talc mine in Haichen, China. Men who were working in the mines in January 1974 and were exposed to talc for > 1 year were included in the study. The cohort was followed from 1974 to 1988. The cause of death was determined by the hospital or at home. Analyses were stratified by time since first exposure (latency). [The Working Group considered that the talc ore that was mined in these mines (Liaoning Province) probably contains chrysotile and possibly tremolite (see Table 1.1). The Working Group noted that the publication was unclear as to whether standardized rate ratios (SRRs) or SMRs were calculated, since both terms were used to refer to the same quantity. Considering the small number of deaths and the fact that the authors mentioned that they used age-standardized mortality rates in the reference population (workers at an iron and steel company), the Working Group interpreted the quantity reported in this study to be an SMR, hence the results are reported here as SMRs. This was also consistent with how this quantity has been interpreted in the literature (e.g. see Chang et al., 2020a). The Working Group also noted that it was uncertain whether ascertainment of cause of death from the home was reliable and that this may have resulted in disease misclassification, and that it was unclear whether it was differential or nondifferential with respect to exposure. The study also presented information on smoking in the cohort, but smoking or exposure to other respiratory carcinogens was not controlled for in the analysis. A strength of the study was that it used another working population as the referent rather than the general population.]

2.1.2 *Cohorts of workers in the rubber industry*

See Table 2.1.

The Working Group reviewed six studies on the rubber industry published between 1976 and 2000 (Monson and Fine, 1978; Blum et al., 1979; Negri et al., 1989; Zhang et al., 1989; Li and Yu, 1999, 2002; Straif et al., 2000). All are cohort studies apart from Li and Yu (1999), which is a nested case–cohort study in which all participants were from a rubber worker cohort. Blum et al. (1979) also reported the results of a nested case–control study on stomach cancer mortality.

Monson and Fine (1978) conducted a retrospective cohort cancer incidence and mortality study of 13 570 White male workers from one rubber plant in Ohio, USA, who had worked for ≥ 5 years before 1 July 1971. Deaths were ascertained between 1 January 1940 and 30 June 1976.

Cause of death was assigned as cancer when any cancer was listed as the underlying or secondary cause of death on the death certificate. Cancer cases were also ascertained by surveying the tumour registries of four hospitals in the Akron area between approximately 1964 and 1974. Expected cancer death rates were based on US White males as the referent. Comparison of nonfatal cancer cases with an external population could not be undertaken, because there was incomplete ascertainment of the nonfatal cancers. The cancer analyses included stratified analyses by work area, employment duration, and year of first employment. There were no analyses by talc exposure or by exposure to any of the many other substances to which workers were exposed at the plant. Talc was used to dust some tyres in the curing area, but no exposure data were included in the paper. [The Working Group noted that one strength of this study was the large size of the cohort and the large numbers of deaths and nonfatal cancers, especially for gastrointestinal tumours and lung cancer. Ascertainment of nonfatal cancers was known to be incomplete. The use of national cancer death rates would not account for geographical variation across the country. A major limitation was the lack of analysis by talc exposure, since the rubber industry involves exposure to many other substances, including known carcinogens. Therefore, the results of this study were considered minimally informative for the evaluation of talc exposure specifically.]

Blum et al. (1979) conducted a retrospective cohort mortality study among workers in two rubber processing plants in the USA, with a combined cohort of about 17 000 workers. Eligible workers were aged 40–84 years as of 1 January 1964. Those retired as of 1 January 1964 were also included. Deaths were ascertained for the 10-year period ending 31 December 1973. Completeness of vital status ascertainment was estimated at 98%. The expected numbers of deaths were estimated on the basis of US death rates. Analyses were reported separately for the two plants. Subsequent to these findings, a nested case–control study was performed using 100 deaths from stomach cancer and 400 internal matched controls. Controls were matched to cases on age, race, sex, company and, for some analyses, on duration of employment for half of the controls. Exposure to four substances in the plants (PAHs, nitrosamines, carbon black, and talc) was classified as high, moderate, low, or no exposure on the basis of work histories, which were rated for possible exposure by three environmental scientists. [The Working Group noted that a strength of the study was the nested case–control design within the cohort, using internally matched controls, although the numbers in this analysis were small. Another strength was the assessment of talc exposure for each of the 100 cases and 400 controls, although this assessment was based on estimates of possible exposure to talc and not on detailed knowledge of actual exposure. Limitations included that the case–control analysis was poorly described, controls were not selected using density sampling, and the analysis used Mantel–Haenszel odds ratios (ORs) to account for the matching variables rather than conditional logistic regression.]

Negri et al. (1989) conducted a retrospective cohort mortality study of male workers in a rubber-tyre factory that was in operation between 1906 and 1981 in Italy. Workers were included in the cohort if they had worked for ≥ 1 year in the factory between 1946 and 1981. Of these, 9% could not be traced and were excluded. This resulted in a cohort of 6629 workers. Death certificates were obtained from registration offices in the municipality of death, and verification of vital status was obtained from registries of current residence of the workers. Follow-up began on 1 January 1946 and ended on 31 December 1981. A total of 978 deaths was registered in this period from 133 678 person-years of observation. Subgroup analyses were performed by period of first employment, age at first exposure, duration of exposure,

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period since last exposure, and 27 job categories. No analyses based on talc exposure or any other specific exposures were performed. [The Working Group noted that strengths of the study were the large size of the cohort and the access to historical employment records, which enabled workers to be categorized according to work groups and period of employment. A limitation of the study was the 9% loss to follow-up. Although no analyses based on talc exposure were performed, the workers in the job category of mechanical maintenance were possibly heavily exposed to asbestos, other fibres, and other known carcinogens in the rubber industry.]

Zhang et al. (1989) conducted a study in a cohort of 1624 workers (957 men, 667 women) employed in a rubber factory in Shanghai, China. Eligibility to enter the cohort was participation in a screening programme for coronary heart disease in 1972. Follow-up for cause of death was from 1 December 1972 to 30 November 1984 by accessing death certificates. Follow-up completeness was 95% overall, but only 91% for the men. Mortality rates for the population in the same district were used to estimate expected numbers of deaths. For lung cancer, subgroup analyses were performed according to five categories of jobs based in different parts of the plant, including the inner-tube workshop (which involved exposure to talc), but cancer deaths in these groups were low. Analyses of lung cancer deaths were stratified by smoking status. [The Working Group noted that the main focus of the paper was the impact of smoking among the rubber workers. One strength of the study was that the authors accounted for smoking history. Although there was an attempt to examine the effect of talc exposure on lung cancer mortality, a limitation was that this was done indirectly under the broad job category of work in the inner-tube workshop of the factory. The method used to determine work in the inner-tube workshop and potential for talc exposure was not stated in the paper. Other limitations include the possibility of surveillance bias because eligibility for inclusion in the cohort was participation in a screening programme, the small size of the cohort, short period of follow-up, and high loss to follow-up for the workers.]

Li and Yu (2002) conducted a cohort study in 1598 rubber factory workers followed from 1973 to 1997 in Shanghai, China. SMRs for workers in different departments (including tyre curing) were calculated using expected numbers of deaths based on Shanghai population rates, stratified by age and calendar period. SMRs for cancers of the lung, stomach, liver, oesophagus, and urinary bladder were reported. [For stomach cancer, the Working Group considered the nested case–cohort study published by Li and Yu (1999), which was conducted within the same cohort, to be more informative, given the case–cohort design focused on this cancer. The Working Group focused on the results of the tube curing, as those workers were indicated as involving exposure to talc in the rubber-industry study by Zhang et al. (1989) in Shanghai. Limitations included the small numbers of observed deaths and the lack of talc exposure assessment. The Working Group also noted the unclear overlap with the other rubber-industry study in Shanghai (Zhang et al., 1989).]

Li and Yu (1999) conducted a case–cohort study on stomach cancer mortality that was nested in a cohort of workers from a rubber-manufacturing plant in Shanghai, China, who had worked for ≥ 1 year in the plant, described in Li and Yu (2002). Thirty-six deaths from stomach cancer (32 men and 4 women) were identified between 1973 and 1995. The subcohort of 188 workers was randomly selected from the larger cohort of 1598, but 13 of these workers had died from stomach cancer and were excluded, leaving 175 workers in the subcohort. Therefore, a total of 211 workers were included in the analysis. Work history data were ascertained from company records and responses to a questionnaire. Jobs were coded into four categories, and cumulative exposure-years were also estimated.

The authors stated that the inner-tube workshop was where talc exposure occurred and conducted analyses by years of exposure in that workshop. [The Working Group noted that a strength of the study included an internal subcohort, which would minimize the impact of other confounding factors better than would a comparison with an external cohort, for example, the general population. A limitation of the exposure assessment was the categorization by work group; although this included the inner-tube workshop where talc was present, there were no estimates of talc exposure levels. Other limitations included the small number of cases, and lack of adjustment for confounding factors such as diet or smoking history. There was no accounting for exposure to other known carcinogens in the rubber industry.]

Straif et al. (2000) conducted a retrospective study in a cohort of 8933 male rubber workers from five rubber plants in Germany who had been hired from 1950, had worked for ≥ 1 year, and were still alive on 1 January 1981. The authors had published a previous paper on this cohort in which analyses had been stratified by work area, years of employment, and date of hire, but not by talc exposure (Straif et al., 1999). The cohort in the paper by Straif et al. (2000) was followed for any deaths from 1 January 1981 until 31 December 1991. Semiquantitative retrospective estimates of exposure to talc and other compounds of interest (nitrosamines, asbestos, and carbon black) were developed from 1950 onwards. Environmental monitoring data were available only from 1979. Talc was widely used in this plant as a filler material and as an anti-tacking material (e.g. in tyre inner tubes) in several areas of the plant. Asbestos was also used until the early 1980s. Exposures were classified as high, medium, and low and were further categorized by number of years of high and/or medium exposure. Results were reported for deaths from cancer of the stomach, larynx, and trachea, bronchus, and lung. For analyses that adjusted for exposure to other substances, the exposure data for talc and asbestos were combined. [The Working Group noted that the strengths of the study were the large cohort, almost complete ascertainment of cause of death, and retrospective exposure assessment for talc and three other exposures. Limitations included the small numbers for some subgroup analyses, that talc was not considered separately from asbestos in the models adjusting for exposure to other substances, and the lack of data on smoking and other potentially confounding carcinogenic exposures such as PAHs.]

2.1.3 Cohorts of workers in the pottery, ceramic, cement, and fibreglass industries

See Table 2.1.

The Working Group reviewed two occupational cohort studies in workers in the pottery and ceramic industry (Thomas and Stewart, 1987; Nie et al., 1992) and one case–control study nested in a cohort in the fibreglass industry (Chiazze et al., 1993).

Four other studies were considered to be uninformative. Two of these (Thomas, 1982, 1990) were related to the paper by Thomas and Stewart (1987). The first study (Thomas, 1982) was a preliminary proportionate mortality ratio (PMR) study on mortality among workers in the pottery industry that found an elevated frequency of lung cancer among White men previously employed in the manufacture of ceramic plumbing fixtures and thus motivated the cohort study by Thomas and Stewart (1987): it was not considered here because no attempt to analyse quantitative talc exposure or a proxy such as duration was performed (only ever versus never employment in different product lines was analysed). The second study (Thomas, 1990) simply reported lung cancer results already reported in Thomas (1982) and Thomas and Stewart (1987). The third was a PMR study in plasterers and cement masons (Stern et al., 2001),

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which was considered uninformative because the plasterers clearly had substantial exposure to asbestos and respirable silica: they experienced a significant increase in asbestosis, and 4 cases of mesothelioma were observed. The fourth was an update through 1982 of mortality in a cohort of man-made mineral fibre workers employed between 1940 and 1963 in 17 plants in the USA (Enterline et al., 1987). This study was considered uninformative because the focus was exposure to mineral fibres, not talc (which was never mentioned in the paper).

Thomas and Stewart (1987) conducted a retrospective cohort mortality study of 2055 White men employed for ≥ 1 year between 1939 and 1966 at three plants of a single company in the USA that manufactured ceramic plumbing fixtures. Crystalline silica was the major occupational exposure for these workers. "Nonfibrous" Montana steatite [tremolite-free] talc had been used in the casting process since 1955. "Tremolitic (fibrous)" (as defined in the publication) talc (discontinued in 1976) was used in spray glazing and glaze making. Maintenance workers had been exposed to both types of talc. Since no measurements of airborne silica or talc were available, exposure was assessed qualitatively by an industrial hygienist. Silica exposure was categorized as none, low, or high; the latter was further categorized as containing no talc, "fibrous" talc, or "nonfibrous" talc. [The Working Group noted that the meaning of "fibrous" talc was not specified in the paper.] The follow-up was 96% complete and covered the period from 1 January 1940 to 1 January 1981. Observed numbers of deaths were compared with numbers expected from calendar period- and age-specific mortality rates for US White men. [The Working Group noted that all jobs with talc exposure also had high exposure to respirable silica. For digestive system cancers and lymphatic and haematopoietic cancers, no analyses of specific organs were performed. Analysis of duration of exposure and time since first exposure to talc was performed only for lung cancer and NMRDs. This study, being based on comparison with the general population, may be biased downwards by the HWE.]

Nie et al. (1992) conducted a cohort study of 12 218 workers (8654 men and 3564 women) employed for > 1 year between 1972 and 1974 in seven porcelain factories in China. Production involved the use of several raw materials, including talc, porcelain stone, feldspar, quartz stone, kaolin, and limestone. Raw material and forming workers were exposed to sand, talc dust, and silica dust, whereas roasting workers were exposed only to sand dust. Samples of talc powder were examined at polarizing phase contrast microscope and shown to contain only granular talc (no fibres). Mortality follow-up covered the period 1972–1989 and ended when workers left the cohort. Expected numbers of deaths were calculated using as referents the age-specific rates for small and medium-sized cities across the whole country in 1987. In the analyses, the cohort was divided into three groups: not exposed to dust or talc, exposed to dust but not talc, and exposed to both dust and talc. [The Working Group noted that there was no follow-up of workers who left the factories. Person-years below 1 year were not excluded (calculation started when the workers joined the cohort), therefore introducing slightly downwards immortal time bias. Mortality from pneumoconiosis (often complicated by tuberculosis) was highly increased in the two groups exposed to dust and/or talc, suggesting substantial confounding by silica exposure.]

Chiazze et al. (1993) conducted a nested case–control study of lung cancer (and NMRDs) to evaluate the role of occupational exposure to several known or potential carcinogens. The study was nested in a retrospective cohort mortality study of man-made mineral fibre workers employed at a fibreglass plant in Newark, Ohio, which was the oldest and largest fibreglass-manufacturing facility in the USA and was previously included in a study on 17 manufacturing plants

in the USA (Enterline et al., 1987). [The Working Group noted that some methodological details were missing in the report by Chiazze et al. (1993), hence some details were abstracted from Enterline et al. (1987).] In the cohort study, vital status had been determined through the US Social Security Administration and other sources; death certificates had been requested from state health departments and the underlying cause of death coded according to the ICD revision in effect at the time of death. In the nested case–control study, the cases were 162 deaths from lung cancer, extracted from the cohort. Controls had been selected from cohort members who had not died from respiratory disease (malignant or non-malignant) and further excluded those whose cause of death was homicide or suicide. Controls (n = 363) were matched 2:1 to cases on year of birth (± 2 years) and survival to the end of follow-up or death (± 2 years). Extensive work was performed to reconstruct workplace exposures to several known or potential carcinogens. Detailed individual work histories were then merged with workplace exposure measurement data, and cumulative exposure to several agents was calculated. Information on smoking and education was collected in an interview survey. A conditional logistic regression model, adjusted for smoking, education, year of hire, age at first hire, and cumulative exposure to respirable fibres, asbestos, formaldehyde, respirable silica, and asphalt fumes was fitted to calculate ORs by categories of cumulative exposure to talc (fibres/mL-days). [The Working Group noted that no information was provided on the type of talc used. The maximum number of workers available for analysis was 144 cases and 260 controls, but numbers by category of cumulative exposure to talc were not reported.]

2.1.4 Studies on workers in the printing industry, pulp and paper industry, and other industries

See Table 2.1.

(a) Cohorts of workers in the printing and pulp and paper industries

There were four studies on cancer risk among workers exposed to talc in either the printing industry (Bulbulyan et al., 1999) or the pulp and paper industry (Langseth and Andersen, 1999; Boffetta and Colin, 2001, a report that became publicly available only in 2023; Langseth and Kjaerheim, 2004). Langseth and Andersen (1999) reported on a cancer incidence study in a cohort of 4247 women working in the pulp and paper industry. Langseth and Kjaerheim (2004) investigated ovarian cancer in a case–control study nested in the cohort described by Langseth and Andersen (1999). In a pooled international cohort study of workers in the pulp and paper industry, which included the cohort studied by Langseth and Andersen (1999), cancer risks were reported as a function of exposure to talc (among other exposures), quantified in a JEM (Boffetta and Colin, 2001).

Bulbulyan et al. (1999) reported a retrospective cohort mortality study in a cohort of 3473 women employed for ≥ 2 years as of 31 December 1978 in one of two large printing plants in Moscow, Russian Federation. The cohort was followed from 1 January 1979 to 31 December 1993. The jobs were classified into four groups: compositors, press operators, bookbinders, and other jobs (jobs considered to be without hazardous exposures); 94% of the women had only one job. The vital status of the workers was obtained from the Moscow Central Address Bureau, and the death certificates (coded according to ICD-9) for all deceased participants were collected from the Moscow Vital Statistics Department. Cancer mortality was reported as SMRs using 5-year age-specific

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rates for the Moscow general population to estimate the expected number of deaths. Russian paper contains talc as a filler, so printing workers, particularly bookbinders, probably had exposure to talc, which the authors indicated might have been contaminated with asbestos. Other potential exposures to known and suspected carcinogens included lead, benzene, benzo[*a*] pyrene and other PAHs, benzidine-based dyes, solvents, kaolin, paper dust, and carbon black. The SMRs were described according to the three main departments (compositors, press operators, and bookbinders). [The Working Group noted as strengths that this was a rather large cohort, with 94% of the workers holding a single job. Few (1.5%) were lost to follow-up. The main limitation of the study with respect to talc exposure was that exposure was defined only by the primary process of production; thus, no quantitative or even qualitative assessment of talc exposure was included. A further limitation was the reported contamination of the talc with asbestos. Finally, the use of SMRs often leads to a HWE and does not allow control for most confounders.]

Langseth and Andersen (1999) reported on a cancer incidence study in a cohort of 4247 women working for ≥ 1 year between 1920 and 1993 in a pulp and paper mill in Norway, who were followed for mortality and cancer incidence from 1953 to the end of 1993. Women who died before 1953 were excluded from the study. This study was part of the multinational pooled cohort study described below (Boffetta and Colin, 2001), and the numbers of person-years of follow-up were virtually identical in the two reports. For each woman, a complete work history was obtained, including departments, job titles, and date of start and end of employment in specific work activities. Three hundred and sixty women (7.8%) were excluded, mainly because of a change in surname after marriage, which prevented subsequent follow-up through linkage. The cohort was linked to the National Cancer Registry (for cancer diagnoses) and Statistics Norway (to identify date of death or date of emigration). Cancer incidence was reported as SIRs, using 5-year age-specific rates for each year for the entire female population in Norway to estimate the expected number of cases. SIRs were presented by duration of employment (cut-point at 3 years). No a priori hypothesis as to the role of talc exposure had been formulated as a risk factor for cancer of the ovary but, given the documented evidence of such an exposure, this role was hypothesized by the authors. [The Working Group noted that the main limitation was that there were no quantitative data on talc exposure; the sole evidence was that talc was known to be used as a filler in the paper. Other limitations noted were that 8% of the women could not be followed up; the power to detect any trend with duration of employment was low, since about one third of the person-years corresponded to women with < 3 years of employment; and, that finally, the use of SIRs did not allow control for confounders other than age and calendar period.]

Langseth and Kjaerheim (2004) investigated ovarian cancer in a case–control study nested in the cohort of 4247 female pulp and paper workers described by Langseth and Andersen (1999), with follow-up extended from 1993 to 1999. The stated aim of this study was to assess whether the observed excess in ovarian cancer was associated with exposure to asbestos, talc, and total dust. During the period 1953–1999, 46 cases of incident ovarian cancer were identified through linkage with the cancer registry. Each case was matched to 4 controls on birth year (± 2 years) using incidence density sampling (controls had to be in the cohort at the time that the case was diagnosed). Overall, 179 controls with intact ovaries and complete work histories were included. A questionnaire including information about production processes, use of specific agents, and changes over the years was filled out by industrial hygienists and senior employees and completed by data from a pulp and paper department-exposure matrix (PAPDEM), an international database of

exposure measurements in the pulp and paper industry. Data on possible confounders (reproductive factors, height, weight, smoking, and family history of ovarian or breast cancer) were obtained by interviewing cases (22%) and controls (49%) or next of kin (54% for cases and 17% for controls). Overall, the response rates were 76.1% of the cases and 65.7% of the controls. Because of the relatively small number of cases, exposures to talc (and asbestos) were categorized as ever/never exposed. Exposure to talc for hygienic use was also assessed. [The Working Group noted as strengths the matching of controls on date of birth within the industrial cohort and the exposure assessment based on detailed work histories and expertise by industrial hygienists and senior employees in each mill. These strengths minimized selection bias and differential exposure misclassification. The main limitation identified by the Working Group was the long period for case diagnosis and detection (from 1953 to 1999) in the context of ovarian cancer, which has a high mortality rate. Consequently, most of the detected cases were deceased before the interview. Indeed, the percentage of interviews with the next of kin (which often provide information that is less reliable than that reported by the patient) was very high, especially among cases. Thus, the difference between cases and controls in terms of response rates and responses reported by the next of kin may have led to a selection bias. Another weakness was the absence of any analysis making use of quantitative exposure data.]

Boffetta and Colin (2001) reported on the Multicentric International Cohort Study of Workers in the Pulp and Paper Industry coordinated by IARC, the aim of which was to investigate mortality and cancer incidence in workers employed in the pulp and paper industry. The population under study was workers employed for ≥ 1 year in pulp and paper companies in 15 countries – Brazil, Canada, Denmark, Finland, France, Italy, Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden, the UK, and the USA. Individuals were identified from factory records and were followed for mortality and (in some countries) cancer incidence, from the year of starting of production that ranged between 1943 and 1985 through the mid-1990s. A total of 103 773 participants were included in the analyses. The exposure characteristics of individual cohort members could not be determined on the basis of their tasks or job titles because these were available only for a part of the pooled cohort available to IARC. The minimum descriptor of the occupational histories in the epidemiological study was the department. Each mill cohort contained workers from many departments, which were coded by using a classification (96 categories) constructed for the study. A specific exposure matrix (PAPDEM; Kauppinen et al., 2002) described exposure to several substances (including talc) using both the prevalence of exposure and the level of exposure, because often only a proportion of workers in a department was exposed to each agent. Person-years at risk were calculated using a modified life-table approach (Coleman et al., 1986). Tabulation of person-years started at the beginning of the observation period or on day one of the second year of employment, if this occurred after the start of the observation period. Expected deaths were computed by multiplying the person-years in each age- and 5-year calendar period-specific stratum by the national reference rates. Expected numbers of cases of incident cancer were similarly computed in the countries reporting incidence (Denmark, Finland, New Zealand, Norway, and Sweden). A 95% confidence interval was computed for each SMR and SIR assuming that the observed number of deaths or incident cases followed a Poisson distribution. SMRs were computed by sex for ever-exposed to talc and ever highly exposed to talc as well as for selected causes by time since first exposed, duration of exposure to talc and duration of high exposure to talc. [The Working Group noted as strengths the very large cohort and detailed

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exposure assessment. The main weakness of the study with respect to talc exposure was that the exposure was defined only by the exposure of the department. The resulting nondifferential exposure misclassification might bias any observed trend with cumulative exposure towards the null. The type of talc used, including whether it was contaminated with asbestos, was not taken into account. No confounding information with respect to smoking was available. Exposure to asbestos and other carcinogenic co-exposures in this industry were evaluated separately but were not accounted for as confounders in the talc analysis. Details with respect to incident case ascertainment were missing in the countries reporting incident cases.]

(b) Studies of workers in other user industries

There were five population-based case–control studies on cancer in which occupational talc exposure was considered as a potential risk factor. These included case–control studies evaluating risk of ovarian cancer (Rosenblatt et al., 1992; Hartge and Stewart, 1994; Leung et al., 2023; reported in Table 2.2), lung cancer (Ramanakumar et al., 2008; reported in Table 2.3), and other cancers (Siemiatycki, 1991; reported in Table 2.4, Table 2.5, and Table 2.6).

Siemiatycki (1991) presented a series of parallel case–control studies carried out in Montreal, Canada, between September 1979 and June 1985. The purpose of this study was to generate hypotheses concerning potential occupational carcinogens. The cases were men aged 35–70 years with incident cancers at one of 20 cancer sites. Lung cancer results have been reported in Ramanakumar et al. (2008), which also includes additional cases recruited in a later phase; hence, for lung cancer, this later publication was considered (Section 2.3). Results for talc exposure were presented for oesophagus, stomach, colon, rectum, pancreas (Section 2.4), urinary bladder, kidney cancer (Section 2.6.1), and non-Hodgkin lymphoma (NHL) (Section 2.6.3) in the study by Siemiatycki (1991).

The main control comparison group was cancer controls; namely, cancer cases from other sites. A small population-based control series was used as an additional control group, but no results for talc were reported with this group of controls. The exposure was assessed in three steps: a self-administered questionnaire on the work history; a detailed interview with a semi-structured section designed to obtain a detailed description of each job; and a final coding by experienced industrial hygienists of these questionnaires with respect to exposures to a large list of substances, including industrial talc. The statistical analysis was based on a Mantel–Haenszel procedure considering each exposure in three categories (none, any exposure, and substantial exposure), adjusting for cancer-site specific confounders. All results were adjusted for age, family income, and cigarette-smoking index. In addition, adjustment for alcohol index was done for oesophageal cancer; for beer index for colorectal cancers; for birthplace for stomach cancer; for ethnic origin for cancers of the colon, rectum, prostate gland, and kidney; for respondent status for cancers of pancreas, bladder, and prostate; for coffee index for bladder cancer; and for the Quetelet index (i.e. BMI) for prostate cancer. Only the resulting ORs for occupational circumstance (substances, occupations, or industries) and cancer site that were significantly elevated at the level of $P = 0.10$ (one-sided) were reported. [The Working Group noted the fact that the controls were cancer controls may have biased the results towards the null for any substance that might have an effect on several cancer sites. Given the one-sided tests at the level $P = 0.10$ and the large number of tests performed, the number of false positive tests is expected to be large. Like most population-based case–control studies on occupational hazards, the exposure assessment was based on questionnaires collecting work histories: this might

lead to differential (recall bias) or nondifferential exposure misclassification. However, the use of questions that did not ask directly about exposure but rather about occupational circumstances in which the investigated exposures arise is much less susceptible to recall bias. Additionally, concern regarding recall bias was mitigated by the use of workers with other cancers as controls. No assessment of whether the talc was contaminated with asbestos was possible with this approach, although the authors considered industrial and cosmetic talc separately.]

Ramanakumar et al. (2008) reported on an analysis of lung cancer and exposure to carbon black, talc, and titanium oxide in two large case–control studies carried out in the Montreal area, Canada, in 1979–1986 and 1996–2001 (Table 2.3). Study I included only men aged 35–70 years (see above, Siemiatycki, 1991), and study II included both men and women aged 35–75 years. In study I, there were 857 cases (79% of eligible cases) and 533 population controls who were frequency-matched on sex and age strata. An additional group of 1349 controls was constituted by sampling among other patients with cancer (at major cancer sites, none of which comprised > 20% of the total). Study II included 1236 cases (response rate, 86%; 471 women and 765 men) and 1512 population controls randomly selected from electoral lists stratified by sex and age to the distribution of the cases. All included participants answered detailed structured questionnaires. A team of chemists and industrial hygienists, who were blind to case or control status, examined the questionnaires and translated the information into potential exposures from a list of 294 substances including industrial talc and occupational exposure to cosmetic talc. Major occupations entailing exposure to industrial talc included: painting, paperhanging, and related occupations; motor-vehicle mechanics and repairmen; labour and construction-related trades; printing press-related occupations. The analysis was based on unconditional logistic regression models adjusted for age, family income, ethnicity, respondent status, years of schooling, tobacco smoking (three variables), and exposure to at least one of the other occupational hazards (asbestos, silica, cadmium compounds). [The Working Group noted as strengths of this study: the inclusion of large numbers of cases and controls, good control for confounders, and an expert exposure assessment blind to case or control status. Like most population-based case–control studies on occupational hazards, the exposure assessment was based on questionnaires collecting work histories: this might lead to differential or nondifferential exposure misclassification. However, as mentioned for the study by Siemiatycki (1991), indirect questions on exposure are less susceptible to recall bias. No assessment of type of talc was possible with this approach but, like the study by Siemiatycki (1991), industrial and cosmetic talc were considered separately.]

Hartge and Stewart (1994) reported on a case–control study exploring the occupational risk factors among 296 cases of epithelial ovarian cancer during 1978–1981 in hospitals in the Washington, District of Columbia metropolitan area, USA (Table 2.2). The controls were 343 women discharged from the same hospitals for conditions unrelated to the exposures under study (talc, ionizing radiation, PAHs, solvents). The study participants were interviewed by trained interviewers using a standardized questionnaire that included lifetime job history and a specific question about exposure to talc on the job. An experienced industrial hygienist assessed the exposure of each job blind to case or control status. Only 12 cases and 31 controls had any definite, probable, or possible exposure to talc. None of the interviewed were employed in any talc mining or talc-user industry. [The Working Group noted several strengths of this study, including the relatively large numbers of cases and controls, good control for confounders, and an expert exposure assessment of a few specific

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exposures that was blind to case or control status. The main limitation was that the study was carried out in a nonindustrial metropolitan area with few occupational exposures to talc, which severely limited the study power. Moreover, there were no details on which occupations were considered exposed to talc, nor was exposure to talc clearly defined. Selection of the controls was not well described, and the Working Group thus could not judge the adequacy of control selection.]

Rosenblatt et al. (1992) evaluated occupational risk factors for ovarian cancer, but none of the occupations evaluated was specific enough to be relevant for talc evaluation. Exposure to talc through hygiene products was also evaluated in this study (see Section 2.2 and Table 2.2). [The Working Group considered that this study was uninformative for evaluating occupational exposure to talc, but that it provided relevant information for assessing personal talc use.]

Leung et al. (2023) conducted an occupational case–control study that included 498 cases of incident epithelial ovarian cancer (diagnosed in 2011–2016 in seven hospitals in Montreal, Canada) and 908 controls aged between 18 and 79 years (Table 2.2). Lifetime occupational history was evaluated for 490 cases and 895 controls. Controls were selected from the population using electoral lists and were frequency-matched to cases on 5-year age categories and electoral district. Main exposure was determined by occupational code and duration of employment in an occupation or industry. A Canadian JEM was used to assess exposure to several specific agents, including cosmetic talc, taking time period into account. Probability of exposure was estimated for each agent. Occupations exposed to cosmetic talc included: other service workers; hairdressers, barbers, beauticians, and related workers. No results were presented on industrial talc. Confounders including age, education, ancestry, parity, marital status, oral contraceptive use, endometriosis, and tubal ligation were controlled for using multivariable unconditional logistic regression. [As the numbers of exposed participants (15 cases and 16 controls) were small and the exposure assessment did not account for personal use, the Working Group considered that the results were minimally informative for the evaluation. Multiple correlated exposures were also a concern.]

2.1.5 Studies on cancer and cosmetic application of talc

(a) Cohort studies on cosmetic talc

See Table 2.1.

This section describes four large prospective cohort studies in the USA that have evaluated the association between exposure to perineal talc or body powder and cancer risk, for individual cohorts and a pooled analysis of the four cohorts that includes the Nurses' Health Study (here, abbreviated NHS-I), the Nurses' Health Study II (NHS-II), the Sister Study, and the Women's Health Initiative Observational Study (WHI-OS). The Working Group noted that NHS-II was included in pooled analyses but not published separately, given that only 76 cases of ovarian cancer had been diagnosed by 2023. The Working Group reviewed seven individual studies published between 2000 and 2021 (Gertig et al., 2000; Karageorgi et al., 2010, NHS-I; Crawford et al., 2012; Houghton et al., 2014; Gonzalez et al., 2016; O'Brien et al., 2019, 2021b) and two pooled cohort studies published in 2020 and 2021 (O'Brien et al., 2020, 2021a). Because data harmonization for the pooled analyses did not account for some of the differences in how exposure to talc and body powder was assessed, the Working Group reviewed reports for both the individual cohorts and the pooled analyses. Goldberg et al. (2024) reported results from an analysis of the Sister Study, determining the relation between everyday use of personal care products, including talcum powder applied to different parts of the body during puberty, and

the risk of breast cancer among Black, Latina, and White participants. For all observational cohort studies in this review, contamination of talc by asbestos could not be excluded.

Gertig et al. (2000) analysed data from the prospective NHS-I cohort to assess the association between perineal use of talc (defined as common use of talcum, baby powder, or deodorizing powder) and epithelial ovarian cancer (including histologically borderline tumours). Only married women were included in the cohort. Use of talc on the perineal area, or on sanitary napkins, and frequency per week was assessed in 1982 by a self-administered questionnaire. Included in this analysis were 78 630 participants, including 307 women with epithelial ovarian cancer diagnosed through 1 June 1996. Pathology reports were used to confirm reported cancers. Within the cohort, 40.4% of women had ever used talc (on the perineal area or on sanitary napkins), based on the 1982 questionnaire data. Proportional hazards analysis was performed, controlling for potential confounders including age, parity, oral contraceptive use, tubal ligation, postmenopausal hormone use, cigarette smoking, and BMI. [The Working Group noted that the prospective design reduced the potential for differential exposure misclassification but did not allow for the assessment of cumulative exposure to talc up to the time of enrolment. Strengths included the control for confounders and the prospective design that reduced selection bias. The prospective design reduces the likelihood of differential exposure misclassification, which can bias results upward; however, concern remained regarding nondifferential exposure misclassification, which is expected to bias results towards the null. However, married female nurses have a somewhat higher socioeconomic status than the general population and are also less likely to be nulliparous. Therefore, the results may not be comparable to those of other studies on women at risk of ovarian cancer, because of differences in the distribution of risk factors, such as parity, that may affect estimates of the hazard ratio (HR) for the association between body powder use and ovarian cancer.]

Karageorgi et al. (2010) reported results from the prospective NHS-I cohort for the association between perineal use of talc (i.e. talcum, baby, or deodorizing powder) or use of talc on sanitary napkins and endometrial cancer. A total of 66 028 participants were included in the analysis, ranging in age from 30 to 55 years at enrolment. Perineal exposure to talc was assessed at a single time point (in 1982). Cases were diagnosed between 1982 and 2004. Included in the analysis were 599 cases of incident cancer with diagnoses confirmed through medical records. Appropriate statistical analysis was applied with covariate adjustment. The final model was adjusted for age, calendar year, age at menarche, age at menopause, parity, age at last birth, postmenopausal hormone use duration, oral contraceptive use duration, BMI, smoking pack-years, report of diabetes, and family history of endometrial cancer. [The Working Group noted that duration of exposure was not assessed. There is a likelihood of nondifferential exposure misclassification. The exposure does not reflect use after the baseline survey.]

Houghton et al. (2014) reported results from the WHI-OS, a large cohort study of more than 93 000 postmenopausal women aged 50–79 years enrolled between 1993–1998. The average age at enrolment was 63.3 years. A self-administered mailed questionnaire at baseline (enrolment) was used to obtain risk factor information, including powder exposure. As of 17 September 2012, a total of 429 cases of incident ovarian cancer were identified and 61 576 participants were included in the analysis. Perineal exposure was assessed for use on "private parts (genital areas)," or on a sanitary napkin or pad or diaphragm. Duration of use was determined. Covariates in the multivariable proportional hazards model included age, race, duration of oral contraceptive use, duration of hormone replacement therapy, family history of

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ovarian cancer, age at last birth, BMI, smoking, tubal ligation, and parity. Analyses were also stratified on tubal ligation status (results not shown) and by ovarian cancer subtypes. The proportion of ever users of powder applied to the perineum was 52.6%. [The Working Group noted that, because of the prospective study design, there was likely to be nondifferential exposure misclassification. The exposure assessment did not distinguish powders containing talc.]

Crawford et al. (2012) reported the results of an analysis of the relation between the use of powder on a diaphragm or the duration of perineal use (on the genital area or on sanitary napkins/pads) of powder and risk of endometrial cancer, using data from the prospective WHI-OS. After exclusions, 48 526 postmenopausal women were included in the analysis. Among these women, there were 447 cases of endometrial cancer (diagnoses were confirmed by medical records). In the cohort, 52% of women reported ever use of powder (on genitals, sanitary napkin, and/or diaphragm). Covariate data collected at enrolment included age, marital status, race, BMI, number of live births, age at last live birth, age at menopause, oral contraceptive use, postmenopausal hormone use, and smoking status; backward covariate selection was applied in the analysis. Of the participants, 85% were White. Perineal use of powder was self-reported, and ever use and duration of use were obtained. Endometrial cancer subtypes were not considered. [The Working Group noted that the strengths of this study were the assessment of the exposure before cancer diagnosis, the large sample size, and the adjustments for covariates. Limitations were potential nondifferential exposure misclassification and that the exposure assessment did not distinguish powders containing talc from those that did not.]

Gonzalez et al. (2016) reported results from the Sister Study, a prospective cohort in the USA and Puerto Rico, into which more than 50 000 women were enrolled from 2003 to 2009 with follow-up through July 2014. All participants had a full or half-sister diagnosed with breast cancer and thus may be at increased risk of ovarian cancer because of genetic or other shared risk factors. The eligible study participants (41 654 women, including 154 who reported a diagnosis of ovarian, fallopian tube, or peritoneal cancer) were interviewed on the telephone using a standardized questionnaire. Those with ovarian cancer were identified through self-report, with approximately two thirds confirmed through medical records. Genital use of talc was assessed in the form of powder or spray applied to sanitary napkins, underwear, diaphragm, cervical cap, or vaginal area within the previous 12 months. The prevalence of genital use of talc in the 12 months before baseline was 14% for non-cases and 12% for cases. Most participants were non-Hispanic White women, and more than half were postmenopausal. The authors reported results from a proportional hazards model that examined the effect of douching and identified this as a possible confounder. Analyses controlled for potential confounders that included age (as the timescale), race, BMI, parity, duration of oral contraceptive use, baseline menopausal status and patency. Tumour histological subtype was not addressed. [The Working Group noted that the relatively small number of cases of ovarian cancer and low prevalence of talc use produced wide confidence intervals for the HR for talc exposure. Nondifferential exposure misclassification was likely because of the prospective study design. Exposure within the previous 12 months does not capture cumulative use. Consequently, the Working Group noted that the results were informative only for recent exposure. The Working Group noted that is reasonable to assume that most of the cases were epithelial ovarian cancer, given the age range of the study participants.]

O'Brien et al. (2019) conducted a large prospective study of uterine cancer risk in the Sister Study (2003–2009) cohort with follow-up through September 2016. A baseline

questionnaire was administered that obtained information on perineal use of talc in the 12 months before enrolment, as described by Gonzalez et al. (2016). In addition, information on perineal use of talc at age 10–13 years was also obtained. There were 271 cases of uterine cancer identified through self-report, and 207 of these were confirmed as invasive uterine cancer. All 271 cases were included in the analysis using Cox proportional hazards regression. The average age at enrolment of the cases was 58.7 years. Covariates included in the analysis were age, race/ethnicity, education, BMI, menopausal status, parity, duration of oral contraceptive use, ever hormone use, tobacco smoking, alcohol use, and age at menarche. The prevalence of ever talc use (in the past 12 months or at age 10–13 years) was 26%. Analyses were performed for medically confirmed invasive cancer cases separately and for talc use at age 10–13 years. [The Working Group noted that exposure misclassification was likely to be nondifferential with respect to cancer outcome.]

O'Brien et al. (2021b) examined the association between douching and genital use of talc and the risk of prevalent and incident cervical cancer using data from the prospective Sister Study cohort. Data were analysed for 523 cases of prevalent and 31 cases of incident cervical cancer. Talc use was determined at two time points, at age 10–13 years and in the 12 months before enrolment. Prevalent cervical cancer was mostly based on self-report. Cox proportional hazards models were used to estimate the associated relative risks and were adjusted for age, race/ethnicity, education, BMI, age at menarche, alcohol use, smoking, marital status, age at first pregnancy, ever induced abortion, hormonal birth control, genital warts, non-HPV (human papillomavirus) sexually transmitted infections, and pelvic inflammatory disease. [The Working Group noted that this study included very few confirmed cases that were prospectively identified (n = 16).]

O'Brien et al. (2020) conducted a pooled cohort analysis evaluating the association between ovarian cancer and body powder use in the genital area. Four large cohort studies were included – NHS-I and NHS-II, WHI-OS, and the Sister Study. Enrolment period ranged from 1976–2009, and 2213 cases of self-reported incident ovarian cancer (1923 confirmed cases) were examined, after study exclusions for missing exposure, prior ovarian cancer, or bilateral oophorectomy. Body powder exposure was defined as ever use or long-term use (≥ 20 years). For the Sister Study, ever use was defined as use in the year before baseline or at age 10–13 years. Long-term use was defined as use for ≥ 20 years in the NHS-II and WHI-OS and as use in the year before baseline and at age 10–13 years in the Sister Study. NHS-I was not included in the analysis for long-term use. The age range at assessment of powder use was 35–81 years. Median age at assessment of powder use across cohorts was 48–63 years. Collectively, 38% of participants reported use of powder in the genital area. Frequent use was reported by 22% of participants. Across the four studies, 2168 women with epithelial ovarian cancer were included after exclusions for missing covariates (of 1884 medically confirmed cases, 139 were borderline). Data on dose and duration were limited. [The Working Group noted that the prospective design reduced the potential for differential exposure misclassification and survival biases. The assessment of exposure differed by cohort and did not allow for the assessment of lifetime or cumulative exposure to body powder. The Sister Study asked about exposure only within the 12 months before enrolment or at age 10–13 years. Participants in NHS-II were asked about powder use only if it was at least weekly in the genital/rectal area. For the studies included, at the time of the analysis, exposure was not updated during the follow-up period leading to the diagnosis; hence, time-varying exposure could not be assessed.]

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O'Brien et al. (2021a) pooled data from four cohort studies, the Sister Study, NHS-I, NHS-II, and WHI-OS, to determine the relation between genital powder use and invasive uterine cancer. Across the four cohorts, a total of 3272 cases were included. The prevalence of ever use of genital powder was 37%. Long-term genital use (> 20 years) of body powder and risk of uterine cancer was also assessed. [The Working Group noted that the number of cases included in the analysis was large. The analyses evaluated the effect of powder use only at baseline, and changes over time were not accounted for. There was no differentiation between types of powder used or identification of what chemicals they contained.]

Goldberg et al. (2024) reported results from an analysis of 45 465 participants in the Sister Study. Associations between everyday use of personal care products, including talcum powder, at age 10–13 years (i.e. during puberty) and the risk of breast cancer among Black, Latina, and White participants were determined. Talcum powder was most frequently used by Black women, although frequent use was not common. Exposure to talc products on different body areas, including under the arms and on genitals, and breast cancer was assessed. [The Working Group noted that a latent class approach captured real-life exposure patterns and that associations with single-product analyses of talc were also determined.]

O'Brien et al. (2024) re-analysed the association between talc exposure and ovarian cancer in the Sister Study cohort, which comprised 49 806 participants who had a full or half-sister diagnosed with breast cancer, using an additional 138 cases (total, n = 292) and updated data on talc use across the life-course, which was collected in a follow-up survey administered in 2017–2019. This added to the initial exposure assessment at enrolment (2003–2009). Because the follow-up questionnaire was administered after many of the ovarian cancer cases had been diagnosed, the authors used multiple imputation and quantitative bias analysis approaches to account for nondifferential exposure misclassification and address issues of differential missing data. [The Working Group noted that this analysis should be considered an update to Gonzalez et al. (2016). This new Sister Study analysis addressed concerns regarding nondifferential exposure misclassification.]

(b) Registry-based case–control studies on cosmetic talc

See Table 2.2.

Approximately two dozen registry-based case–control studies of cancer and cosmetic talc use have been published to date (Harlow and Weiss, 1989; Chen et al., 1992; Shushan et al., 1996; Chang and Risch, 1997; Cook et al., 1997; Mills et al., 2004; Rosenblatt et al., 2011; Neill et al., 2012; Terry et al., 2013; Wu et al., 2015; Cramer et al., 2016; Schildkraut et al., 2016; Davis et al., 2021; Peres et al., 2021; Phung et al., 2022). To be defined as a registry-based study, the study had to use cases that had been identified through a cancer registry or otherwise feasibly considered to capture all incident cases in a defined geographical region over a specified time period. With the exception of an endometrial cancer case–control study conducted by Neill et al. (2012), all population-based case–control studies of the association between cosmetic talc use and cancer included in the present evaluation have focused on ovarian cancer. Most of the studies included both borderline and invasive ovarian tumours, and some included primary fallopian tube and peritoneal cancers under the umbrella of an ovarian cancer diagnosis.

Control participants were required to be free of the cancer of interest during the specified time period and representative of those in the same geographical region as the cases. They were usually matched to cases on specific demographic characteristics such as age, race/ethnicity, and geographical region. Most, but not all, ovarian

Table 2.2 Epidemiological studies on exposure to talc and cancer of the ovary and other organs in the female genital tract

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bulbulyan et al. (1999) Russian Federation 1979–1993 Cohort	3473 women employed at one of two printing plants as of 31 December 1978, with a minimum of 2 yr of employment. Exposure assessment method: See Table 2.1.	Uterine cervix, mortality	SMR by primary employment process (Moscow referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Compositor	1	[1.4 (0–8)]		
			Press operators	1	[1.1 (0–6.2)]		
			Bookbinders	2	0.9 (0.1–3.3)		
			Total cohort	6	1 (0.4–2.2)		
		Uterine corpus, mortality	SMR by primary employment process (Moscow referent):				
			Compositor	1	[1.3 (0–7)]		
			Press operators	2	2 (0.2–7.2)		
			Bookbinders	0	[0 (0–1.6)]		
			Total cohort	5	0.8 (0.2–1.8)		
		Ovary, mortality	SMR by primary employment process (Moscow referent):				
			Compositor	0	[0 (0–2.8)]		
			Press operators	1	[0.6 (0–3.3)]		
			Bookbinders	12	2.9 (1.5–5)		
			Total cohort	13	1.2 (0.6–2)		
		Ovary, mortality	Duration of employment, bookbinders (SMR, Moscow referent):				
			2–14 yr	5	1.9 (0.6–4.3)		
			≥ 15 yr	7	3.5 (1.4–7.1)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	4247 (1724 with employment in a paper mill department); cohort of 4247 women who worked for ≥ 1 yr between 1920 and 1993 in a pulp and paper mill in Norway. Exposure assessment method: See Table 2.1.	Uterine cervix, incidence	Duration of employment (SIR, national referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			< 3 yr	5	0.8 (0.25–1.79)		
			≥ 3 yr	24	1.2 (0.75–1.74)		
		Ovary, incidence	Duration of employment (SIR, national referent):				
			< 3 yr	6	1.2 (0.42–2.5)		
			≥ 3 yr	31	1.6 (1.1–2.29)		
			Total cohort	37	1.5 (1.07–2.09)		
		Ovary, incidence	Time since first exposure, long-term workers in paper mill department (SIR, national referent):				
			3–14 yr	4	3.8 (1.05–9.18)		
			15–29 yr	6	2.3 (0.83–4.94)		
			≥ 30 yr	8	1.8 (0.79–3.56)		
			Total	18	2.1 (1.26–3.36)		
		Ovary, incidence	Year of first exposure, long-term workers in paper mill department (SIR, national referent):				
			1920–1939	3	1.4 (0.27–4.02)		
			1940–1959	10	2.4 (1.26–4.82)		
			1960–1974	5	3.4 (1.07–7.85)		
			Total	18	2.1 (1.26–3.36)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Langseth and Andersen (1999) (cont.)		Ovary, incidence	Time since first exposure by year of first exposure, long-term workers in paper mill department (SIR, national referent):			Age and calendar period	
			3–14 yr, 1920–1939	0	0		
			3–14 yr, 1940–1959	2	5.2 (0.63–18.85)		
			3–14 yr, 1960–1974	2	4.3 (0.52–15.51)		
			15–29 yr, 1920–1939	0	0		
			15–29 yr, 1940–1959	4	2.7 (0.74–6.91)		
			15–29 yr, 1960–1974	2	2.3 (0.28–8.21)		
			≥ 30 yr, 1920–1939	3	1.5 (0.32–4.47)		
			≥ 30 yr, 1940–1959	4	1.7 (0.47–4.38)		
			≥ 30 yr, 1960–1974	1	7.1 (0.18–39.56)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Langseth and Kjaerheim (2004) Norway Enrolment, 1920–1993/follow-up, 1953–1999 Nested case–control	Source cohort; see Table 2.1. Cases: 46 cases of epithelial ovarian cancer selected from the Norwegian pulp and paper cohort, identified through the Cancer Registry of Norway. Controls: 179; four controls per case drawn by incidence density sampling. Matched on birth year. Controls were free of ovarian cancer and had intact ovaries. Exposure assessment method: See Table 2.1.	Ovary (epithelial), incidence	Occupational talc exposure in Norwegian pulp and paper industry (OR):			Year of birth, calendar time	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: Many of the cases and some of the controls were deceased at time of interview – asked relatives instead so missing data and misclassification were important concerns. See Table 2.1 for further limitations.
			Never	23	1		
			Ever	23	1.1 (0.56–2.18)		
		Ovary (epithelial), incidence	Talc use by personal hygiene on diapers, sanitary napkins, non-genital area or husband's use in genital area (OR):				
			Never	7	1		
			Ever	12	1.15 (0.41–3.21)		
Boffetta and Colin (2001) (publicly available since 2023) 15 countries between 1943 and 1985 to the mid-1990s Cohort	103 773 (18 241 women); workers employed for ≥ 1 yr in pulp and paper companies with complete data. Exposure assessment method: See Table 2.1.	Uterine cervix, mortality	Talc exposure (SMR):			Age, period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Ever-exposed	7	0.94 (0.38–1.94)		
			Ever highly exposed	1	0.45 (0.01–2.49)		
		Uterine corpus and uterus unspecified (ICD-9, 179, 181–182), mortality	Talc exposure (SMR):				
			Ever-exposed	5	0.95 (0.31–2.22)		
			Ever highly exposed	2	1.85 (0.22–6.69)		
		Ovary, mortality	Talc exposure (SMR):				
			Ever-exposed	14	1.13 (0.62–1.9)		
			Ever highly exposed	8	2.7 (1.17–5.32)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Ovary, incidence	Talc exposure (SIR):			Age, period, country	
			Ever-exposed	20	1.27 (0.78–1.97)		
			Ever highly exposed	8	2.53 (1.09–4.99)		
		Ovary, mortality	Years since first exposure to talc (SMR):				
			0–15 yr	5	1.28 (0.42–3)		
			16–25 yr	4	1.18 (0.32–3.02)		
			26–34 yr	4	1.39 (0.38–3.57)		
			≥ 35 yr	1	0.45 (0.01–2.51)		
			Trend-test *P*-value, 0.481				
		Ovary, mortality	Cumulative exposure to talc (SMR):				
			0–3 ppm-yr	5	5.91 (1.92–13.8)		
			4–10 ppm-yr	2	2.45 (0.3–8.86)		
			11–26 ppm-yr	1	1.37 (0.03–7.62)		
			≥ 27 ppm-yr	0	0 (0–6.48)		
			Trend-test *P*-value, 0.028				
		Ovary, mortality	Years of high exposure to talc (SMR):				
			0–1 yr	4	5.42 (1.48–13.9)		
			2–6 yr	3	3.34 (0.69–9.77)		
			7–17 yr	1	1.39 (0.03–7.74)		
			≥ 18 yr	0	0 (0–6.09)		
			Trend-test *P*-value, 0.040				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gertig et al. (2000) Nurses' Health Study (NHS-I), USA Enrolment, 1976/follow-up, 1982 through 1 June 1996 Cohort	78 630; participants were 121 700 married registered nurses enrolled in 1976, aged 30–55 yr, from 11 US states. Baseline questionnaire was administered in 1982. 307 cases of epithelial ovarian cancer (including borderline cases) diagnosed through 1 June 1996 were included. Cancer ascertainment: self-reported in follow-up questionnaires (emailed every 2 yr) and confirmed through pathology reports. Exposure assessment method: See Table 2.1.	Ovary (epithelial), incidence	Frequency of talc use on perineum (relative risk):			Age, parity, duration of OC use, BMI, tubal ligation history, smoking status, postmenopausal hormone use	*Exposure assessment critique*: See Table 2.1. *Other strengths*: The Cox proportional hazard model adjusted for potential confounders. For other strengths see Table 2.1. *Other limitations*: The sample size was moderate. For other limitations see Table 2.1.
			Never	186	1		
			< 1 time/wk	43	1.14 (0.81–1.59)		
			1–6 times/wk	30	0.99 (0.67–1.46)		
			Daily	48	1.12 (0.82–1.55)		
		Ovary (epithelial), incidence	Talc use (perineal or sanitary napkins) (relative risk):				
			Never	179	1		
			Ever	128	1.09 (0.86–1.37)		
		Ovary (epithelial), incidence	Talc use on sanitary napkins (relative risk):				
			No	242	1		
			Yes	32	0.89 (0.61–1.28)		
		Ovary (epithelial), incidence	Talc use, perineal and sanitary napkins (relative risk):				
			None	179	1		
			Either (but not both)	103	1.15 (0.9–1.46)		
			Both	25	0.9 (0.59–1.37)		
		Ovary (serous; epithelial), incidence	Talc use (perineal or sanitary napkins) (relative risk):				
			Never	101	1		
			Ever	84	1.26 (0.94–1.69)		
		Ovary (serous; epithelial; invasive only), incidence	Talc use (perineal or sanitary napkin) (relative risk):				
			Never	84	1		
			Ever	76	1.4 (1.02–1.91)		
		Ovary (mucinous; epithelial), incidence	Talc use (perineal or sanitary napkins) (relative risk):			Age, parity, duration of OC use, tubal ligation history	
			Never	30	1		
			Ever	20	0.93 (0.53–1.66)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gertig et al. (2000) (cont.)		Ovary (epithelial endometrioid), incidence	Talc use (perineal or sanitary napkins) (relative risk):			Age, parity, duration of OC use, tubal ligation history	
			Never	26	1		
			Ever	16	0.91 (0.49–1.87)		
		Ovary (epithelial), incidence	Perineal use of talc (relative risk):			NR	
			Never use	NR	1		
			Ever use and had never had a tubal ligation	NR	0.97 (0.71–1.32)		
		Ovary (epithelial), incidence	Perineal use of talc, women with patent reproductive tracts (relative risk):			NR	
			Never	NR	1		
			Ever	NR	1.15 (0.89–1.49)		
Karageorgi et al. (2010) NHS-I, USA Enrolment, 1976/follow-up, 1982–2004 Cohort	66 028 women 30–55 yr in the prospective NHS cohort were included; 599 cases of endometrial cancer diagnosed between 1982 and 2004 and confirmed by medical record review as invasive type I endometrioid adenocarcinoma were included. Exposure assessment method: See Table 2.1.	Endometrium, incidence	Perineal use of talc (RR):			Age, parity, age at last birth, age at menarche, menopausal status, age at menopause, duration of OC use, postmenopausal hormone use duration, BMI, smoking, diabetes, family history of uterine cancer, calendar year	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Never	334	1		
			Ever	265	1.13 (0.96–1.33)		
		Endometrium, incidence	Regular perineal use of talc (at least once/wk) (RR):				
			No	397	1		
			Yes	202	1.17 (0.99–1.4)		
		Endometrium, incidence	Perineal use of talc, postmenopausal women (RR):				
			Never	287	1		
			Ever	242	1.21 (1.02–1.44)		
		Endometrium, incidence	Frequency of perineal use of talc, postmenopausal women (RR):				
			Never	287	1		
			< 1/wk	57	1.09 (0.81–1.45)		
			1–6/wk	87	1.28 (1–1.63)		
			Daily	98	1.24 (0.98–1.56)		
			Trend-test *P*-value, 0.04				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Karageorgi et al. (2010) (cont.)		Endometrium, incidence	Regular perineal use of talc, postmenopausal women (at least once/week) (RR):			Age, parity, age at last birth, age at menarche, age at menopause, duration of OC use, postmenopausal hormone use duration, BMI, smoking, diabetes, family history of uterine cancer, calendar year	
			No	344	1		
			Yes	185	1.24 (1.03–1.48)		
		Endometrium, incidence	Perineal use of talc, premenopausal women (RR):			Age, parity, age at last birth, age at menarche, duration of OC use, BMI, smoking, diabetes, family history of uterine cancer, calendar year	
			Never	47	1		
			Ever	23	0.69 (0.4–1.19)		
		Endometrium, incidence	Regular perineal use of talc, premenopausal women (at least once/wk) (RR):				
			No	53	1		
			Yes	17	0.77 (0.42–1.39)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Crawford et al. (2012) WHI-OS, USA Enrolment, 1993–1998/ follow-up, through 12 September 2005 Cohort	48 526; prospective WHI-OS participants from 24 states in the USA. Postmenopausal women aged 50–79 yr were included. After exclusions for history of cancer other than non-melanoma skin cancer or hysterectomy at baseline, 48 526 were included and 447 cases of endometrial cancer were identified. Exposure assessment method: See Table 2.1.	Endometrium, incidence	All perineal use of powder (HR):			Age, race, BMI, number of live births, age at menopause, OC use, postmenopausal hormone use status, smoking status	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: Endometrial subtypes were not considered. Additional limitations in Table 2.1.
			Never	202	1		
			Ever	233	1.06 (0.87–1.28)		
		Endometrium, incidence	Duration of genital use of powder (HR):				
			Never	271	1		
			< 1 yr	47	1.03 (0.75–1.4)		
			1–4 yr	26	0.88 (0.58–1.31)		
			5–9 yr	15	0.71 (0.42–1.2)		
			10–19 yr	18	0.91 (0.56–1.46)		
			≥ 20 yr	57	1.02 (0.76–1.36)		
			Trend-test *P*-value, 0.69				
		Endometrium, incidence	Duration of diaphragm powder use (HR):				
			Never	360	1		
			< 1 yr	11	1.3 (0.71–2.38)		
			1–4 yr	13	0.8 (0.46–1.39)		
			5–9 yr	15	1.31 (0.78–2.2)		
			10–19 yr	12	1.09 (0.61–1.94)		
			≥ 20 yr	23	3.06 (2–4.7)		
			Trend-test *P*-value, < 0.001				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Houghton et al. (2014) WHI-OS, USA Enrolment, 1993–1998/ follow-up, through 17 September 2012 Cohort	61 576 postmenopausal women aged 50–79 yr were included. After exclusions for history of cancer other than non-melanoma skin cancer, bilateral oophorectomy, or an unknown number of ovaries at baseline, 61 576 participants were included, and 429 adjudicated incident ovarian cancers (including borderline) were identified. Exposure assessment method: See Table 2.1.	Ovary, incidence	Perineal use of powder on genital area (HR):			Age, race, duration of OC use, duration of hormone replacement therapy, family history of ovarian cancer, age at last birth, BMI, smoking, tubal ligation, parity	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Never	247	1		
			Ever	181	1.12 (0.92–1.36)		
			< 9 yr	112	1.23 (0.98–1.54)		
			≥ 10 yr	68	0.98 (0.75–1.29)		
			Trend-test *P*-value, 0.67				
		Ovary, incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):				
			Never	197	1		
			Ever	232	1.06 (0.87–1.28)		
			< 9 yr	135	1.09 (0.88–1.36)		
			≥ 10 yr	97	1.02 (0.8–1.3)		
			Trend-test *P*-value, 0.77				
		Ovary (serous), incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):				
			Never	87	1		
			Ever	117	1.16 (0.88–1.53)		
		Ovary (serous; invasive only), incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):				
			Never	80	1		
			Ever	105	1.13 (0.84–1.51)		
		Ovary (mucinous), incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):				
			Never	12	1		
			Ever	13	1.03 (0.47–2.27)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Houghton et al. (2014) (cont.)		Ovary (endometrioid), incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):			Age, race, duration of OC use, duration of hormone replacement therapy, family history of ovarian cancer, age at last birth, BMI, smoking, tubal ligation, parity	
			Never	13	1		
			Ever	20	1.29 (0.64–2.61)		
		Ovary (others), incidence	Perineal use of powder combined (genital area, sanitary napkins, diaphragm) (HR):				
			Never	47	1		
			Ever	54	1.04 (0.7–1.54)		
Gonzalez et al. (2016) SIS, USA Enrolment, 2003–2009/follow-up, through July 2014 Cohort	41 654; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Excluded participants with bilateral oophorectomies or ovarian cancer before enrolment; 154 incident ovarian cancers observed (ovary, 135; fallopian tubes, 7; peritoneum, 4; uncertain origin, 8). Exposure assessment method: See Table 2.1.	Ovary, fallopian tubes, peritoneum, incidence	Genital use of talc (powder or spray) in the 12 mo before enrolment (HR):			Age, race, BMI, parity, duration of OC use, baseline menopause status, patency	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Never	130	1		
			Ever	17	0.73 (0.44–1.2)		
		Ovary, fallopian tubes, peritoneum, incidence	Genital use of talc (powder or spray) in the 12 mo before enrolment (HR):			Age, race, BMI, parity, duration of OC use, baseline menopause status, patency, douching	
			Never	130	1		
			Ever	17	0.7 (0.42–1.1)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2019) SIS, USA Enrolment, 2003–2009/follow-up, through September 2016 Cohort	33 609; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Excluded participants with hysterectomies or uterine cancer before enrolment; 271 incident invasive uterine cancers observed. Exposure assessment method: See Table 2.1.	Uterine corpus, incidence	Genital use of talc (powder or spray) in the 12 mo before enrolment and/or at age 10–13 yr (HR):			Age, race/ethnicity, education, BMI, menopausal status, parity, duration of OC use, ever hormone use, smoking, alcohol use, age at menarche	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			No	178	1		
			Yes	90	1.2 (0.94–1.6)		
		Uterine corpus, incidence	Genital use of talc (powder or spray) in the 12 mo before enrolment (HR):				
			No	221	1		
			Yes	47	1.1 (0.82–1.6)		
		Uterine corpus, incidence	Genital use of talc (powder or spray) at age 10–13 yr (HR):			Age, race/ethnicity, age at menarche, relative weight at age 10 yr	
			No	198	1		
			Yes	59	1.2 (0.9–1.6)		
		Uterine corpus, incidence	Frequency of genital use of talc (powder or spray) in the 12 mo before enrolment and/or at age 10–13 yr (HR):			Age, race/ethnicity, education, BMI, menopausal status, parity, duration of OC use, ever hormone use, smoking, alcohol use, age at menarche	
			No	178	1		
			Yes, sometimes	51	1.1 (0.81–1.5)		
			Yes, frequently	39	1.4 (0.99–2)		
			Trend-test *P*-value, 0.07				
		Uterine corpus (medically confirmed invasive only), incidence	Genital use of talc (powder or spray) in the 12 mo before enrolment and/or at age 10–13 yr (HR):				
			No	NR	1		
			Yes	NR	1.2 (0.84–1.6)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2021b) SIS, USA Enrolment, 2003–2009/follow-up, through September 2017 Cohort	48 509; prospective SIS cohort that included women without breast cancer, but with a full or half-sister who had been diagnosed with breast cancer. Participants with cervical cancer before enrolment (n = 523) were excluded from analyses of incident cervical cancer; 31 incident cervical cancers observed (16 confirmed out of 26 self-reported with medical documentation and 15 self-reported without documentation and assumed to be true cases). Exposure assessment methods: See Table 2.1.	Uterine cervix, incidence	Genital use of talc in the 12 mo before enrolment and/or at age 10–13 yr (HR):			Age, race/ ethnicity, education, BMI, age at menarche, marital status, age at first pregnancy, ever induced abortion, hormonal birth control, alcohol use, smoking status, genital warts, non-HPV STIs, pelvic inflammatory disease	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: Mostly prevalent cases (n = 523) and few incident cases (n = 31), and very few confirmed cases (n = 16). Data on some key exposures were not available, e.g. HPV and abnormal Pap smear results. Additional limitations in Table 2.1.
			No	19	1		
			Yes	10	1.38 (0.66–2.86)		
		Uterine cervix, incidence	Genital use of talc in the 12 mo before enrolment (HR):				
			No	22	1		
			Yes	7	1.79 (0.78–4.11)		
		Uterine cervix, pre-enrolment prevalence	Genital use of talc at ages 10–13 yr (HR):			Age, weight relative to peers at age 10 yr, race/ethnicity, childhood socioeconomic status, age at menarche, in utero diethylstilbestrol exposure, regular drinking before age 14 yr, smoking before age 14 yr	
			Never	399	1		
			Ever	96	0.95 (0.76–1.19)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2020) USA NHS-I (1976; 1982–2016), NHS-II (1989; 2013–2017), SIS (2003–2009; 2003–2017), WHI-OS (1993–1998; 1993–2017) Cohort	257 044 (NHS-I, 81 869; NHS-II, 61 261; SIS, 40 647; WHI-OS, 73 267); NHS-I includes registered nurses in 1976; NHS-II includes registered nurses in 1989. Powder use queried in 1982 for NHS-I and 2013 for NHS-II. SIS includes breast cancer-free women with a sister or half-sister diagnosed with breast cancer. WHI-OS were postmenopausal women residing near one of the 40 recruiting clinical centres. Women with a history of ovarian cancer or known bilateral oophorectomy before baseline were excluded. Incident cases included both invasive and borderline diagnoses. Exposure assessment method: See Table 2.1.	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Use of powder in the genital area (HR):			Age, race/ ethnicity, education, BMI, parity, oral conceptive use, tubal ligation, hysterectomy, menopausal status, ever use of hormonal therapy, study	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Frequency of ever use was 38%. Evaluated association among high-grade serous cases. Adjustment for many key covariates using proportional hazards regression. For other strengths, see Table 2.1. *Other limitations*: See Table 2.1.
			Never used	NR	1		
			Ever used	[954]	1.08 (0.99–1.17)		
			Long-term use	[113]	1.01 (0.82–1.25)		
			Used powder ≥ 1 time/wk	[395]	1.09 (0.97–1.23)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Cohort (HR, ever used powder in the genital area versus never):			Age, race/ ethnicity, education, BMI, parity, oral conceptive use, tubal ligation, hysterectomy, menopausal status, ever use of hormonal therapy	
			NHS-I	NR	1.07 (0.95–1.2)		
			NSH-II	NR	0.81 (0.47–1.38)		
			SIS	NR	1.02 (0.76–1.38)		
			WHI-OS	NR	1.11 (0.95–1.3)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Use of powder in the genital area, women with patent reproductive tracts (HR):			Age, race/ ethnicity, education, BMI, parity, oral conceptive use, tubal ligation, hysterectomy, menopausal status, ever use of hormonal therapy, study	
			Never used	NR	1		
			Ever used	[623]	1.13 (1.01–1.26)		
			Long-term use	[64]	1 (0.76–1.32)		
			Used powder ≥ 1 time/wk	[285]	1.19 (1.03–1.37)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2020) (cont.)		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Cohort, women with patent reproductive tracts (HR, ever used powder in the genital area versus never),			Age, race/ ethnicity, education, BMI, parity, oral conceptive use, tubal ligation, hysterectomy, menopausal status, ever use of hormonal therapy	
			NSH	NR	1.16 (1.01–1.33)		
			NSH-II	NR	0.98 (0.52–1.83)		
			SIS	NR	0.84 (0.55–1.31)		
			WHI-OS	NR	1.13 (0.92–1.39)		
		Ovary (serous), incidence	Use of powder in the genital area (HR):			Age, race/ ethnicity, education, BMI, parity, oral conceptive use, tubal ligation, hysterectomy, menopausal status, ever use of hormonal therapy, study	
			Never used	NR	1		
			Ever used	NR	1.1 (0.97–1.25)		
		Ovary (mucinous), incidence	Use of powder in the genital area (HR):				
			Never used	NR	1		
			Ever used	NR	1.03 (0.69–1.54)		
		Ovary (endometrioid), incidence	Use of powder in the genital area (HR):				
			Never used	NR	1		
			Ever used	NR	1.15 (0.83–1.58)		
		Ovary (clear cell), incidence	Use of powder in the genital area (HR):				
			Never used	NR	1		
			Ever used	NR	1.17 (0.73–1.89)		
		Ovary (others), incidence	Use of powder in the genital area (HR):				
			Never used	NR	1		
			Ever used	NR	0.97 (0.79–1.2)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2021a) USA NHS-I (1976; 1982–2016), NHS-II (1989; 2013–2017), SIS (2003–2009; 2003–2018), WHI-OS (1993–1998; 1993–2019) Cohort	209 185 (NHS-I, 67 724; NHS-II, 53 589; SIS, 33 837; WHI-OS, 54 035); NHS-I includes registered nurses in 1976; NHS-II includes registered nurses in 1989 who voluntarily enrolled in the study. Powder used queried in 1982 for NHS-I and 2013 for NHS-II. SIS includes breast cancer-free women with a sister or half-sister diagnosed with breast cancer. WHI-OS were postmenopausal women residing near one of the 40 recruiting clinical centres. Women with a history of uterine cancer or known hysterectomy before baseline were excluded. Exposure assessment method: See Table 2.1.	Uterine corpus, incidence	Genital use of powder (HR):			Age, study	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: The results of the study were informative for the evaluation of an association between ever perineal use of talc and uterine cancer.
			Never used	NR	1		
			Ever used	[1423]	1.13 (1.05–1.21)		
			Long-term use (> 20 yr)	[213]	1.28 (1.1–1.49)		
			Used powder ≥ 1/wk	[602]	1.24 (1.12–1.37)		
			Trend-test *P*-value, 0.0009 (duration), < 0.001 (frequency)				
		Uterine corpus, incidence	Genital use of powder (HR):			Age, BMI, study	
			Never used	NR	1		
			Ever used	[1423]	1.03 (0.95–1.1)		
			Long-term use (> 20 yr)	[213]	1.13 (0.97–1.32)		
			Used powder ≥ 1/wk	[602]	1.05 (0.95–1.16)		
			Trend-test *P*-value, 0.10 (duration); 0.40 (frequency)				
		Uterine corpus, incidence	Genital use of powder (HR):			Age, BMI, race/ethnicity, education, smoking status, OC use, menopausal status, menopause status by age at menopause interaction term, type of hormone therapy use, age at menarche, bilateral oophorectomy, study	
			Never used	NR	1		
			Ever used	[1423]	1.01 (0.94–1.09)		
			Long-term use (> 20 yr)	[213]	1.12 (0.96–1.31)		
			Used powder ≥ 1/wk	[602]	1.05 (0.95–1.16)		
			Trend-test *P*-value, 0.14 (duration); 0.46 (frequency)				
		Uterine corpus (medically confirmed), incidence	Genital use of powder (HR):				
			Never used	NR	1		
			Ever used	NR	1 (0.93–1.09)		
			Long-term use (> 20 yr)	NR	1.05 (0.89–1.24)		
			Used powder ≥ 1/wk	NR	1.02 (0.91–1.15)		

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Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2021a) (cont.)		Uterine corpus: (epithelial, endometrioid), incidence	Genital use of powder (HR):			Age, BMI, race/ethnicity, education, smoking status, OC use, menopausal status, menopause status by age at menopause interaction term, type of hormone therapy use, age at menarche, bilateral oophorectomy, study	
			Never used	NR	1		
			Ever used	NR	1 (0.91–1.09)		
			Long-term use (> 20 yr)	NR	0.99 (0.82–1.19)		
			Used powder ≥ 1 time/wk	NR	1.01 (0.89–1.15)		
		Uterine corpus (epithelial, non-endometrioid), incidence	Genital use of powder (HR):				
			Never used	NR	1		
			Ever used	NR	0.96 (0.76–1.22)		
			Long-term use (> 20 yr)	NR	1.46 (1–2.11)		
			Used powder ≥ 1 time/wk	NR	0.75 (0.47–1.19)		
		Uterine corpus, incidence	Age (HR for ever vs never genital use of powder):			BMI, race/ ethnicity, education, smoking status, OC use, menopausal status, menopause status by age at menopause interaction term, type of hormone therapy use, age at menarche, bilateral oophorectomy, study	
			< 60 yr	NR	0.95 (0.8–1.12)		
			≥ 60 yr	NR	1.03 (0.95–1.11)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2024) SIS, USA Enrolment, 2003–2009/follow-up, through September 2021 Cohort	49 806; SIS prospective cohort of women aged 35–74 yr who had a full or half-sister previously diagnosed with breast cancer, but who did not have breast cancer themselves at enrolment. Analyses of ovarian cancer (n = 292) excluded women with pre-baseline ovarian cancer or prior bilateral oophorectomies. Analyses of uterine cancer (n = 433) excluded women with pre-baseline uterine cancer or prior hysterectomies. Exposure assessment method: See Table 2.1.	Ovary, incidence	Genital use of talc (bias corrected, including recall bias) (HR):			Age, race/ethnicity, attained education, measured BMI at enrolment, self-reported BMI at ages 30–39 yr, age at menarche, hormonal birth control use, menopausal status, hormone therapy use, smoking status, alcohol use, geographical region	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Never	NR	1		
			Ever	NR	1.4 (1.04–1.89)		
		Ovary, incidence	Frequency of genital use of talc (bias corrected including recall bias) (HR):				
			Never	NR	1		
			Sometimes	NR	1.18 (0.83–1.69)		
			Frequent	NR	1.81 (1.29–2.53)		
			Trend-test P-value, 0.001				
		Ovary, incidence	Duration of genital use of talc (bias corrected, including recall bias) (HR):				
			Never	NR	1		
			Short-term (1 decade only)	NR	1.17 (0.84–1.62)		
			Long-term (≥ 2 decades)	NR	2.01 (1.39–2.91)		
			Trend-test P-value, 0.001				
		Ovary, incidence	Timing of genital use of talc (bias corrected, including recall bias) (HR, ever vs never use):				
			Teens	NR	0.98 (0.71–1.37)		
			20s	NR	1.88 (1.37–2.57)		
			30s	NR	2.08 (1.5–2.89)		
			Year before baseline	NR	0.83 (0.61–1.14)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2024) (cont.)		Ovary (serous), incidence	Genital use of talc (bias corrected, including recall bias) (HR):			Age, race/ ethnicity, attained education, measured BMI at enrolment, self-reported BMI at ages 30–39 yr, age at menarche, hormonal birth control use, menopausal status, hormone therapy use, smoking status, alcohol use, geographical region, BMI by menopausal status interaction	
			Never	NR	1		
			Ever	NR	1.62 (1.06–2.48)		
		Ovary (non-serous), incidence	Genital use of talc (bias corrected, including recall bias) (HR):				
			Never	NR	1		
			Ever	NR	1.29 (0.79–2.09)		
		Ovary, incidence	Duration of genital use of talc (bias corrected including recall bias) (HR):				
			Non-genital talc user	NR	1		
			Genital talc user while had patent reproductive tract	NR	1.55 (1.14–2.09)		
			Only used genital talc after hysterectomy or tubal ligation	NR	1.38 (0.69–2.75)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2024) (cont.)		Uterine corpus, incidence	Genital use of talc (bias corrected) (HR):			Age, race/ ethnicity, attained education, measured BMI at enrolment, self-reported BMI ages 30–39 yr, age at menarche, hormonal birth control use, menopausal status, hormone therapy use, smoking status, alcohol use, geographical region	
			Never	NR	1		
			Ever	NR	1.01 (0.82–1.25)		
		Uterine corpus, incidence	Frequency of genital use of talc (bias corrected) (HR):				
			Never	NR	1		
			Sometimes	NR	0.99 (0.75–1.29)		
			Frequent	NR	1.03 (0.79–1.33)		
			Trend-test *P*-value, 0.88				
Cramer and Xu (1995) Boston Area, USA Recruitment: phase I, 1978–1981; phase II, 1984–1987 Case–control	Cases: 450 cases of epithelial ovarian cancer, including borderline malignancies, identified in hospitals in the greater Boston area. During phase I recruitment, 297 eligible cases were identified (13 could not be contacted, 14 declined, and 14 had died or migrated before interview) (Cramer et al., 1982). For phase II recruitment, 294 cases were identified, but only 69% agree to be interviewed and the final sample was restricted to 235 White women.	Ovary (epithelial), incidence	Genital use of talc (OR):			Age, precinct of residence	*Strengths*: Case–control study with hospital-identified cases and population-based controls matched on age and residence. The sample size was sufficiently large to evaluate ever use of talc. *Limitations*: Differential exposure misclassification cannot be ruled out but was probably nondifferential.
			No	249	1		
			Yes	201	1.6 (1.2–2.1)		
		Ovary (epithelial), incidence	Genital use of talc, women who had pelvic surgery (hysterectomy or tubal ligation) (crude OR):			None	
			No	25	1		
			Yes	27	[2.73 (1.28–5.84)]		
		Ovary (epithelial), incidence	Genital use of talc, women without pelvic surgery (OR):			None	
			No	224	1		
			Yes	174	[1.45 (1.09–1.93)]		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer and Xu (1995) (cont.)	Controls: 454; selected from general population, matched on age and precinct of residence. Women with history of bilateral oophorectomy were excluded as controls. It is not specified how controls were identified, but previous publications (Cramer et al., 1982; Harlow and Hartge, 1995) refers to the use of the published list of residents (Massachusetts Town Book). For phase I recruitment, 475 controls were identified, and 215 were finally included and interviewed (45%) (Cramer et al., 1982). For phase II recruitment of the 526 contacted, 239 agreed to participate (45%) (Harlow et al., 1992). Exposure assessment method: Questionnaire administered through in-person interview. Questions on use of talc in perineal hygiene.						Histological subtype-specific analyses were not conducted. No assessment of frequency or duration of use. No adjustment for potential confounding. Unclear if hospital identification of cases would be fully representative of region. Asbestos contamination of the talc cannot be excluded. *Other comments*: ORs for genital use of talc for those with and without pelvic surgery calculated using counts reported in the manuscript.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge et al. (1983) Hospitals in Washington DC area, USA Cases diagnosed, 1974–1977; Interviews, NR Case–control	Cases: 135; pathologically confirmed primary epithelial ovarian cancer treated in participating hospitals. Controls: 171; hospital-based from same hospitals, for conditions other than gynaecological, psychiatric, or malignant diseases, or pregnancy. Frequency-matched to cases on age, race, and hospital. Exposure assessment method: Talc added to questionnaire after study began; sample described here part of broader case–control sample described in Hartge and Stewart (1994).	Ovary (epithelial), incidence	Body talc use (OR):			Age, race, hospital	*Strengths*: Asked specifically about genital use of talc. *Limitations*: Hospital-based, small sample size. Asbestos contamination of the talc cannot be excluded *Other comments*: Question about ovarian talc added after the study began, so 135 cases and 171 controls were asked.
			No body talc	77	1		
			Some body talc	54	0.8 (0.5–1.2)		
		Ovary (epithelial), incidence	Location of body talc use (OR):				
			No body talc	77	1		
			All over	37	0.7 (0.4–1.2)		
			Genital area, sanitary napkins, or underwear	7	2.5 (0.7–10)		
			Legs only	1	-		
			Not genital area	6	0.8 (0.3–2.5)		
			Unknown location	3	0.3 (0.1–1.2)		
		Ovary (epithelial), incidence	Diaphragm use (OR):				
			No diaphragm	92	1		
			Diaphragm, no talc	14	1.6 (0.7–3.7)		
			Diaphragm, with talc	25	0.8 (0.4–1.4)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hartge and Stewart (1994) Hospitals in Washington, DC area, USA Cases diagnosed, 1978–1981; interviews, NR Case–control	Cases: 296 cases of epithelial ovarian cancer diagnosed in hospitals in the Washington DC area. Controls: 343 patients discharged from the same hospitals as cases for conditions "unrelated to any of the exposures under study" (conditions not specified) and matched on age and race. Exposure assessment method: Participants were interviewed regarding their job history. Job/industry combinations were evaluated by industrial hygienist for potential talc exposure.	Ovary (epithelial), incidence	Length of occupational exposure to talc (OR): None < 5 yr 5–9 yr ≥ 10 yr	 263 5 2 5	 1 0.5 (0.1–1.4) 0.3 (0.1–1.4) 0.5 (0.2–1.5)	Age, race, parity, gynaecological surgery	*Strengths*: A relatively large case–control study with an industrial hygiene assessment of potential exposure to talc, ionizing radiation, PAHs, and solvents blind to case–control status. *Limitations*: A study in a nonindustrial metropolitan area with few exposures to known or suspected carcinogens. Asbestos contamination of the talc cannot be excluded.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Whittemore et al. (1988) Hospitals in northern California, USA Cases diagnosed, 1983–1985 Case–control	Cases: 188 cases of primary epithelial ovarian cancer selected from residents in northern California, aged 18–74 yr, who were diagnosed at one of seven hospitals in northern California. Controls: 539 (source, 1, 280; source 2, 259); Two sources of controls: source 1, women hospitalized at the same hospital as cases (controls with bilateral oophorectomy, or admitted for psychiatric, obstetric, gynaecological, malignant conditions were excluded); source 2, controls selected in the general population using random-digit dialling telephone contact.	Ovary (epithelial), incidence	Perineal use of talc (OR):			Age, race, study factors (hospital/date or geographical area), parity, surgical sterilization (tubal ligation or hysterectomy)	*Strengths*: Two sources of controls showed robust findings. Adjustment for a few potential confounders. *Limitations*: Small sample size. Possibility of differential exposure misclassification. Because of small sample size, the result may be limited for the evaluation. Asbestos contamination of the talc cannot be excluded.
			Never	91	1		
			Ever	97	1.37 (0.97–1.95)		
		Ovary (epithelial), incidence	Talcum powder use (OR):			Age, race, study factors (hospital/date or geographical area), parity, OC use	
			None	75	1		
			Perineum only	22	1.45 (0.81–2.6)		
			Sanitary pads only	5	0.62 (0.21–1.8)		
			Diaphragm only	9	1.5 (0.63–3.58)		
			Any two of perineum, pads, and diaphragm	67	1.36 (0.91–2.04)		
			All three of perineum, pads, and diaphragm	1	0.35 (0.04–2.94)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Whittemore et al. (1988) (cont.)	Hospital controls were matched on age, race, hospital, and date of admission; population controls matched on age, race, telephone area code and prefix (details on matching from Wu et al., 1988). Exposure assessment method: Ever use, frequency and duration of talc was collected using structured interview in-person.	Ovary (epithelial), incidence	Frequency of talcum powder use on the perineum (OR):			Age, race, study factors (hospital/date or geographical area), parity	
			None	97	1		
			1–20 times/mo	41	1.27 (0.82–1.96)		
			≥ 20 times/mo	44	1.45 (0.94–2.22)		
			Continuous (per 30 times/ mo)	182	1.3 (0.88–1.92)		
		Ovary (epithelial), incidence	Duration of talcum powder use, before tubal ligation or hysterectomy, on the perineum (OR):				
			None	103	1		
			1–9 yr	34	1.6 (1–2.57)		
			≥ 10 yr	50	1.11 (0.74–1.65)		
		Ovary (epithelial), incidence	Perineal use of talc and surgical sterilization (OR):				
			No talc use, no sterilization	70	1		
			Talc use, no sterilization	71	1.33 (0.88–2.01)		
			No talc use, with sterilization	21	0.5 (0.29–0.88)		
			Talc use, with sterilization	26	0.75 (0.43–1.29)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Booth et al. (1989) London and Oxford, UK; hospital-based Interviews, 1978–1983 Case–control	Cases: 235 women aged < 65 yr with epithelial ovarian cancer diagnosed in 13 hospitals in London and two in Oxford. Only cases with an interview within 2 yr from diagnosis were included. Controls: 451 women aged < 65 yr selected from the same hospitals as cases (not hospitalized for gynaecological, circulatory, gallbladder, thyroid conditions, or for uterine, urinary bladder, or breast cancer, rheumatoid arthritis, or melanoma) and 2:1 matched on age.	Ovary (epithelial), incidence	Frequency of talc use in the genital area (relative risk):			Age, social class	*Strengths*: used multiple logistic regression analysis and adjusted for age and social class. *Limitations*: Hospital-based controls may have modified behaviour because of disease and may not represent the source population of the cases. Potential differential exposure misclassification. Asbestos contamination of the talc cannot be excluded. The sample size was small and no histological subtype-specific analysis was conducted.
			Never	76	1		
			Rarely	6	0.9 (0.3–2.4)		
			Monthly	7	0.7 (0.3–1.8)		
			Weekly	57	2 (1.3–3.4)		
			Daily	71	1.3 (0.8–1.9)		
			Trend-test *P*-value, 0.05				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Booth et al. (1989) (cont.)	For 63 cases recruited in a cancer hospital, controls were selected from another hospital when not available from the same hospital and analyses used an unmatched approach (adjusting for age and SES). Women with history of bilateral oophorectomy were excluded. Exposure assessment method: Standardized questionnaire was administered by trained interviewer. Frequency of talc use on genital areas was obtained. Duration of use was not obtained.						

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Harlow and Weiss (1989) Western Washington state, USA; population-based 1980–1985 Case–control	Cases: 116 White women, aged 20–79 yr, with a serous or mucinous borderline ovarian tumour diagnosed 1980–1985 and recorded by the Seattle–Puget Sound Cancer Surveillance System; response rate, 68%. Controls: 158 White women, identified via random-digit dialling; similar to cases in terms and county; had not had bilateral oophorectomy. Response rate, 74%. Exposure assessment method: Questionnaire.	Ovary: borderline (serous or mucinous), incidence Ovary: borderline (serous or mucinous), incidence	Perineal exposure to powder (OR):			Age, parity, use of OCs	*Strengths*: population-based case–control design. *Limitations*: focused on borderline rather than invasive disease; low response rates. Asbestos contamination of the talc cannot be excluded
			None	67	1		
			Any	49	1.1 (0.7–2.1)		
			Type of powder used (OR):				
			None	67	1		
			Cornstarch only (no combined use)	4	0.8 (0.2–3.8)		
			Baby powder only	18	0.8 (0.4–1.9)		
			Baby powder only or combined use	22	0.9 (0.5–2)		
			Talc, unspecified (no combined use)	13	1 (0.4–2.4)		
			Deodorizing powder only	10	3.5 (1.2–28.7)		
			Deodorizing powder only or combined use	14	2.8 (1.1–11.7)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cook et al. (1997) Western Washington state, USA; population-based 1986–1988 Case–control	Cases: 313 White women aged 20–79 yr at diagnosis with invasive or borderline epithelial ovarian cancer (diagnosed between 1986 and 1988), identified from Cancer Surveillance System of western Washington state; 64% of eligible cases were interviewed. Controls: 422 women identified using random-digit dialling, selected from a pool of 3604 controls selected for several cancer studies, frequency-matched to cases on 5-yr age group. Of the controls eligible for this study (721), 72.3% agreed to the interview. Potential controls reporting a history of bilateral oophorectomy were excluded. Exposure assessment method: Questionnaire.	Ovary (epithelial), incidence	Lifetime genital application of powder (OR):			Age	*Strengths*: Detailed assessment of type and location of powder applied. *Limitations*: High mortality in cases, low response rates, minimal confounding adjustment (age and other type of powder only); possibility of differential exposure misclassification. Asbestos contamination of the talc cannot be excluded.
			None	154	1		
			Any	159	1.5 (1.1–2)		
		Ovary (epithelial), incidence	Exclusive method of powder application (OR):				
			None	154	1		
			Perineal dusting only	55	1.8 (1.2–2.9)		
			Diaphragm storage in powder only	22	0.8 (0.4–1.4)		
			Powder on sanitary napkins only	12	1.5 (0.6–3.6)		
			Genital deodorant spray only	18	1.5 (0.8–3)		
		Ovary (epithelial), incidence	Cumulative lifetime days of perineal genital powder dusting (OR):			Age, other methods of genital powder application	
			None	154	1		
			≤ 2000 days	20	1.8 (0.9–3.5)		
			2001–5000 days	24	1.6 (0.9–2.9)		
			5001–10 000 days	21	1.2 (0.6–2.4)		
			> 10 000 days	28	1.8 (0.9–3.4)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cook et al. (1997) (cont.)		Ovary (epithelial), incidence	Type of powder used with perineal dusting, diaphragm storage or sanitary napkins (OR):			Age, other types of powders used	
			No lifetime use	154	1		
			Any talcum powder	33	1.6 (0.9–2.8)		
			Any baby powder	52	1.1 (0.7–1.8)		
			Any cornstarch	8	0.8 (0.3–2)		
			Any deodorizing powder	24	1.1 (0.6–2)		
			Any bath/body powder	52	1.5 (0.9–2.4)		
		Ovary (serous), incidence	Genital use of powder (OR):			Age	
			None	60	1		
			Any	71	1.7 (1.1–2.5)		
		Ovary (mucinous), incidence	Genital use of powder (OR):				
			None	29	1		
			Any	14	0.7 (0.4–1.4)		
		Ovary (endometrioid), incidence	Genital use of powder (OR):				
			None	19	1		
			Any	17	1.2 (0.6–2.3)		
		Ovary (others), incidence	Genital use of powder (OR):				
			None	46	1		
			Any	57	1.8 (1.1–2.8)		

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Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rosenblatt et al. (1992) Johns Hopkins Hospital, Baltimore, USA 1981–1985 Case–control	Cases: 77 cases of pathologically confirmed epithelial ovarian cancer diagnosed within 6 mo of admission in Johns Hopkins hospital, and resident in the USA. Controls: 46 female inpatients in Johns Hopkins hospital, without malignant or gynaecological conditions. Controls were matched on age, race, and date of admission. Controls could not be found for all cases, so a posteriori matching was performed; 31 matched sets consisted of 2 cases and 1 control. Exposure assessment method: Questionnaire administered in the hospital or on the telephone.	Ovary (epithelial), incidence	Genital use of fibres (OR):			Age, race, date of admission, number of live births	*Limitations*: The study size was small, with 46 matched case–control sets. The duration of "genital fibre" exposure cannot be interpreted as an effect of talc. The selection of confounders included in the models was post hoc and only based on significance, which may have biased the results. Asbestos contamination of the talc cannot be excluded.
			No	10	1		
			Yes	67	1 (0.2–4)		
		Ovary (epithelial), incidence	Diaphragm use with powder (OR):			Age, race, date of admission, number of live births, education	
			No	60	1		
			Yes	14	3 (0.8–10.8)		
		Ovary (epithelial), incidence	Genital use of bath talc (OR):			Age, race, date of admission	
			No	54	1		
			Yes	22	1.7 (0.7–3.9)		
		Ovary (epithelial), incidence	Sanitary napkin with talc exposure (OR):			Age, race, date of admission, highest weight 1 yr before diagnosis	
			No	49	1		
			Yes	21	4.8 (1.3–17.8)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chen et al. (1992) Beijing, China, population-based 1984–1986 Case–control	Cases: 112 cases of newly diagnosed epithelial ovarian cancer were identified through the Beijing Cancer Registry, which covers the Beijing metropolitan area. Of the 220 patients identified, 47% could not be located or were dead; 112 of 116 were interviewed (4 refused to participate). Controls: 224 controls were selected from the same area (commune) as cases, screening the neighbourhood or village census lists. Women were matched on age to cases. Women with serious illness (including gynaecological conditions) were excluded as controls; 15 controls refused participation. Exposure assessment method: Questionnaire.	Ovary (epithelial), incidence	Use of dusting powder on the lower abdomen and perineum for ≥ 3 mo (OR): Never Ever	 105 7	 1 3.9 (0.9–10.6)	Age, neighbourhood (commune), education, parity	*Strengths*: Non-USA population. *Limitations*: Low contact rate in cases because of high mortality and inability to locate; high response in matched controls; over exclusion of controls for other gynaecological conditions; unclear what that powder assessment questions were. Asbestos contamination of the talc cannot be excluded.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tzonou et al. (1993) Athens, Greece; hospital-based Recruitment: 1989–1991 Case–control	Cases: 189 women residents in the Greater Athens area aged < 75 yr who underwent surgery for epithelial ovarian cancer (1989–1991) in two major cancer hospitals in Athens. Controls: 200; women residents at Greater Athens area aged < 75 yr among visitors of patients admitted in the same ward and time as cases. No matching criteria reported. Exposure assessment method: In-person interview.	Ovary (epithelial), incidence	Talc application in the perineum (OR): No Yes	 183 6	 1 1.05 (0.28–3.98)	Age, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking, alcohol, coffee, analgesics, tranquillizers, hair dyes	*Strengths*: Non-USA population (Greece); selected as controls visitors rather than hospitalized women; thus, controls may be more representative of source population than in other hospital-based case–control studies. *Limitations*: Very small sample, very few women exposed to talc (6 cases, 7 controls). Asbestos contamination of the talc cannot be excluded.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Green et al. (1997) Eastern Australia; hospital-based Case diagnosis, August 1990 to December 1993; interviews, NR Case–control	Cases: 824 women aged 18–79 yr diagnosed with epithelial ovarian cancer, registered in gynaecological treatment centres in New South Wales, Victoria, and Queensland. Participation rate, 90%. Controls: 855 controls were matched on age, urban/rural district of residence and randomly chosen from electoral lists. Women with history of bilateral oophorectomy or ovarian cancer were excluded. Response rate, 73%. Exposure assessment method: In-person interview. Talc exposure to perineal area was obtained from face-to-face interviews; 40% were exposed to talc.	Ovary (epithelial), incidence Ovary (epithelial), incidence	Perineal use of talc (OR): Never Ever Perineal use of talc and surgical tubal occlusion (OR): No perineal talc use and no surgical tubal occlusion No perineal talc use and surgical tubal occlusion Perineal talc use and no surgical tubal occlusion Perineal talc use and surgical tubal occlusion	 NR NR NR NR NR NR	 1 1.3 (1.1–1.6) 1 0.6 (0.5–0.84) 1.3 (1–1.7) NR	Age at diagnosis and place of residence, parity, duration of OC use, education, BMI, smoking, family history of cancer	*Strengths*: Population-based case–control study. Standardized questionnaire from face-to-face interviews. Adjusted for covariates using multivariable logistic regression. Ample sample size. Examined association in those with no tubal ligation or hysterectomy. *Limitations*: Possibility of differential exposure misclassification. Asbestos contamination of the talc cannot be excluded.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shushan et al. (1996) Israel; population-based Case diagnosis, 1990 to 1 September 1993; interviews, 1993–1994 Case–control	Cases: 200 women born between 1929 and 1957 (aged 36–64 yr), alive, with primary invasive or borderline epithelial ovarian cancer reported in the Israel Cancer Registry, diagnosed between 1990 and 1 September 1993; 70% participation among the identified cases. Controls: 408 women born between 1929–1957. Controls selected using random-digit dialling within the same area codes as cases. Women with history of bilateral oophorectomy were excluded. Of eligible women, only 53% could be interviewed (10.7% of households contacted could not participate because of not speaking Hebrew). Exposure assessment method: Questionnaire.	Ovary (epithelial), incidence	Talc use (OR): Never or seldom Moderate or a lot	 178 21	 1 [1.97 (1.06–3.66)]	Geographical area	*Strengths*: Population-based, non-US population. *Limitations*: Small sample size, no adjustment, and talc use not a major exposure of interest in the paper. Asbestos contamination of the talc cannot be excluded.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang and Risch (1997) SON study, Ontario, Canada; population-based 1 November 1989 to 31 October 1992 Case–control	Cases: 450 women aged 35–79 yr with invasive and borderline epithelial ovarian cancer diagnoses, identified via Ontario Cancer Registry (see Risch et al., 1994). Acceptance rate, 71.3%. Controls: 564 women identified through the Ontario ministry of finance. Matching on age (by three 15-yr age groups). Women with history of bilateral oophorectomy excluded. Acceptance rate, 64.5%. Exposure assessment method: Questionnaire; self-report with in-person interviews; duration of use, frequency.	Ovary (epithelial), incidence	Dusting or powdering behaviour (OR):			Age, year of OC use, parity, breastfeeding, tubal ligation, hysterectomy, 1st degree family history of breast/ ovarian cancer	*Exposure assessment critique*: Limitations: differential misclassification possible; 8.7% of cases died before interviews. Asbestos contamination of the talc cannot be excluded. *Other strengths*: Population-based, non-US population. *Other limitations*: Low response rates, possibility of selection bias. *Other comments*: Corresponds to the Southern Ontario Ovarian Cancer Study (SON) included in the pool analysis by Terry et al. This original analysis included some extra details.
			Never used	NR	1		
			Regular application of talc	198	1.42 (1.08–1.86)		
			Regular application of cornstarch	2	0.305 (0.06–1.66)		
			Use of cornstarch sometimes and talc sometimes	4	0.681 (0.18–2.55)		
		Ovary (epithelial), incidence	Type of talc exposure (OR):				
			Never used talc	NR	1		
			Sanitary napkin	51	1.262 (0.81–1.96)		
			After bathing	172	1.312 (1–1.73)		
		Ovary (epithelial), incidence	Frequency of after-bath talc use (OR):				
			Never used talc	NR	1		
			< 10 times/mo	76	1.836 (1.24–2.73)		
			10–25 times/ mo	54	1.128 (0.74–1.72)		
			> 25 times/mo	41	0.951 (0.61–1.49)		
			Continuous (per 10 applications/ mo)	NR	0.89 (0.74–1.07)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang and Risch (1997) (cont.)		Ovary (epithelial), incidence	Years of after-bath talc use (OR):			Age, year of OC use, parity, breastfeeding, tubal ligation, hysterectomy, 1st degree family history of breast/ ovarian cancer	
			Never used talc	NR	1		
			< 30 yr	60	1.697 (1.09–2.64)		
			30–40 yr	71	1.435 (0.96–2.15)		
			> 40 yr	41	0.865 (0.54–1.38)		
			Continuous (per 10 yr of use)	NR	1.091 (0.98–1.21)		
		Ovary (epithelial), incidence	Years of after-bath talc use (OR):				
			Continuous (per 10 yr of use), before 1970	NR	1.09 (0.98–1.22)		
			Continuous (per 10 yr of use), after 1970	NR	1.095 (0.89–1.35)		
		Ovary (epithelial), incidence	Years of after-bath talc use (OR):				
			Continuous (per 10 yr of use), before tubal ligation/ hysterectomy	NR	1.105 (0.99–1.24)		
			Continuous (per 10 yr of use), after tubal ligation/ hysterectomy	NR	1.031 (0.82–1.29)		
		Ovary (serous), incidence	Regular perineal use of talc (OR):				
			Never	NR	1		
			Ever	109	1.336 (0.96–1.85)		
		Ovary (mucinous), incidence	Regular perineal use of talc (OR):				
			Never	NR	1		
			Ever	35	1.585 (0.97–2.58)		
		Ovary (endometrioid), incidence	Regular perineal use of talc (OR):				
			Never	NR	1		
			Ever	36	1.671 (1–2.79)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wong et al. (1999) Buffalo, New York, USA; hospital-based Cases treated, October 1982 to October 1995 Case–control	Cases: 462 cases of epithelial ovarian cancer in women treated in Roswell Park Cancer Institute between 1982 and 1995 and registered in the Roswell Park Tumour Registry. Controls: 693 controls were selected from the Roswell Park Tumour Registry (colorectal cancer, 326; stomach cancer, 23; small intestine, 11; leukaemia, 134; skin cancer, 261) and frequency-matched to the cases on age. Exposure assessment method: Self-administered questionnaires to all patients of the hospital at admission. Ever use and duration of genital use of talc was assessed.	Ovary (epithelial), incidence	Perineal use of talc (OR):			Age, parity, OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographical location, history of tubal ligation or hysterectomy	*Strengths*: Moderate sample size. Use of information collected at admission of cases in the hospital might avoid survival bias. Adjustment for potential confounders using logistic regression analysis. Use of cancer controls might reduce differential exposure misclassification *Limitations*: Hospital controls do not represent the same source population as the cases or healthy general population. Number of specific histological subtypes was small. Asbestos contamination of the talc cannot be excluded.
			Never	241	1		
			Ever	221	0.92 (0.24–3.62)		
		Ovary (epithelial), incidence	Site of talc use (OR):				
			Never used	241	2		
			Sanitary napkin [only]	13	0.9 (0.4–2)		
			Genital or thigh area [only]	157	1 (0.8–1.3)		
			Both	51	1.1 (0.7–1.7)		
		Ovary (epithelial), incidence	Duration of talc use (OR):				
			None	241	1		
			1–9 yr	39	0.9 (0.6–1.5)		
			10–19 yr	49	1.4 (0.9–2.2)		
			≥ 20 yr	101	0.9 (0.6–1.2)		
		Ovary (epithelial), incidence	Genital use of talc, women with patent reproductive tracts (OR):			Age, parity, OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographical location	
			Never	130	1		
			Ever	121	1.2 (0.8–1.6)		
		Ovary (epithelial), incidence	Genital use of talc, women with a history of tubal ligation or hysterectomy (OR):				
			Never	111	1		
			Ever	100	0.8 (0.5–1.2)		
		Ovary (serous), incidence	Perineal use of talc (OR):				
			Never	NR	1		
			Ever	NR	1.2 (0.7–2.1)		
		Ovary (mucinous), incidence	Perineal use of talc (OR):				
			Never	NR	1		
			Ever	NR	1.5 (0.6–4)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wong et al. (1999) (cont.)		Ovary (endometrioid), incidence	Perineal use of talc (OR):				
			Never	NR	1		
			Ever	NR	1.4 (0.7–2.7)		
		Ovary (clear cell), incidence	Perineal use of talc (OR):				
			Never	NR	1		
			Ever	NR	1.6 (0.6–4.3)		
Godard et al. (1998) Montreal, Canada; hospital-based Recruitment, 1995–1996 Case–control	Cases: 170 French-Canadian women in Montreal aged 20–84 yr with histologically confirmed diagnosis of primary ovarian cancer (invasive or borderline) of epithelial origin. Selection through gynaecological oncology clinics in two largest teaching hospitals in Montreal. Response rate, 87%. Controls: 170; frequency-matched on age, ethnicity. Identified through random-digit dialling, selected from the same page of the telephone list as cases. 10.7% of eligible controls refused to participate. Exposure assessment method: questionnaire on perineal use of talc	Ovary (epithelial), incidence	Perineal use of talc (OR):			Age, age at last childbirth, age at menarche, age at last OC use, tubal ligation or hysterectomy, alcohol use, ethnicity	*Strengths*: Histologically confirmed diagnoses. Logistic regression analysis adjusted for potential confounders. *Limitations*: small study sample (92 were high-grade serous cases). Possible differential exposure misclassification; duration of use was not evaluated. Low exposure prevalence. Asbestos contamination of the talc cannot be excluded. *Other comments*: Interviews were conducted: among cases, 70% in-person interview; 30% telephone; among controls, 100% by telephone.
			Never	NR	1		
			Ever	NR	2.49 (0.94–6.58)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer et al. (2016) NEC study, eastern Massachusetts and New Hampshire, USA; population-based Phase 1, 1992–1997; Phase 2, 1998–2002; Phase 3, 2003–2008 Case–control	Cases: 2041 women residing in eastern Massachusetts and New Hampshire, aged 18–80 yr, with an ovarian cancer diagnosis involving epithelial tumours of ovarian, primary peritoneal, and fallopian tube origin, including borderline malignancies. Controls: 2100; mix of random-digit dialling, driver's license lists, and town resident lists; frequency-matched on age and region of residence; potential controls that did not have ovaries were excluded.	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Any genital use of talc (OR):			Reference age, study phase, study centre	*Exposure assessment critique*: Key strengths were the detailed exposure assessment over an extended time period; comprehensive exposure assessment information with ability to calculate talc-years, susceptibility windows. Key limitations were the potential for differential exposure misclassification; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Detailed consideration of possible modifiers. *Other limitations*: Case mortality, low response rates (~50% of controls).
			No	1399	1		
			Yes	642	1.33 (1.16–1.52)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Type of powder used genitally (OR):				
			No genital use	1394	1		
			Cornstarch use only	5	0.58 (0.19–1.74)		
			Common brand names	363	1.3 (1.1–1.54)		
			Other brand(s)	279	1.35 (1.15–1.64)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Potential exposure in women with no personal use (OR):				
			Partner use, with or without diaphragm or condoms	77	0.6 (0.68, 1.35)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Frequency of genital use of talc (OR):				
			No genital use	1399	1		
			1–7 days/mo	227	1.17 (0.96–1.44)		
			8–29 days/mo	133	1.37 (1.05–1.78)		
			≥ 30 days/mo	267	1.46 (1.2–1.78)		
			Trend-test *P*-value, < 0.0001				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer et al. (2016) (cont.)	Exposure assessment method: Interviewer-administered questionnaires. Many details about products, duration, frequency. Questions asked whether participants ever "regularly" or "at least monthly" apply powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital–rectal area; also had details on type of powder use, frequency of use, age began using; calculated "talc-years".	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Duration of genital use of talc (OR):			Reference age, study phase, study centre	*Other comments*: Data on partner use showed no increased risk; cornstarch only was classified as unexposed (14 women) for most analyses, but use of cornstarch only was inversely associated with ovarian cancer.
			Never used	1399	1		
			< 8 yr	152	1.31 (1.03–1.68)		
			8–19 yr	145	1.31 (1.02–1.68)		
			20–35 yr	178	1.35 (1.07–1.7)		
			> 35 yr	152	1.33 (1.03–1.71)		
			Trend-test *P*-value, 0.002				
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Genital use of talc, mo/yr (OR):				
			No genital use	1399	1		
			1–3 mo/yr	60	1.11 (0.77–1.61)		
			4–11 mo/yr	56	1.13 (0.77–1.66)		
			12 mo/yr	229	1.35 (1.09–1.67)		
			Trend-test *P*-value, 0.006				
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Total genital applications of talc (among those reporting mo/yr of use) (OR):				
			No genital use	1399	1		
			≤ 360 applications	103	1.1 (0.83–1.47)		
			361–1800 applications	96	1.39 (1.01–1.88)		
			1801–7200 applications	63	1.16 (0.8–1.66)		
			> 7200 applications	83	1.49 (1.06–2.1)		
			Trend-test *P*-value, 0.02				
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Age first used genital talc (OR):				
			Never used	1399	1		
			< 20 yr	363	1.19 (1.01–1.41)		
			20–29 yr	183	1.71 (1.34–2.17)		
			≥ 30 yr	87	1.31 (0.95–1.8)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer et al. (2016) (cont.)		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Time since exposure ended (OR):			Reference age, study phase, study centre	
			No genital use	1399	1		
			≥ 35 yr	52	1.18 (0.79–1.75)		
			25–34 yr	88	1.24 (0.91–1.7)		
			15–24 yr	82	1.3 (0.94–1.8)		
			5–14 yr	95	1.36 (1–1.85)		
			Currently using or recently stopped	314	1.38 (1.15–1.65)		
			Trend-test *P*-value: < 0.0001				
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Race (OR for ever genital use of talc vs never users):			Reference age, study phase, study centre, BMI, height, weight, parity, ever breastfed, OC use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history of ovarian or early onset breast cancer, personal history of breast cancer, hysterectomy or tubal ligation, menopausal status and hormone therapy, current smoking, ever smoked, asthma, alcohol, acetaminophen, aspirin, or ibuprofen	
			White	612	1.35 (1.17–1.55)		
			African-American	19	5.08 (1.32–19.6)		
			Hispanic	6	1.1 (0.3–4.12)		
			Asian	2	0.04 (0.01–0.34)		
			Other	3	-		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer et al. (2016) (cont.)		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Menopausal status and hormone therapy (OR for ever genital use of talc vs never users):			Reference age, study phase, study centre, race, BMI, height, weight, parity, ever breastfed, OC use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history of ovarian or early onset breast cancer, personal history of breast cancer, hysterectomy or tubal ligation, current smoking, ever smoked, asthma, alcohol, acetaminophen, aspirin, or ibuprofen	
			Premenopausal	247	1.41 (1.13–1.75)		
			Postmenopausal, no HT	238	0.97 (0.78–1.2)		
			Postmenopausal, HT	157	2.21 (1.63–3)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cramer et al. (2016) (cont.)		Ovary (serous; invasive only), incidence	Genital use of talc (OR):			Reference age, study phase, study centre, parity, breastfeeding, OC use, hormone therapy use, IUD, endometriosis or painful periods, personal history of breast cancer, Jewish ethnicity, tubal ligation, BMI	
			Never	[629]	1		
			Ever	[339]	1.42 (1.19–1.69)		
		Ovary (mucinous; invasive only), incidence	Genital use of talc (OR):				
			Never	[74]	1		
			Ever	[21]	0.87 (0.53–1.44)		
		Ovary (endometrioid) (invasive only), incidence	Genital use of talc (OR):				
			Never	[218]	1		
			Ever	[109]	1.38 (1.06–1.8)		
		Ovary (clear cell) (invasive only), incidence	Genital use of talc (OR):				
			Never	[84]	1		
			Ever	[30]	1.01 (0.65–1.57)		
Ness et al. (2000) Delaware Valley, USA; hospital-based 1994–1998 Case–control	Cases: 767 women aged 20–69 yr with invasive or borderline epithelial ovarian cancer interviewed within 6 mo of the diagnosis. Cases selected from 39 hospitals in Delaware Valley. Response rate, 88%.	Ovary (epithelial), incidence	Location of talc use (not mutually exclusive) (OR):			Age, residence, number of pregnancies, family history of ovarian cancer, race, OC use, tubal ligation, hysterectomy, breastfeeding	*Strengths*: Population-based case–control study. Central pathology review. Large sample size. Adjustment for potential confounders using logistic regression analysis. *Limitations*: Differential exposure misclassification. Asbestos contamination of the talc cannot be excluded. *Other comments*: Included both invasive and borderline ovarian cancer cases.
			Never	349	1		
			Feet, arms, or breasts	335	1.4 (1.1–1.6)		
			Genital or rectal area	161	1.5 (1.1–2)		
			Sanitary napkin	77	1.6 (1.1–2.3)		
			Underwear	70	1.7 (1.2–2.4)		
			Diaphragm/ cervical cap	10	0.6 (0.3–1.2)		
			Male partner	56	1 (0.7–1.4)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ness et al. (2000) (cont.)	Controls: 1367; Two different control group sources: women aged < 65 yr selected through random-digit dialling, frequency-matched on age and telephone exchange code; women aged 65–69 yr selected through the Health Care Financing Administration list, frequency-matched on age and county of residence. Response rate, 74%. Exposure assessment method: standardized questionnaire in in-person interviews. Ever use and duration of use was obtained for whether applications were to the genital/rectal area, sanitary napkin or underwear or feet.	Ovary (epithelial), incidence	Duration of talc use (non-genital (i.e. feet, arms, breasts) or genital/rectal areas) (OR): Never < 1 yr 1–4 yr 5–9 yr ≥ 10 yr	 401 17 76 40 233	 1 2 (1–4) 1.6 (1.1–2.3) 1.2 (0.8–1.9) 1.2 (1–1.5)	Age, residence, number of pregnancies, family history of ovarian cancer, race, OC use, tubal ligation, hysterectomy, breastfeeding	

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mills et al. (2004) Central California, USA; population-based 2000–2001 Case–control	Cases: 256 women diagnosed with invasive or borderline epithelial ovarian cancer living in Central Valley, California, between 2000 and 2001. Identified through Cancer Registry of Central California in Fresno and Cancer Surveillance Program in Sacramento. Response rate, 40%. Controls: 1122 women aged > 18 yr with at least one intact ovary at the time of interview, identified through random-digit dialling. Controls were frequency-matched to cases on age and race/ethnicity. Response rate, 57%. Exposure assessment method: Talcum powder questions: genital use as an adult, calendar years of use, frequency of use, and total duration of use	Ovary (epithelial), incidence	Perineal use of talc (OR):			Age, race/ ethnicity, duration of OC use, breastfeeding	*Strengths*: Population-based, diverse population (large proportion was Hispanic). *Limitations*: Low case response rates because of deaths/illness (40%); 57% response rate for controls. Multivariable models did not include body size, which could upwardly bias effect estimates. Differential exposure misclassification may have occurred. Asbestos contamination of the talc cannot be excluded.
			Never	143	1		
			Ever	106	1.37 (1.02–1.85)		
		Ovary (epithelial), incidence	Frequency of perineal use of talc (OR):				
			Never	143	1		
			Rarely to several times per month	34	1.34 (0.87–2.08)		
			1–3 times/wk	31	1.16 (0.74–1.81)		
			4–7 times/wk	41	1.74 (1.14–2.64)		
			Trend-test *P*-value, 0.015				
		Ovary (epithelial), incidence	Duration of perineal use of talc (OR):				
			Never	143	1		
			≤ 3 yr	18	1.01 (0.58–1.76)		
			4–12 yr	32	1.86 (1.16–2.98)		
			13–30 yr	29	1.45 (0.9–2.32)		
			> 30 yr	21	1.22 (0.72–2.08)		
			Trend-test *P*-value, 0.045				
		Ovary (epithelial), incidence	Cumulative use of perineal talc (frequency × duration) (OR):				
			Never	143	1		
			1st quartile	18	1.03 (0.59–1.8)		
			2nd quartile	28	1.81 (1.1–2.97)		
			3rd quartile	34	1.74 (1.11–2.73)		
			4th quartile	20	1.06 (0.62–1.83)		
			Trend-test *P*-value, 0.051				
		Ovary (epithelial), incidence	Year of first perineal use of talc (OR):				
			Never use	143	1		
			Before/during 1975	52	1.22 (0.84–1.77)		
			After 1975	47	1.92 (1.27–2.91)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mills et al. (2004) (cont.)		Ovary (epithelial), incidence	Age at first perineal use of talc (OR):			Age, race/ ethnicity, duration of OC use, breastfeeding	
			Never use	143	1		
			< 20 yr	30	0.95 (0.61–1.48)		
			20–24 yr	26	2.41 (1.43–4.09)		
			≥ 25 yr	43	1.8 (1.19–2.73)		
		Ovary (epithelial), incidence	Timing of first perineal use of talc, parous women (OR):				
			Never use	113	1		
			At or before first birth	36	0.98 (0.64–1.48)		
			After first birth	42	2.51 (1.63–3.87)		
		Ovary (epithelial), incidence	Years since last perineal use of talc (OR):				
			Never use	143	1		
			Current users	32	1.27 (0.81–1.98)		
			1–2 yr	27	2.4 (1.43–4.05)		
			3–20 yr	20	1.57 (0.9–2.73)		
			> 20 yr	20	1.13 (0.66–1.94)		
		Ovary (serous; invasive only), incidence	Perineal use of talc (OR):				
			Never	46	1		
			Ever	42	1.77 (1.12–2.81)		
		Ovary (mucinous; invasive only), incidence	Perineal use of talc (OR):				
			Never	6	1		
			Ever	10	2.56 (0.89–7.39)		
		Ovary (endometrioid), incidence	Perineal use of talc (OR):				
			Never	21	1		
			Ever	14	1.28 (0.62–2.62)		
		Ovary (clear cell), incidence	Perineal use of talc (OR):				
			Never	8	1		
			Ever	3	0.63 (0.15–2.64)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mills et al. (2004) (cont.)		Ovary (epithelial), incidence	Perineal use of talc, women with tubal ligation (OR):			Age, race/ ethnicity, duration of OC use, breastfeeding	
			Never	29	1		
			Ever	22	0.88 (0.46–1.68)		
		Ovary (epithelial), incidence	Perineal use of talc, women without tubal ligation (OR):				
			Never	113	1		
			Ever	84	1.54 (1.1–2.16)		
		Ovary (epithelial), incidence	Ever perineal use of talc, women with a hysterectomy (≥ 2 yr ago) (OR):				
			Never	27	1		
			Ever	27	1.79 (0.91–3.52)		
		Ovary (epithelial), incidence	Perineal use of talc, women without hysterectomy (or hysterectomy < 2 yr ago) (OR):				
			Never	116	1		
			Ever	79	1.33 (0.95–1.87)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2015) UCS study, Los Angeles, USA; population-based Multiple case–control studies conducted in 1992–2008 Case–control	Cases: 1701; newly diagnosed invasive epithelial ovarian cancer, aged 18–74 yr (up to 79 yr for cases diagnosed 2003–2008), identified through the University of Southern California Cancer Surveillance programme (SEER Los Angeles). 63% participation rate. Patients with previous cancer excluded. Controls: 2391 residents of Los Angeles County with at least one intact ovary. Matching on race/ethnicity, year of birth. response rate, 70%. Exposure assessment method: Self-report, in-person interviews; ever use.	Ovary (epithelial), incidence	Genital use of talc (OR):			Race/ethnicity, age, interviewer, study, menopausal status, age at menarche, hormone therapy use, BMI, education, income, live births, OC use, tubal ligation, endometriosis, family history of ovarian cancer	*Exposure assessment critique*: Key limitations were the potential for differential exposure misclassification; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Cases identified through population-based tumour registry (large county); Large sample size for the analysis restricted to Hispanic women. *Other limitations*: low response rates; high mortality (17% died, probably missing rapidly fatal cases); possibility of recall bias. *Other comments*: same as the UCS study included in OCWAA (Davis et al. 2021), although details reported in papers (e.g. dates) were sometimes inconsistent. An update to a previous publication, Wu et al. (2009), which included fewer participants.
			None or < 1 yr	1000	1		
			Yes	701	1.46 (1.27–1.69)		
			Continuous (per 5 yr of use)	1701	1.14 (1.09–1.2)		
		Ovary (epithelial), incidence	Genital use of talc, non-Hispanic White women (OR):			Age, interviewer, study, menopausal status, age at menarche, hormone therapy use, BMI, education, income, live births, OC use, tubal ligation, endometriosis, family history of ovarian cancer	
			None or < 1 yr	744	1		
			Yes	521	1.41 (1.21–1.67)		
			Continuous (per 5 yr of use)	1265	1.14 (1.08–1.21)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wu et al. (2015) (cont.)		Ovary (epithelial), incidence	Genital use of talc, Hispanic women (OR):			Age, interviewer, study, menopausal status, age at menarche, hormone therapy use, BMI, education, income, live births, OC use, tubal ligation, endometriosis, family history of ovarian cancer	
			None or < 1 yr	189	1		
			Yes	119	1.77 (1.2–2.62)		
			Continuous (per 5 yr of use)	308	1.18 (1.02–1.36)		
		Ovary (epithelial), incidence	Genital use of talc, African-American women (OR):				
			None or < 1 yr	67	1		
			Yes	61	1.56 (0.8–3.04)		
			Continuous (per 5 yr of use)	128	1.15 (0.9–1.47)		
Rosenblatt et al. (2011) DOV study. Western Washington state, USA; population-based 2002–2005 Case–control	Cases: 812 English-speaking female residents in the study area, aged 35–74 yr, diagnosed with primary invasive or borderline epithelial ovarian cancer between 2002 and 2005. Eligible cases had a residential telephone at time of diagnosis. Cases identified through SEER. Response rate, 76.6%.	Ovary (epithelial), incidence	Perineal use of powder after bathing (OR):			Age, calendar year of diagnosis, county, No. of full-term births, duration of hormonal birth control	*Exposure assessment critique*: Key limitations were possible differential misclassification; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Population-based study; analysis by calendar year. *Other limitations*: Low response rates. *Other comments*: DOV was included in Terry et al. (2013) pooled analysis. This reference includes more detailed exposure assessment than is in Terry et al.
			No (or < 1 yr of regular use)	699	1		
			Yes	112	1.27 (0.97–1.66)		
		Ovary (epithelial), incidence	Duration of perineal use of powder after bathing (OR):				
			Never used (or < 1 yr)	699	1		
			1–9.9 yr	33	1.39 (0.85–2.28)		
			10–19.9 yr	29	1.46 (0.87–2.45)		
			20–34.9 yr	30	1.28 (0.78–2.1)		
			≥ 35 yr	19	0.91 (0.51–1.62)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rosenblatt et al. (2011) (cont.)	Controls: 1313; selected through random-digit dialling using stratified sampling in 5 yr age categories, 1-year calendar intervals and two county strata. 84.1% response rate. Eligible controls had at least one ovary and no prior history of ovarian cancer. Exposure assessment method: In-person interviews; duration, time and age at first use, lifetime number of applications	Ovary (epithelial), incidence	Lifetime no. of applications of perineal powder after bathing (OR):			Age, calendar year of diagnosis, county, No. of full-term births, duration of hormonal birth control	
			Never used (or < 1 yr)	699	1		
			1–1599	26	1.21 (0.71–2.06)		
			1600–4799	45	2.08 (1.32–3.27)		
			4800–9999	20	0.87 (0.5–1.53)		
			≥ 10 000	18	0.87 (0.48–1.57)		
		Ovary (epithelial), incidence	Age at first regular use of perineal powder after bathing (OR):				
			Never used (or < 1 yr)	699	1		
			< 15 yr	12	0.74 (0.37–1.5)		
			15 to < 20 yr	27	1.2 (0.71–2.03)		
			20 to < 30 yr	32	1.25 (0.77–2.03)		
			≥ 30 yr	41	1.69 (1.08–2.64)		
		Ovary (epithelial), incidence	Age at last regular use of perineal powder after bathing (OR):				
			Never used (or < 1 yr)	699	1		
			< 35 yr	25	1.14 (0.66–1.97)		
			35 to < 50 yr	35	1.42 (0.88–2.31)		
			50 to < 60 yr	25	1.25 (0.73–2.13)		
			≥ 60 yr	26	1.21 (0.72–2.05)		
		Ovary (epithelial), incidence	Calendar year of first regular use of perineal powder after bathing (OR):				
			Never used (or < 1 yr)	699	1		
			≤ 1959	19	0.86 (0.48–1.53)		
			1960–1969	24	1.1 (0.65–1.89)		
			1970–1979	26	1.12 (0.66–1.89)		
			≥ 1980	43	2.03 (1.28–3.24)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rosenblatt et al. (2011) (cont.)		Ovary (epithelial), incidence	Time since first regular use of perineal powder after bathing (OR):			Age, calendar year of diagnosis, county, No. of full-term births, duration of hormonal birth control	
			Never used (or < 1 yr)	699	1		
			≤ 25 yr	42	1.77 (1.12–2.78)		
			25 to < 38 yr	38	1.46 (0.91–2.32)		
			38 to < 45 yr	16	0.87 (0.47–1.61)		
			≥ 45 yr	16	0.82 (0.44–1.52)		
		Ovary (epithelial), incidence	Time since last regular use of perineal powder after bathing (OR):				
			Never used (or < 1 yr)	699	1		
			Current user	52	1.3 (0.89–1.91)		
			≤ 12 yr	26	1.74 (0.98–3.1)		
			13–23 yr	14	0.85 (0.44–1.66)		
			≥ 24 yr	19	1.13 (0.61–2.08)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Neill et al. (2012) Australia; population-based 2005–2007 Case–control	Cases: 1399 women aged 18–79 yr living in Australia with newly diagnosed epithelial endometrial cancer between 2005 and 2007. Recruited from treatment clinics and state cancer registries. Response rate, 67%. Type I included low-grade endometrioid and mucinous endometrial adenocarcinomas; type II included all other epithelial subtypes including serous and clear cell cancers, high-grade endometrioid cancers, and carcinosarcomas. Controls: 740; frequency-matched on state and age (5-yr categories), sampled from national electoral roll. Women with a history of hysterectomy were excluded. Response rate, 53%. Exposure assessment method: Standardized telephone interview; duration and frequency, cumulative exposure.	Uterine corpus (epithelial endometrial), incidence	Perineal use of talc (OR):			Age, age at menarche, parity, OC use, hormone therapy use, BMI (1 yr before diagnosis/ recruitment), smoking, state	*Exposure assessment critique*: A key strength was the detailed collection of talc information. Key limitations were possible differential misclassification; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Verified endometrial cancer; population-based case–control selection. *Other limitations*: Low response rates. *Other comments*: 66 died before inclusion.
			Never use of talc at either body site (perineal or upper body)	363	1		
			Ever	528	0.88 (0.68–1.14)		
		Uterine corpus (epithelial endometrial), incidence	Frequency of perineal use of talc (OR):				
			Never any talc use	363	1		
			Infrequent	45	0.68 (0.4–1.15)		
			Few times/mo	80	0.88 (0.56–1.41)		
			Few times/wk	96	1.32 (0.82–2.11)		
			Daily	291	0.82 (0.61–1.11)		
			Trend-test *P*-value, 0.44				
		Uterine corpus (epithelial endometrial), incidence	Duration of perineal use of talc (OR):				
			Never any talc use	363	1		
			1–20 yr	164	1.21 (0.84–1.75)		
			21–40 yr	134	1.1 (0.73–1.65)		
			41–60 yr	157	0.82 (0.57–1.17)		
			61–80 yr	43	0.25 (0.15–0.43)		
			Trend-test *P*-value, < 0.001				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Neill et al. (2012) (cont.)		Uterine corpus (epithelial endometrial), incidence	Perineal use of talc (combined frequency and duration) (OR):			Age, age at menarche, parity, OC use, hormone therapy use, BMI (1 yr before diagnosis/ recruitment), smoking, state	
			Never any talc use	363	1		
			Low (< 5 talc-years)	141	0.95 (0.65–1.37)		
			Moderate (5 to < 20 talc-years)	102	1 (0.66–1.54)		
			High (20 to < 40 talc-years)	95	1.01 (0.64–1.6)		
			Very high (≥ 40 talc-years)	146	0.67 (0.47–0.96)		
			Trend-test *P*-value, 0.07				
		Uterine corpus (type I endometrial), incidence	Perineal use of talc (OR):				
			Never use of talc at either body site (perineal or upper body)	NR	1		
			Ever	NR	0.88 (0.67–1.15)		
		Uterine corpus (type II endometrial), incidence	Ever perineal use of talc (OR):				
			Never use of talc at either body site (perineal or upper body)	NR	1		
			Ever	NR	0.91 (0.59–1.39)		

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Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Terry et al. (2013) Australia, Canada, and USA OCAC consortium: AUS (2002–2006), DOV (2002–2009), HAW (1993–2008), HOP (2003–2008), NCO (1999–2008), NEC (1992–2008), SON (1989–1992), USC (1993–1997) Case–control	Cases: 8525; cases pooled from studies participating in the OCAC consortium as of April 2010 with data on powder use. Controls: 9859; controls pooled from studies participating in the OCAC consortium as of April 2010 with data on powder use. Exposure assessment method: variable, mostly self-administered questionnaires; duration and frequency, lifetime number of applications	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Powder use (OR):			Age (5-yr group and continuous), study, OC use duration, parity, tubal ligation, BMI, race/ ethnicity	*Exposure assessment critique*: A key strength was that studies included had different ways of defining talc use but were able to isolate reporting of genital use. Key limitations were possible differential misclassification; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Large pooled analysis, able to consider subtypes and dose–response relation. *Other comments*: Overlap with individual studies and other pooled studies (Chang and Risch, 1997 (SON); Merritt et al., 2008 (AUS); Moorman et al., 2009 (NCO); Rosenblatt et al., 2011 (DOV); Kurta et al., 2012 (HOP); Cramer et al., 1999 (NEC); and Wu et al., 2009 (USC)). The AUS, DOV, and NEC studies provided new data for incorporation into the pooled analysis.
			No powder use	4643	1		
			Non-genital use only	1282	0.98 (0.89–1.07)		
			Genital use	2600	1.24 (1.15–1.33)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Quartile (age-specific) of lifetime genital applications of powder (OR):				
			Never users	5384	1		
			1st quartile	534	1.14 (1–1.31)		
			2nd quartile	541	1.23 (1.08–1.41)		
			3rd quartile	542	1.22 (1.07–1.4)		
			4th quartile	586	1.32 (1.16–1.52)		
			Trend-test *P*-value, 0.17				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Terry et al. (2013) (cont.)		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Quartile (age-specific) of lifetime genital applications of powder, excluding women who only used after hysterectomy/ligation (OR):			Age (5-yr group and continuous), study, OC use duration, parity, tubal ligation, BMI, race/ ethnicity	
			Never users	NR	1		
			1st quartile	NR	1.19 (1.03–1.38)		
			2nd quartile	NR	1.19 (1.03–1.38)		
			3rd quartile	NR	1.21 (1.04–1.39)		
			4th quartile	NR	1.36 (1.18–1.57)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	BMI (OR for ever genital use of powder vs never users):				
			< 30 kg/m^2	NR	1.28 (1.17–1.39)		
			> 30 kg/m^2	NR	1.14 (0.98–1.32)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Year of first use (OR for ever genital use of powder vs never users):				
			Before 1952	NR	1.08 (0.93–1.25)		
			1952–1961	NR	1.36 (1.19–1.56)		
			1962–1972	NR	1.27 (1.11–1.46)		
			After 1972	NR	1.31 (1.15–1.51)		
		Ovary (serous; invasive only), incidence	Genital use of powder (OR):				
			Never	2519	1		
			Ever	1197	1.24 (1.13–1.35)		
		Ovary (mucinous; invasive only), incidence	Genital use of powder (OR):				
			Never	269	1		
			Ever	94	1.06 (0.82–1.36)		
		Ovary (endometrioid; invasive only), incidence	Genital use of powder (OR):				
			Never	723	1		
			Ever	304	1.2 (1.03–1.4)		
		Ovary (clear cell, invasive only), incidence	Genital use of powder (OR):				
			Never	420	1		
			Ever	187	1.26 (1.04–1.52)		

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Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Phung et al. (2022) Australia, Denmark, and USA OCAC consortium: AUS (2002–2005),CON (1999–2003), DOV (2002–2009), HAW (1993–2008), HOP (2003–2009), NEC (1992–2008), UCI (1995–2005), USC (1993–2010) Case–control	Cases: 7996 women with pathologically confirmed high-grade serous, low-grade serous, mucinous, endometrioid, clear cell, and other invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnoses. Cases pooled from studies in the OCAC consortium: AUS, CON, DOV, HAW, HOP, NEC, UCI, USC. Controls: 12 039 women with at least one intact ovary, without ovarian cancer diagnosis at the reference date. Exposure assessment method: Interviewer-administered or self-administered questionnaires. Ever use.	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Talc use, women without endometriosis (OR, pooled based on 50 imputed data sets):			Age, race/ ethnicity, education, study site	*Exposure assessment critique*: Key limitations were the potential for differential exposure misclassification; powder use was assessed differently in the included studies; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Large sample size; study was able to investigate effect modification by endometriosis. *Other limitations*: Part of a larger paper with little detail on talc questions or results, and no frequency or time-based analyses. *Other comments*: Analysis by endometriosis status. Overlap with individual studies and pooled studies; includes two studies not part of Terry et al. – the CON and UCI studies.
			Never	2172	1		
			Non-genital use	1391	0.76 (0.49–1.19)		
			Genital use	827	1.12 (1.01–1.25)		
		Ovary (epithelial), fallopian tubes, peritoneum, incidence	Talc use, women with endometriosis (OR, pooled based on 50 imputed data sets):				
			Never	220	1		
			Non-genital use	162	0.83 (0.39–1.77)		
			Genital use	79	1.38 (1.04–1.84)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schildkraut et al. (2016) AACES study: Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas, USA; population-based Recruitment, December 2010 through August 2015 Case–control	Cases: 584 African-American women aged 20–79 yr with newly diagnosed invasive epithelial ovarian cancer, identified via rapid case ascertainment from combination of SEER, state cancer registries, and hospital-based systems. Analysis restricted to women with data on talc body powder and covariates. Controls: 745 African-American women identified through random-digit dialling, frequency-matched on region of residence and age, had at least one intact ovary. Analysis restricted to women with data on talc body powder and covariates. Exposure assessment: Questionnaire, telephone interview; duration and frequency; number of applications.	Ovary (epithelial), incidence	Body powder use (OR):			Age at diagnosis/ interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast/ovarian, interview year	*Exposure assessment critique*: Key strengths were the inclusion of some data on occupational exposure; collection of detailed information on talc use over the life-course. Key limitations were potential differential misclassification; strong evidence that differential exposure misclassification may be present from evidence of increased reporting of talc use after 2014 when lawsuits were reported; and that asbestos contamination of the talc cannot be excluded. *Other strengths*: Only African-American women included, who are historically high talc users. *Other comments*: Data were included in OCWAA consortium studies (Davis et al., 2021), although only those interviewed before 2014.
			Never use	217	1		
			Ever (genital or non-genital)	367	1.39 (1.1–1.76)		
		Ovary (epithelial), incidence	Body powder use (OR):				
			Never use	217	1		
			Only non-genital	119	1.31 (0.95–1.79)		
			Any genital	248	1.44 (1.11–1.86)		
		Ovary (epithelial), incidence	Body powder use, women interviewed before 2014 (OR):				
			Never use	147	1		
			Only non-genital use	76	1.4 (0.96–2.03)		
			Any genital use	128	1.19 (0.87–1.63)		
		Ovary (epithelial), incidence	Body powder use, women interviewed in or before 2014 (OR):				
			Never use	70	1		
			Only non-genital use	43	1.26 (0.69–2.32)		
			Any genital use	120	2.91 (1.7–4.97)		
		Ovary (epithelial), incidence	Frequency of genital use of body powder (OR):				
			Never use	217	1		
			Less than daily	88	1.12 (0.8–1.58)		
			Daily	158	1.71 (1.26–2.33)		
			Trend-test *P*-value, < 0.01				
		Ovary (epithelial), incidence	Duration of genital use of body powder (OR):				
			Never use	217	1		
			< 20 yr	101	1.33 (0.95–1.86)		
			≥ 20 yr	144	1.52 (1.11–2.07)		
			Trend-test *P*-value, 0.02				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schildkraut et al. (2016) (cont.)		Ovary (epithelial), incidence	Lifetime genital applications of body powder (OR):			Age at diagnosis/ interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast/ovarian, interview year	
			Never use	217	1		
			< 3600	92	1.16 (0.83–1.63)		
			≥ 3600	152	1.67 (1.23–2.26)		
			Trend-test *P*-value, < 0.01				
		Ovary (epithelial), incidence	Occupational talc exposure (OR):				
			Never	NR	1		
			Ever	NR	1.31 (0.88–1.93)		
		Ovary (serous), incidence	Body powder use (OR):				
			Never use	156	1		
			Only non-genital use	71	1.1 (0.76–1.58)		
			Any genital use	165	1.38 (1.03–1.85)		
		Ovary: (non-serous), incidence	Body powder use (OR):				
			Never use	44	1		
			Only non-genital use	42	2.28 (1.39–3.74)		
			Any genital use	58	1.63 (1.04–2.55)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Davis et al. (2021) USA OCWAA consortium: AACES (2010–2015), CCCS (1994–1998), NCO (1999–2003), USC (1998–2002), Nested case–control within WHI-OS (1994–2018) Case–control	Cases: 3420 (620 African-American, 2800 White); cases pooled from studies within OCWAA: NCO, USC, CCCS, and AACES, and a nested case–control study within the WHI observational study. Eligibility restricted to interview year before 2014. Controls: 7881 (1146 African-American, 6735 White); matching on age and race (NCO, UCS, CCCS, AACES), additionally on zip code (UCS, AACES). In the WHI nested case–control study, 6 controls per case were matched on race, age, and last questionnaire completed before ovarian cancer diagnosis. Eligibility restricted to interview year before 2014. Exposure assessment method: Questionnaire; interviewer-administered or self-administered questionnaires. Duration and frequency.	Ovary (epithelial), incidence	Genital use of powder (OR):			Age, education, OC use, family history of breast/ ovarian cancer, tubal ligation, hysterectomy, interview year, BMI, menopause status, smoking, study site	*Exposure assessment critique*: A key strength was that exclusion of AACES data after 2013 and the inclusion of one study with prospectively collected data (WHI-OS) helped reduce differential misclassification on effect estimates. Key limitations were the possibility of differential misclassification, especially after 2014; and that asbestos contamination of the talc cannot be excluded. *Other comments*: Overlap with individual studies and pooled studies. Overlap with Terry et al. (2013) included NCO and USC. Overlap with AACES (Schildkraut et al., 2016) and WHI-OS (Houghton et al., 2014).
			No	2373	1		
			Yes	1047	1.32 (1.17–1.48)		
		Ovary (epithelial), incidence	Frequency of genital use of powder (OR):				
			No genital use	2047	1		
			At least once/ wk	103	1.34 (1.01–1.79)		
			More than once/wk	650	1.31 (1.15–1.48)		
			Trend-test *P*-value, 0.98				
		Ovary (epithelial), incidence	Duration of genital use of powder (OR):				
			No genital use	2374	1		
			≤ 20 yr	534	1.43 (1.22–1.68)		
			> 20 yr	483	1.28 (1.08–1.51)		
			Trend-test *P*-value, 0.97				
		Ovary (epithelial), incidence	Genital use of powder, African-American women (OR):				
			No	398	1		
			Yes	222	1.22 (0.97–1.53)		
		Ovary (epithelial), incidence	Genital use of powder, White women (OR):				
			No	1975	1		
			Yes	825	1.36 (1.19–1.57)		
		Ovary (epithelial), incidence	Genital use of powder, women with patent reproductive tracts (OR):			Age, education, OC use, family history of breast/ ovarian cancer, interview year, BMI, menopause status, smoking, study site	
			No	NR	1		
			Yes	NR	1.27 (1.09–1.48)		
		Ovary (epithelial), incidence	Genital use of powder, women without patent reproductive tracts (OR):				
			No	NR	1		
			Yes	NR	1.42 (1.17–1.72)		

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Davis et al. (2021) (cont.)		Ovary (serous; epithelial), incidence	Genital use of powder (OR):			Age, education, OC use, family history of breast/ ovarian cancer, tubal ligation, hysterectomy, interview year, BMI, menopause status, smoking, study site	
			No	1451	1		
			Yes	658	1.32 (1.15–1.51)		
		Ovary (serous; epithelial), incidence	Frequency of genital use of powder (OR):				
			No genital use	1229	1		
			At least once/ wk	65	1.34 (0.95–1.87)		
			More than once/wk	389	1.31 (1.13–1.52)		
			Trend-test *P*-value, 0.88				
		Ovary (serous; epithelial), incidence	Duration of genital use of powder (OR):				
			No genital use	1452	1		
			≤ 20 yr	334	1.42 (1.17–1.71)		
			> 20 yr	277	1.32 (1.09–1.6)		
			Trend-test *P*-value, 0.71				
		Ovary (epithelial), incidence	Genital use of powder (OR):				
			No	900	1		
			Yes	383	1.29 (1.1–1.52)		
		Ovary (epithelial), incidence	Frequency of genital use of powder (OR):				
			No genital use	796	1		
			At least once/ wk	37	1.29 (0.87–1.92)		
			More than once/wk	257	1.29 (1.09–1.54)		
			Trend-test *P*-value, 0.79				
		Ovary (epithelial), incidence	Duration of genital use of powder (OR):				
			No genital use	900	1		
			≤ 20 yr	198	1.44 (1.16–1.78)		
			> 20 yr	151	1.19 (0.94–1.5)		
			Trend-test *P*-value, 0.58				

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Leung et al. (2023) Greater Montreal Area, Canada 2011–2016 Case–control	Cases: 498 women aged 18–79 yr, residents in greater Montreal Area, able to speak English or French, with a diagnosis of epithelial ovarian cancer (including peritoneal and fallopian tube). Cases identified from seven Montreal hospitals. Response rate, 78%.	Ovary (epithelial), fallopian tubes, peritoneum, incidence Ovary (epithelial), fallopian tubes, peritoneum, incidence	Occupational exposure to cosmetic talc (OR): Never Uncertainly Ever Duration of occupational exposure to cosmetic talc (OR): Never exposed < 8 yr ≥ 8 yr	 357 118 15 357 11 4	 1 0.9 (0.69–1.17) 1.66 (0.8–3.46) 1 1.68 (0.72–3.93) 1.51 (0.36–6.3)	Age, education, ancestry, parity, marital status, electoral district	*Exposure assessment critique*: This was a high-quality semiquantitative exposure assessment of cosmetic talc. Key strengths were assessment by an experienced team using a JEM developed using case–by-case assessments in the same geographical region.

Table 2.2 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Leung et al. (2023) (cont.)	Controls: 908; identified from the Quebec Electoral List, frequency-matched on age and electoral district. Response rate, 56%. Exposure assessment method: Lifetime occupational histories for jobs held for ≥ 6 mo were collected during in-person interviews by trained interviewers, and occupations and industries were coded by an industrial hygienist. Exposure to 258 agents was assessed using CANJEM (Siemiatycki and Lavoué, 2018).	Ovary (epithelial), fallopian tubes, peritoneum, incidence	Cumulative occupational cosmetic talc exposure (OR):				Key limitations were nondifferential misclassification from using a general population JEM; and lack of information on the purity of talc being used. *Other strengths*: Adjusted for potential confounders. *Other limitations*: Exposure prevalence was low and did not account for personal talc use. Multiple correlated exposures were also a concern.
			Never exposed	357	1		
			Low	8	1.34 (0.52–3.43)		
			High	7	2.25 (0.52–7.41)		

AACES, African-American Cancer Epidemiology Study; AUS, Australian Cancer Study; BMI, body mass index; CANJEM, Canadian Job Exposure Matrix; CCCS, Cook County Case Study; CI, confidence interval; CON, Connecticut Ovarian Cancer Study; DC, District of Columbia; DOV, Disease of the Ovary and their Evaluation Study; HAW, Hawaii Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction Study; HPV, human papillomavirus; HR, hazard ratio; HT, hormone therapy; ICD, International Classification of Diseases; IUD, intrauterine device; JEM, job-exposure matrix; mo, month(s); NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; NR, not reported; OC, oral contraceptive; OCAC, Ovarian Cancer Association Consortium; OCWAA, Ovarian Cancer in Women of African Ancestry; OR, odds ratio; Pap, Papanicolaou; RR, rate ratio; SEER, Surveillance, Epidemiology and End Results Program; SIR, standardized incidence ratio; SIS, Sister Study; SMR, standardized mortality ratio; SON, Southern Ontario Ovarian Cancer Study; STI, sexually transmitted disease; UCI, University of California, Irvine Ovarian Cancer Study; UK, United Kingdom; USA, United States of America; USC, University of Southern California, Study of Lifestyle and Women's Health; vs, versus; WHI-OS, Women's Health Initiative Observational Study; wk, week(s); yr, year(s).

cancer case–control studies excluded controls with no remaining ovarian tissue.

Assessments of personal talc use were heterogeneous. Most studies focused on perineal or genital use of talc, including the application of talc to underwear, sanitary napkins, or diaphragms, although some included additional sites as well. Many of the studies attempted to capture some other measures of talc use, such as frequency of use, duration of use, age at first or most recent use, and type of talc product used (e.g. talc, cornstarch, baby powder, deodorizing powder) (Shushan et al., 1996; Chang and Risch, 1997; Cook et al., 1997; Mills et al., 2004; Rosenblatt et al., 2011; Neill et al., 2012; Terry et al., 2013; Wu et al., 2015; Cramer et al., 2016; Schildkraut et al., 2016; Davis et al., 2021). In some cases, the studies did not refer to talc specifically, but instead considered exposure to any type of body powder (Harlow and Weiss, 1989; Cook et al., 1997; Rosenblatt et al., 2011; Terry et al., 2013; Schildkraut et al., 2016; Davis et al., 2021).

First, the registry-based case–control studies on ovarian or endometrial cancer are discussed in chronological order of publication (considering the first ever publication identified on talc from the study). This includes several large, pooled analyses of ovarian cancer, which combined results from many of the earlier, smaller studies (Terry et al., 2013; Davis et al., 2021; Peres et al., 2021; Phung et al., 2022). The following studies were considered uninformative because they included preliminary or overlapping data from the New England Cancer Case–Control Study of Ovarian Cancer (NEC), which was evaluated in full detail in Cramer et al. (2016): Cramer et al. (1999); Vitonis et al. (2011); Gates et al. (2008); and Gabriel et al. (2019).

For a three-county region in western Washington state, USA, Harlow and Weiss (1989) reported results from a study that included 116 White women diagnosed with serous or mucinous borderline ovarian tumours between 1980 and 1985 and recorded by the Seattle–Puget Sound Cancer Surveillance System. Controls were 158 White women who had not had a bilateral oophorectomy and were similar to cases in terms of age and county of residence. These were identified via random-digit dialling. Participants had an age range of 20–79 years. The response rate was 68% for cases and 74% for controls. The study questionnaire included questions about perineal use of powder, including method of use (diaphragm storage, after bathing, sanitary napkins) and type of powder used (cornstarch, baby powder, deodorizing powder, unspecified). [The Working Group considered that this study should be given lesser weight than some others because of the inclusion of borderline but not invasive disease, since it is thought that not all borderline cases become malignant ovarian cancers. Differential exposure misclassification may have occurred, given the retrospective nature of the data collection.]

Cook et al. (1997) reported on a case–control study from the same three counties in western Washington state, USA. Cases were 313 White women aged 20–79 years diagnosed with borderline or invasive ovarian cancer and reported to the cancer registries between 1986 and 1988. Controls were 422 White women without prior bilateral oophorectomy, identified via random-digit dialling, and frequency-matched to cases on 5-year age group. The response rate was 64% for cases and 72% for controls. Study participants were asked whether they ever stored diaphragms in powder, dusted the perineal area after bathing, powdered sanitary napkins, or used genital deodorant sprays. They were also asked about duration and frequency of powder use and type of powder use (cornstarch, talcum powder, baby powder, deodorizing powder, and scented bath or body powder). [Because the data were collected retrospectively, differential exposure misclassification may be present.]

Chen et al. (1992) included 112 cases of epithelial ovarian cancer identified via the Beijing Cancer Registry, China, between 1984 and 1986.

Controls were 224 women from the geographical area covered by the cancer registry, matched to cases on age. The response rate was high for the controls (15 total refusals), but 47% of the cases originally approached had either died or could not be located. Participants were asked if they had ever used dusting powder on the lower abdomen or perineum for ≥ 3 months. [Low response rates for the cases may indicate selection bias, with lower-stage cancer cases more likely to be represented than higher-stage cases. Differential exposure misclassification remained a concern given the retrospective nature of the data collection, but public perceptions of the association between talc use and ovarian cancer risk are probably different in China, relative to the USA.]

Women born between 1929 and 1957 (aged 36–64 years) with primary invasive or borderline epithelial ovarian tumours reported to the Israel National Cancer Registry between 1 January 1990 and 1 September 1993 were eligible to participate as cases in the study by Shushan et al. (1996). Of these, 70% participated, resulting in 200 cases included. The control participants were 408 women without a history of bilateral oophorectomy and born between 1929 and 1957. They were selected via random-digit dialling within the same area codes as the cases [response rate, 53%]. Participants were categorized as "never/seldom" talc users or "moderate/a lot" talc users, with no information provided on whether talc use was specific to the perineal or genital area. [The results of this study may be affected by differential exposure misclassification. Public perceptions of the health effects of talc use among the Israeli population during this time period are unknown.]

Chang and Risch (1997) reported results from the Southern Ontario Ovarian Cancer Study (SON), which included 450 cases of invasive or borderline ovarian cancer identified via the Ontario cancer registry and 564 population-based controls without bilateral oophorectomy identified through the ministry of finance and matched to cases within three 15-year age groups (1 November 1989 to 31 October 1992). Acceptance rates were 71.3% for cases and 64.5% for controls. Participants were asked if they used talc regularly and if so, what types they used and their duration and frequency of use. Women who regularly applied talc to the perineum after showering or bathing or who dusted powder on sanitary napkins were specifically identified as users of genitally applied talc. Information on cornstarch use was also collected. [Differential exposure misclassification may be present given the retrospective nature of the data collection.]

Cramer et al. (2016) described the recruitment of participants into the NEC in three phases (1992–1997, 1998–2002, and 2003–2008). In total, 2041 women with borderline or invasive epithelial tumours of the ovary, peritoneum, or fallopian tubes living in eastern Massachusetts and New Hampshire, USA, were identified via local tumour boards and cancer registries. The 2100 controls were frequency-matched to cases on age and geography using a mix of random-digit dialling, drivers' licence lists, and town resident lists. Response rates were 71% for cases and 54% for controls. Study participants were initially asked if they regularly (at least once per month) applied powder to their genital or rectal area, sanitary napkins or tampons, underwear, or on other body areas. Users were also asked about the type of powder used, age they began using, and frequency and duration of use. The latter two responses were used to calculate lifetime exposure. Overall and histological subtype-specific effect estimates were reported. [Although response rates were high for cases, the poor response for controls may have introduced selection bias, if the included controls were not representative of the underlying population from which the cases arose. Retrospective data collection may have resulted in differential exposure misclassification.]

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Mills et al. (2004) conducted a population-based case–control study on ovarian cancer among women living in 22 counties of central California, USA, between 2000 and 2001. Cases were 256 women diagnosed with borderline or invasive epithelial ovarian cancer. This corresponded to a response rate of 40%. Random-digit dialling was used to identify women with no history of ovarian cancer or bilateral oophorectomy to serve as controls; 1122 women were included (response rate, 57%), frequency-matched to cases on age and race/ethnicity. All participants were asked detailed questions about their history of use of talc in the genital area, including calendar years of use, frequency of use, and duration of use. This was used to create a cumulative use metric. The authors evaluated ovarian cancer associations with year of first use, age at first use, first use relative to age at first birth, and years since last use. They also included histological subtype-specific analyses and potential effect measure modification by tubal ligation, hysterectomy, and other factors. [The poor response rate for cases may be an indication of selection bias, with women who had lower-stage or less aggressive disease being more likely to be represented in the study sample. Data were collected retrospectively, meaning differential exposure misclassification may be a concern.]

Wu et al. (2015) included as cases a racially and ethnically diverse sample of 1701 women with epithelial ovarian cancer living in Los Angeles County, California, USA, identified through the Los Angeles County Cancer Surveillance Program between 1992 and 2008. The case participation rate was 63.2%. The controls were 2391 neighbourhood women with at least one intact ovary who were individually matched to cases on year of birth and race/ethnicity. This was done via a neighbourhood control selection algorithm with supplementation from the records of the Health Care Financing Administration for women aged > 65 years, as required (response rate, 70%). The study questionnaire included a question on ever use of talc in the genital area: those with < 1 year of use were considered never users. [The Working Group noted that this study is named as the University of Southern California Study of Lifestyle and Women's Health (USC) and the Los Angeles County Ovarian Cancer Study (LACOCS) in the pooled analysis by Terry et al. (2013) and Davis et al. (2021), respectively. Differential exposure misclassification may be a concern as data were collected retrospectively, although the inclusion of very short-term users (< 1 year) in the non-user category could potentially diminish these effects, compared with other studies.]

Rosenblatt et al. (2011) describe the Diseases of the Ovary and their Evaluation (DOV) study, which included 812 cases of invasive or borderline epithelial ovarian cancer identified via the Surveillance, Epidemiology, and End Results (SEER) registry in western Washington state, USA, in 2002–2005, as well as 1313 controls identified via random-digit dialling. Cases and controls were frequency-matched on age, calendar time, and county. The participation rates were 76.6% of eligible cases and 84.1% of eligible controls. Women were asked whether they ever directly applied powder to the perineum after bathing or if they ever used powder on sanitary napkins or diaphragms. Details on types of powder used, frequency of use, and ages a woman started and stopped using were also recorded. This information was used to estimate lifetime number of powder applications. [Data on powder use were collected retrospectively, which may have resulted in differential exposure misclassification.]

In the only identified registry-based case–control study on talc use and endometrial cancer, Neill et al. (2012) presented the findings of the Australian National Endometrial Cancer Study (ANECS) in 1399 women with newly diagnosed endometrial cancer and 740 state- and age-matched controls, in Australia, in 2005–2007. Cases were identified via treatment clinics

and state cancer registries (response rate, 67%). Controls were sampled from national electoral rolls, excluding women with prior hysterectomy (response rate, 53%). Study participants were asked if they had ever used talc or powder in the genital area, including use on diaphragms, sanitary pads, or underwear. Users were asked about their age at first use and duration and frequency of use. Similar questions were asked about the use of talc on other body parts. [The Working Group noted that response rates for the controls were low, which could be an indication of selection bias resulting from the under-representation of certain population groups. Differential exposure misclassification may be a consequence of retrospective data collection, but potentially to a lesser degree than for ovarian cancer. Public perceptions of the potential health effects of talc use in Australia are unknown.]

A pooled analysis authored by Terry et al. (2013) brought together data from eight case–control studies participating in the Ovarian Cancer Association Consortium (OCAC) as of April 2010. For most of the individual studies, the results had been published previously as separate reports including: Chang and Risch (1997) (SON); Merritt et al. (2008) (Australian Cancer Study, AUS); Moorman et al. (2009) (the North Carolina Ovarian Cancer Study, NCO), Rosenblatt et al. (2011) (DOV), Kurta et al. (2012) (Hormones and Ovarian Cancer Prediction Study, HOP), [presumably published concurrently to Terry et al. (2013)]), Cramer et al. (1999) (NEC) and Wu et al. (2009) (USC). The AUS, DOV, and NEC studies provided new data for incorporation into the pooled analysis. The remaining case–control study (the Hawaii Ovarian Cancer Study, HAW) had not been published separately. The NEC and USC studies were also published separately (Cramer et al., 2016 and Wu et al., 2015, respectively), after the pooled analysis by Terry et al. (2013), and those publications were separately reviewed by the Working Group. [The Working Group did not provide details on the individual studies incorporated in Terry et al. (2013), or other large, pooled analyses, if the reported information was highly similar across publications. Hence, the studies by Merritt et al. (2008), Moorman et al. (2009), and Kurta et al. (2012) were not separately reviewed by the Working Group.]

In total, the pooled analysis by Terry et al. (2013) included 8525 cases of ovarian, fallopian tube, or peritoneal cancer and 9859 controls. Controls were matched to cases on 5-year age groups and study. The authors estimated pooled ORs and 95% confidence intervals for the associations between ever use and estimated lifetime exposure to genitally applied powder (on the basis of combined frequency and duration, categorized as age-specific quartiles) and ovarian cancer. Terry et al. (2013) included histological subtype-specific effect estimates for serous, mucinous, endometrioid, and clear cell ovarian cancer. [The term "powder" is used in the manuscript because some of the studies did not specifically ask about talc use or query participants about type of powder used. All estimates were calculated with respect to genital or perineal powder use, specifically. Because all the studies included in Terry et al. (2013) were retrospective case–control studies, any differential exposure misclassification would bias pooled estimates as well. Notably, the pooled analysis included some data collected after 2006, the year in which the initial report for *IARC Monographs* Volume 93 was published (Baan et al., 2006). This report may have influenced international public awareness of the possible carcinogenic effects of genital use of talc.]

An analysis by Phung et al. (2022) used many of the studies previously pooled in Terry et al. (2013) (AUS, DOV, HAW, HOP, NEC, and USC) plus data from three additional unpublished studies: the Connecticut Ovary Study (CON), USA; the Malignant Ovarian Tumor Study (MAL), Denmark; and the University of California, Irvine Ovarian Cancer Study (UCI),

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USA. In this pooled sample of 8500 cases and 13 592 controls comprising women with at least one intact ovary, all results were stratified by endometriosis status. Analyses of genital use of talc and ovarian cancer excluded participants from the MAL study (504 cases and 1553 controls), which did not collect data on talc use, and used imputation to address missing data issues. Talc use data were missing for 5% of women in the Australia-based study and 41.4% of women in the USA-based studies. [Because the study by Phung et al. (2022) was based on a similar sample and did not provide overall (i.e. unstratified) estimates, the analysis by Terry et al. (2013) was considered by the Working Group to be the main source for summary estimates across all OCAC studies.]

The African-American Cancer Epidemiology Study (AACES), as reported by Schildkraut et al. (2016), included 584 African-American women with invasive epithelial ovarian cancer and 745 African-American women with at least one intact ovary and no history of ovarian cancer. Participants were recruited from 11 states throughout the USA between December 2010 and August 2015. Controls were identified through random-digit dialling and were frequency-matched to cases on age and region. Response rates were not reported. Participants in the study were asked if they had ever used talc, cornstarch, baby, or deodorizing powders at least once per month for 6 months. Those that met this threshold of "regular" use were asked about frequency and duration of use, age at first use, and whether they used talc on the genital area (including underwear, sanitary napkins, and diaphragms). Frequency and duration metrics were used to estimate lifetime number of applications. [Response rates were not explicitly reported in this paper.]

A second group of case–control studies on ovarian cancer were pooled as the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium (Davis et al., 2021; Peres et al., 2021). [The Working Group noted that the studies by Peres et al. (2021) and Davis et al. (2021) were published concurrently and have similar sample sizes (Davis et al., 2021: 3420 cases, 7881 controls; Peres et al., 2021: 3416 cases, 7643 controls), but as the study by Davis et al. (2021) was focused specifically on the association between genital use of powder and ovarian cancer and Peres et al. (2021) considered a broader array of ovarian risk factors in addition to genital use of powder, the Working Group reported only the results from Davis et al. (2021).]

Overlap between the OCAC (Terry et al., 2013; Phung et al., 2022) and Davis et al. (2021) included NCO (Moorman et al., 2009) and USC (also referred to as LACOCS in the OCWAA original publication) (Wu et al., 2009, 2015). The remaining OCWAA data came from AACES (Schildkraut et al., 2016), the Cook County Case Study (CCCS, published separately by Kim et al. (2010), which was not reviewed separately by the Working Group, as the study did not report additional data of interest compared with the pooled analysis) and one prospective cohort study (WHI-OS, originally published as Houghton et al., 2014) re-sampled as a matched case–control study. Analyses considering frequency and duration of genital use of powder and ovarian cancer histological subtypes were included. Because the original AACES publication reported evidence of possible differential exposure misclassification in participants interviewed in 2014 or later, women interviewed after 2013 were excluded from all pooled analyses. [The Working Group noted that the exclusion of AACES data after 2013 and the inclusion of one study with prospectively collected data (WHI-OS) would help to diminish the influence of differential misclassification on these effect estimates, but that some residual biases may remain, especially given that some of the data were collected after the *IARC Monographs* Volume 93 evaluation was published.]

(c) Other case–control studies on cosmetic talc

See Table 2.2.

There were 11 case–control studies for which cases were recruited in hospitals and not through cancer registries. Those studies that recruited through registries are reviewed in Section 2.1.5(b). The studies with case recruitment through hospitals were conducted in the USA (Hartge et al., 1983; Whittemore et al., 1988; Rosenblatt et al., 1992; Cramer and Xu, 1995; Eltabbakh et al., 1998; Wong et al., 1999; Ness et al., 2000), UK (Booth et al., 1989), Australia (Green et al., 1997), Canada (Godard et al., 1998; Leung et al., 2023) and Greece (Tzonou et al., 1993). Of the studies reviewed, two large studies were considered to be particularly informative for the evaluation (Green et al., 1997; and Ness et al., 2000): both covered large geographical regions and, because of this wide geographical coverage, were akin to population-based case–control studies. Nine other studies provided little information for the evaluation (Hartge et al., 1983; Booth et al., 1989; Rosenblatt et al., 1992; Tzonou et al., 1993; Cramer and Xu, 1995; Godard et al., 1998; Leung et al., 2023; Whittemore et al., 1988; and Wong et al., 1999). One study was considered uninformative because cases overlapped with those in the study by Wong et al. (1999), which had a more appropriate control selection (Eltabbakh et al.,1998).

Cramer and Xu (1995) combined two case–control studies conducted between 1978–1981 and 1984–1987 in the same hospitals in Boston, Massachusetts, USA. The combined study included 450 cases of pathologically confirmed epithelial ovarian cancer, with both invasive and borderline diagnoses. Controls (454 women) were selected from the general population and were matched to the cases on age and precinct of residence. Study participants were reported to range in age from < 40 to > 70 years. [The Working Group considered the selection of cases and controls in this study to be reasonably representative of the general population of the geographical region evaluated. The Working Group noted that there may be differential exposure misclassification. These results have limited informativeness for the evaluation.]

Hartge et al. (1983) investigated the association between talc use and epithelial ovarian cancer in a case–control study conducted between 1974 and 1977. There were 135 cases identified and 171 controls treated at the same hospitals as the cases. The controls were frequency-matched to cases on age, race, and hospital and had conditions other than gynaecological, psychiatric, or malignant diseases or pregnancy. The participants were asked about talc or body powder use, including use on sanitary napkins, underwear or near the genital area. The analysis adjusted for race, age, and gravidity. [The Working Group noted the small sample size and the possibility of chance findings. Differential exposure misclassification could not be ruled out. The study was of minimal informativeness for the evaluation.]

Whittemore et al. (1988) conducted a small case–control study that included 188 cases of epithelial ovarian cancer and 539 controls. Cases were identified from the San Francisco Bay area, USA, between 1983 and 1985. Two control groups of women were included: 280 were chosen from hospitalized patients and 259 were chosen from the general population via random-digit dialling. Both control groups were matched on age and race. Data on ever use, frequency and duration of talcum powder use on the perineum, on sanitary pads, or on diaphragms were collected using structured in-person interviews. Potential confounders included parity, oral contraceptive use, tubal ligation, or hysterectomy. The prevalence of ever use in the controls was about 40%. [The Working Group noted that this study was conducted before 2014 and that differential exposure misclassification was likely. Histological subtype was not considered. The unknown assortment of diseases causing hospitalization in

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the control group of patients might have caused differences in behaviour compared with that in the general population. Because of the small sample size, the results of this study had little informativeness for the evaluation.]

Booth et al. (1989) conducted a hospital-based case–control study in London and Oxford, UK, between 1978 and 1983. The study included 235 cases of pathologically confirmed epithelial ovarian cancer. Women were under the age of 65 years at diagnosis. Two age-matched controls were selected from among women being treated at the same hospital as the case when feasible, and 451 controls were included. For 63 cases, no match could be found with a control from the same cancer hospital; thus, controls were selected from another hospital. Information on talc use on the genital area, as well as on other important covariates, including reproductive and menstrual history, exogenous hormone use, and cigarette smoking, was collected during interview using a standardized questionnaire. Frequency, but not duration, of talc use was obtained. [The Working Group noted that there was potential for differential exposure misclassification in this study and that hospitalized controls are problematic because of the presence of other diseases that may have changed behaviour. Thus, the study was minimally informative for the evaluation.]

Rosenblatt et al. (1992) conducted a case–control study comprising 77 cases of ovarian cancer and 46 age- and race-matched controls ascertained between 1981 and 1985. Controls were treated at the same hospital with conditions other than gynaecological and malignant diseases. Genital exposure to fibre from different sources, defined as asbestos, talc, or fibreglass of unspecified type, was assessed. None of the study participants indicated that they were exposed to fibreglass in this study. In addition, more specific exposure to talc (talc on sanitary napkin, talc body powder after bathing, talc on diaphragm) was also assessed. The specific source of the exposure was not considered. Other potential confounders, including reproductive factors, family history, and contraceptive use were obtained via questionnaire. [The Working Group considered that it was difficult to assess the appropriateness of the selection of controls with other undisclosed conditions, including whether they were at risk of developing ovarian cancer. This study was therefore considered of little informativeness for the evaluation.]

Tzonou et al. (1993) reported results from a case–control study of epithelial ovarian cancer conducted between 1989 and 1991 in Athens, Greece. Cases included 189 women who underwent surgery for ovarian cancer at two major hospitals. Eligible controls included 200 women without a cancer diagnosis and with intact ovaries (reported in Polychronopoulou et al., 1993) who were visiting patients at the same hospitals. All participants were under the age of 75 years and were interviewed in-person. Adjusted ORs were estimated using multivariable logistic regression. Several potential confounders were included in the model, including age, education, weight, age at menarche, menopausal status, and parity to calculate the association for talc use in the perineal area. The prevalence of talc use in the controls was low (3.5%). [The Working Group considered that there was little selection bias and that there was the possibility of differential exposure misclassification. Because of the low prevalence of talc use and inadequate statistical power, the study was of limited informativeness for the evaluation.]

Green et al. (1997) conducted a large case–control study in Australia. Included were 824 cases of incident epithelial ovarian cancer, diagnosed between 1990 and 1993, who were identified from gynaecological oncology treatment centres in three Australian states, as well as 855 controls. Pathological confirmation was undertaken, but subtype analysis was not conducted. Controls were frequency-matched on age and urban/rural district of residence and randomly selected from the electoral roll. Face-to-face interviews were

conducted. Information on talc exposure of the perineal area was obtained, and the prevalence of ever use was about 40%. Multivariable logistic regression controlled for several potential confounding variables, including parity, duration of oral contraceptive use, education, BMI, smoking, and family history. The effect of perineal use of talc was also evaluated among women without surgical tubal occlusion. [The Working Group considered this study comparable to a population-based case–control study, because of its comprehensive ascertainment of cases and selection of population-based controls. The possibility of differential exposure misclassification to talc could not be excluded. This study was considered informative for the evaluation.]

Wong et al. (1999) reported results from a case–control study of 499 cases of epithelial ovarian cancer and 755 controls who were frequency-matched to cases on age. Cases were listed in the Roswell Park Tumor Registry and treated at Roswell Park Cancer Institute between 1982 and 1995. Controls had non-gynaecological malignancies diagnosed during the same period. Self-administered questionnaires were used to collect exposure data and potential confounders. Unconditional logistic regression models were fitted that adjusted for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographical location, and history of tubal ligation or previous hysterectomy. The prevalence of ever talc use among controls was 44.9%. [The Working Group noted that using cancer controls might reduce differential exposure misclassification. The controls included those with other diseases in the same hospital, which may have influenced the responses concerning talc use and may also not be representative of the same source population as the cases, because this was a tertiary-care hospital. The study was therefore considered minimally informative for the evaluation.]

Godard et al. (1998) conducted a case–control study on histologically confirmed primary invasive ovarian cancer and borderline tumours: 170 cases and 170 randomly selected population controls frequency-matched to cases on age and ethnic group. All participants were French-Canadian women aged 20–84 years. The cases were identified from among patients in gynaecology oncology clinics of two large Montreal teaching hospitals between 1995 and 1996. Standardized questionnaires were administered to patients. Multivariable logistic regression was used. The prevalence of talc use on the perineum among controls was somewhat low (4.7%). [The Working Group noted as limitations that the sample size was small; recruitment was not population-based since two gynaecology clinics were used to recruit cases; there was the possibility of residual confounding and differential exposure misclassification; and the duration and frequency of use were not evaluated. This study was therefore of limited informativeness for the evaluation.]

Ness et al. (2000) conducted a population-based case–control study in women aged 20–69 years that included 767 cases of epithelial ovarian cancer (invasive and borderline) and 1367 controls. The cases were diagnosed between 1994 and 1998 in 39 hospitals in the Delaware Valley of Pennsylvania, New Jersey, and Delaware, USA. Controls were initially identified through random-digit dialling and frequency-matched on age and telephone exchange code to cases aged ≤ 65 years. Additional controls were frequency-matched on age and county of residence to cases aged 65–69 years through Health Care Financing Administration lists, to maximize response rates in this older age group. Cases included 616 women with a diagnosis of invasive epithelial ovarian cancer and 151 women with borderline diagnoses. Centralized pathology review was conducted on a random sample of 120 cases. Standardized in-person interviews were used to obtain data on other ovarian cancer

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risk factors including gravidity, tubal ligation, and hysterectomy. [The Working Group noted as limitations that histological subtypes were not considered, and borderline cases were included; and that because body powder exposure was self-reported, differential exposure misclassification could not be excluded. This study was considered informative for the evaluation.]

2.1.6 Studies on cancer and medical use of talc

See Table 2.1.

The Working Group considered four cohort studies and one case–control study that evaluated the use of talc for medical purposes (Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979; Lange et al., 1988; Viskum et al., 1989; Nielsen et al., 1994; Chang et al., 2019). [Three of the four cohort studies were uninformative because of small sample sizes. Viskum et al. (1989) evaluated a case series of 99 patients treated with talc pleurodesis, but the study was considered uninformative because only 3 cases of lung cancer (one contralateral) and no mesothelioma cases were reported, and no expected case numbers were reported. The study by Lange et al. (1988) was considered uninformative for the evaluation of cancer in people treated with talc pleurodesis because of the absence of cancer risk estimates in a small cohort (n = 114).] In a study by the Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit (1979), 210 patients treated with talc or kaolin were followed for mesothelioma or lung cancer mortality. [The Working Group considered that the size of the cohort and the number of observed events (0 for mesothelioma, 3 for lung cancer) were not informative for cancer follow-up.] The case–control study by Nielsen et al. (1994) assessed talc exposure during abdominal surgery and risk of peritoneal mesothelioma among participants identified from the Danish Cancer Registry. [This study was considered uninformative because of concerns about the small sample size (68 cases included), accuracy in diagnosis of the cases, and the selection of controls with a diagnosis of either uterine or pancreatic cancer.]

The report by Chang et al. (2019) explored the risk of stomach cancer related to oral intake of talc without asbestos in the form of a herbal decoction used as an antipyretic and diuretic agent in Chinese traditional medicine. The study population was a cohort identified through the population-based database, the National Health Insurance Research Database (NHIRD), which is a comprehensive registry of the population of Taiwan, China, and was established in 2005. The study cohort was defined by selecting a random sample of patients enrolled in the registry of beneficiaries. Those alive in 2005 were followed from 1997 to 2013, and 1849 stomach cancers were identified. This was a very large study that included 584 077 people without talc exposure and 21 575 with talc exposure who were identified through claims data. Those aged < 20 years were excluded, as were patients with a peptic ulcer or *Helicobacter pylori* infection. All participants were Asian, and both men and women were included. [The Working Group noted as strengths that the assessment of talc in a prospective study and its basis on medical claims avoided differential exposure misclassification; and that appropriate statistical analysis was employed. Limitations were that because only people who were alive in 2005 were followed, those with incident stomach cancer who had died before 2005 were not included, and survival bias had a slight impact on the results; and also that information on personal use of talc was not obtained, which would lead to underestimation of total talc exposure and possible attenuation of the risk association. The informativeness of the study for the evaluation of the association between oral talc exposure and stomach cancer was lessened because of unmeasured survival bias.]

2.2 Cancer of the ovary

See Table 2.2.

The association between talc (including body powder) exposure and ovarian cancer has been the subject of many epidemiological investigations. The potential link has been researched using two types of study design: case–control studies (both hospital- and registry-based) and prospective cohort studies. Both occupational and personal talc exposures have been considered.

[The Working Group noted that the included studies of personal use of talc refer to genital or perineal application of talc, unless otherwise specified. The occupational studies included women with job titles known to have involved general exposure to talc, but none incorporated quantitative assessments of individual exposure levels. Type of exposure (i.e. occupational versus personal) would have implications for the dose of talc that comes in direct physical contact with genital organs or the female reproductive tract. Levels of asbestos contamination of the talc were not assessed for any of the talc exposures (industrial or personal use) described in these individual studies.]

[The Working Group additionally noted that there was some variability in how ovarian cancer was defined across studies. In most studies, the case definition was limited to invasive epithelial ovarian cancer, but some studies included (or were limited to) borderline ovarian cancer or additionally included cancers of the fallopian tubes or peritoneum. Other than in a few studies where noted, the Working Group did not expect these variations in case definition to change the interpretation of the results.]

2.2.1 Cohort studies

Bulbulyan et al. (1999) (see Section 2.1.4(a)) conducted a study in the Russian Federation in 3473 women employed for ≥ 2 years in one of two printing plants where talc was used as filler pigment in paper. Having worked as a bookbinder as a primary process of employment was found to be associated with increased mortality from ovarian cancer, compared with the general Moscow population (SMR, 2.9; 95% CI, 1.5–5.0). No quantitative assessment of talc exposure was performed. Results by duration of employment showed an SMR of 3.5 (95% CI, 1.4–7.1) for bookbinders employed for ≥ 15 years.

Langseth and Andersen (1999) (see Section 2.1.4(a)) considered a cohort of 4247 women in Norway who had worked for ≥ 1 year in a pulp and paper mill where talc was used as a coating agent. More cases of ovarian cancer were observed than were expected (SIR, 1.5; 95% CI, 1.07–2.09). Among long-term workers in the paper mill department, relative rates decreased with time since first exposure (SIR for 3–14 years since first exposure, 3.8; 95% CI, 1.05–9.18; SIR for ≥ 30 years since first exposure, 1.8 (95% CI, 0.79–3.56), and were highest among those with first exposure in 1960–1974 (SIR, 3.4; 95% CI, 1.07–7.85). Langseth and Kjaerheim (2004) conducted a nested case–control study in the pulp and paper mill cohort in Norway. Eligible employees had worked for ≥ 1 year between 1920 and 1993 (see Section 2.1.4(a)); 46 cases of ovarian cancer were each matched to 4 controls. The OR for occupational exposure to talc was 1.10 (95% CI, 0.56–2.18) after adjustment for calendar time and year of birth. The authors also assessed personal perineal use of talc, observing an OR of 1.15 (95% CI, 0.41–3.21) for ever use.

In a publication that first became publicly available in 2023, Boffetta and Colin (2001) reported on a pooled analysis coordinated by IARC of cancer incidence and mortality rates among 18 241 women working in the pulp and paper industry across 15 countries (including the Norwegian pulp and paper mill cohort described above; Langseth and Andersen, 1999) (see Section 2.1.4(a)). Having ever worked in a department involving any exposure to talc was not strongly associated with ovarian cancer incidence

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(SIR, 1.27; 95% CI, 0.78–1.97) or mortality (SMR, 1.13; 95% CI, 0.62–1.90), but having ever worked in a department that involved high exposure to talc was positively associated with both ovarian cancer incidence (SIR, 2.53; 95% CI, 1.09–4.99) and mortality (SMR, 2.70; 95% CI, 1.17–5.32). There was no excess ovarian cancer mortality or incidence for women ever exposed (SMR, 0.21; 95% CI, 0.01–1.15; 1 case observed) or ever highly exposed to asbestos (0 observed cases); however, the analysis did not account for asbestos contamination of talc in pulp and paper industry. There were no clear trends in mortality by cumulative exposure to talc or time since first talc exposure, and comparisons were based on 20 incident cases and 14 deaths from ovarian cancer among exposed workers (8 cases and deaths among highly exposed women).

Gertig et al. (2000) examined how genital use of powder was associated with ovarian cancer in the NHS-I, a prospective cohort of 121 700 female nurses from across the USA (see Section 2.1.5(a)). The cohort was originally enrolled in 1976, and questions about frequency of ever use of "talcum powder, body powder or deodorizing powder" on the perineal area or on sanitary napkins appeared in a 1982 follow-up questionnaire. The analysis included person-time from 1982 through 1 June 1996, during which time 307 women were diagnosed with epithelial ovarian cancer. The relative risk for ever genital use of talc (perineal application or sanitary napkin; ever-exposed, 40%) was 1.09 (95% CI, 0.86–1.37), with a positive association seen between ever genital use of talc and invasive serous ovarian cancer (relative risk, 1.40; 95% CI, 1.02–1.91). There were no differences by location of application and no consistent increase in risk with more frequent use. When limited to women with patent reproductive tracts at baseline, the relative risk was 1.15 (95% CI, 0.89–1.49). [The Working Group noted that although the questionnaire assessed ever use of talc during the lifetime, exposure was assessed on a single questionnaire, and no data were captured on duration or timing of use; therefore, some women who were considered to have non-patent reproductive tracts at enrolment probably used talc before surgery.]

Houghton et al. (2014) used data from WHI-OS to examine the association between ever use of powder and incident ovarian cancer (see Section 2.1.5(a)). The WHI-OS included 93 676 postmenopausal women, aged 50–79 years, enrolled between 1993 and 1998 from 40 clinical centres across the USA. The exposure assessment included separate questions on ever use of powder applied directly to the genitals, ever use of powder on sanitary napkins or pads, and, among diaphragm users, ever use of powder on a diaphragm. With each question, participants specified the duration of powder use. Among 61 576 women included in the study, 52.6% reported ever using powder in the genital area, and 429 women developed ovarian cancer over an average of 12.4 years of follow-up. The HR for ever perineal use of powder (including genital use, sanitary napkins/pads, or diaphragm) and ovarian cancer was 1.06 (95% CI, 0.87–1.28), with a marginally higher HR seen for genital use alone (HR, 1.12; 95% CI, 0.92–1.36). HRs did not increase with longer duration of use, and there were no notable differences by ovarian cancer histological subtype. [The Working Group noted as limitations that talc exposure was included only on the baseline questionnaire, and no data on frequency of use or timing of first use were collected, so the relative timing of exposure and hysterectomy or tubal ligation could not be established.]

In the prospective USA-based Sister Study cohort, which included women who had one or more sisters previously diagnosed with breast cancer, Gonzalez et al. (2016) examined associations between self-reported application of talc to a "sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area" in the 12 months before enrolling in the study (2003–2009) and incident ovarian cancer (including peritoneal

and fallopian tube cancers) (see Section 2.1.5(a)). The observed multivariable-adjusted HR was 0.73 (95% CI, 0.44–1.2) and did not differ by patency status at enrolment. This was based on 154 cases of ovarian cancer diagnosed among 41 654 eligible participants between enrolment and July 2014, with an exposure prevalence of 14%. [The Working Group noted as a limitation that the exposure period examined here, i.e. the year before enrolment, was probably a poor measure of usual adult use, given that talc use is often directly tied to menstruation, and most of the women in the cohort (56% of non-cases) were postmenopausal at the time of enrolment. The cases were more likely to be postmenopausal at enrolment (69%), and therefore may have been more likely to be misclassified as non-users. This would induce a downward bias in the observed effect.]

O'Brien et al. (2020) carried out a pooled analysis that included all of the large prospective cohort studies known to have collected data on use of powder in the genital area (see Section 2.1.5(a)). It included updated data on incident ovarian cancer from NHS-I (originally published as Gertig et al., 2000), WHI-OS (originally published as Houghton et al., 2014), and the Sister Study (originally published as Gonzalez et al., 2016), as well as previously unpublished data from NHS-II.

For the pooled sample, 38% of participants reported ever using powder in the genital area. The estimated HR for ever use was 1.08 (95% CI, 0.99–1.17), after adjusting for age (as the timescale), race/ethnicity, education, BMI, parity, ever use of oral contraceptives, hysterectomy status, tubal ligation, menopausal status, ever use of hormone therapy, and study. Among women who had patent reproductive tracts at enrolment, the HR was 1.13 (95% CI, 1.01–1.26).

Pooling across the Sister Study, WHI-OS, and NHS-II, long-term genital use of talc (defined in different ways in each cohort) was not associated with ovarian cancer incidence (overall HR, 1.01; 95% CI, 0.82–1.25; HR for women with a patent reproductive tract, 1.00; 95% CI, 0.76–1.32), compared with never use. Frequent use was assessed in the Sister Study, NHS-I, and NHS-II and there was some evidence of a positive association with ovarian cancer (HR, 1.09; 95% CI, 0.97–1.23), particularly among women with patent reproductive tracts (HR, 1.19; 95% CI, 1.03–1.37). The histological subtype-specific effect estimates (HRs) for ever versus never use were: serous ovarian cancer, 1.10 (95% CI, 0.97–1.25); endometrioid, 1.15 (95% CI, 0.83–1.58); mucinous, 1.03 (95% CI, 0.69–1.54); clear cell, 1.17 (95% CI, 0.73–1.89); and other histological subtypes, 0.97 95% CI, (0.79–1.20). [The Working Group noted that a limitation of the pooled study was its use of the "common denominator" exposures across all studies, meaning that exposure could be defined only according to the cohort with the least detailed information. Another was the uncertainty in the timing of patency, as most studies did not collect data on ages at which powder was used. A notable strength was the addition of new cases beyond those included in previous publications for NHS-I, Sister Study, and WHI-OS, and previously unpublished data from NHS-II.]

O'Brien et al. (2024) re-analysed the association between talc and ovarian cancer in the Sister Study cohort using an additional 138 cases (total, n = 292) and updated data on talc use across the life-course, which were collected in a follow-up survey administered in 2017–2019 (see Section 2.1.5(a)). Because the follow-up questionnaire was administered after many of the cases of ovarian cancer had been diagnosed, the authors used multiple imputation and quantitative bias analysis approaches to account for differential misclassification and address issues with missing data. Under moderate assumptions about the influence of differential misclassification (referred to here as "recall bias"; i.e. assuming that 25% of non-frequent, short-term users of talc with ovarian cancer misreported their exposure

and that 10% of non-cases who reported no use were actually short-term and infrequent users), the estimated HR for ever genital use of talc across the life-course and incident ovarian cancer was 1.40 (95% CI, 1.04–1.89). HRs were higher for more frequent and longer-term use (*P* for trend, 0.001 for both), and high for genital use of talc in women aged 20–29 years (HR, 1.88; 95% CI, 1.37–2.57) or 30–39 years (HR, 2.08; 95% CI, 1.50–2.89). There were no notable differences by histological subtype, but there was some evidence that the association was stronger among women who reported genital use of talc when they had a patent reproductive tract (HR, 1.55; 95% CI, 1.14–2.09). [The Working Group noted that this new Sister Study analysis should be considered an update to Gonzalez et al. (2016), especially as it improved upon the previously mentioned issue of potentially differential misclassification. However, Gonzalez et al. (2016) remains a valid assessment of the association between recent genital use of talc and incident ovarian cancer and would not be affected by differential misclassification given its fully prospective design.]

[The Working Group noted as limitations that the cohort studies captured only partial details about the participants' genital use of powder, with great variability in how, when, and what types of powder exposure were assessed. Because exposure assessment occurred before the diagnosis of any cancers, these studies avoided the possibility of differential exposure misclassification. Unless otherwise discussed, exposure misclassification in prospective studies was likely to be nondifferential by case status and would therefore tend to bias effect estimates towards the null.]

2.2.2 Case–control studies

Cramer and Xu (1995) evaluated ever use of talc in the genital area and risk of ovarian cancer by combining data from two case–control studies conducted in the Boston area, Massachusetts, USA, in 1978–1981 and 1984–1987 (see Section 2.1.5(c)). Altogether, the study included 450 cases and 454 controls. In age-adjusted models, genital use of talc was positively associated with ovarian cancer (OR, 1.6; 95% CI, 1.2–2.1). Ever genital use of talc was reported by 34% of women in the control group. Based on reported numbers, crude estimates for the association between genital use of talc and ovarian cancer were higher for women who had experienced pelvic surgery [OR, 2.73; 95% CI, 1.28–5.84] than for women with no history of pelvic surgery [OR, 1.45; 95% CI, 1.09–1.93]. [The Working Group noted as a limitation that there was minimal confounding adjustment in this analysis, leaving open the possibility that there may be unmeasured confounding by factors such as body size, reproductive factors, or exogenous hormone use. If cases were inherently more likely to report exposure than controls, differential exposure misclassification may have occurred. This would bias the estimated effects upwards. Results stratified by pelvic surgery status referred to any prior surgery and did not correspond to surgical status at time of talc use.]

In a hospital-based case–control study of ovarian cancer conducted in the Washington, District of Columbia metropolitan area, USA, in 1974–1977, Hartge et al. (1983) (see Section 2.1.5(c)) reported an OR of 2.5 (95% CI, 0.7–10.0) for ever genital use of talc (exposure prevalence in controls, 2%), relative to never use. An OR of 0.8 (95% CI, 0.5–1.2) was reported for ever use of any talc on the body (including but not limited to genital use). Information on personal use of talc was collected for a total of 135 cases and 171 controls. Information on occupational exposure to talc was available for a larger sample (296 cases, 343 controls), as reported by Hartge and Stewart (1994) (see Section 2.1.4(b)). On the basis of an industrial hygienist's classification of occupations, 12 cases (4%) and 31 controls (10%) had definite, probable, or possible exposure to talc. All ORs for years of talc exposure (relative

to no exposure) were < 1.0 (e.g. ≥ 10 years of talc exposure, OR, 0.5; 95% CI, 0.2–1.5, after adjusting for race, age, parity, and gynaecological surgery). [The Working Group noted as a limitation that the adjustment set was unclear for the assessment of personal use of talc in the study by Hartge et al. (1983). Controls were matched to cases on age, race, and hospital. Reported ORs agreed with unadjusted ORs, but age, race, and gravidity were evaluated and determined not to be confounders (results not shown). Differential exposure misclassification may be present. The inverse association between long-term occupational exposure and ovarian cancer could be an indication that HWSB was present, i.e. that women without ovarian cancer were able to keep working longer.]

In a case–control study of primary epithelial ovarian cancer conducted in California, USA, in 1983–1985, that included both hospital- and population-based controls, Whittemore et al. (1988) (see Section 2.1.5(c)) reported an OR for ever versus never use of talc on the perineum of 1.37 (95% CI, 0.97–1.95), adjusted for parity and surgical sterilization. The study included 188 cases and 539 controls, with 46% of control participants reporting using talc in the perineal area. The OR for women who applied talc ≥ 20 times per month was 1.45 (95% CI, 0.94–2.22). No differences in method of talc application (direct to the perineum, sanitary napkins, or diaphragm) were observed, with estimates largely overlapping, especially for "perineum only", "diaphragm only" application. Using talc for 1–9 years with a patent reproductive tract (no tubal ligation, no hysterectomy), relative to never use, was positively associated with ovarian cancer (OR, 1.6; 95% CI, 1.00–2.57). However, this trend did not continue with the highest exposure duration category (OR for ≥ 10 years of use with a patent reproductive tract, 1.11; 95% CI, 0.74–1.65). [The Working Group noted as a limitation that the lack of adjustment for body size, reproductive factors other than parity, and exogenous hormone use could potentially confound the results. Differential exposure misclassification may have occurred.]

A hospital-based case–control study (1978–1983; 235 cases, 451 controls) conducted in the UK (Booth et al., 1989) (see Section 2.1.5(c)) reported a positive association between weekly genital use of talc and ovarian cancer (OR, 2.0; 95% CI, 1.3–3.4), adjusted for age and social class. The positive association did not extend to daily users (OR, 1.3; 95% CI, 0.8–1.9; *P* for trend, 0.05). Ever use was reported by 59% of controls. [The Working Group noted as a limitation that unmeasured confounding by body size, reproductive factors, and exogenous hormone use could potentially bias effect estimates. Differential misclassification could have occurred, biasing the results upwards.]

In the population-based study by Harlow and Weiss (1989) on borderline ovarian tumours in western Washington state, USA, in 1980–1985, 40.5% of controls reported any perineal exposure to powder (see Section 2.1.5(b)). After adjusting for age, parity, and oral contraceptive use, the OR for any perineal use of powder and borderline ovarian cancer was 1.1 (95% CI, 0.7–2.1) among 116 cases and 158 controls. When type of powder used was considered, ever use of deodorizing powder was positively associated with disease (OR, 2.8; 95% CI, 1.1–11.7), with little evidence that use of baby powder, talc, or cornstarch contributed to risk. [The Working Group considered that this study was minimally informative, given the use of borderline-only disease as the outcome.]

In the population-based case–control study reported by Cook et al. (1997), approximately 39% of the 422 controls (all White women from western Washington state, USA, 1986–1988) reported ever using powder on the genital area (see Section 2.1.5(b)). Ever powder use was associated with an increased risk of ovarian cancer (OR, 1.5; 95% CI, 1.1–2.0; 313 cases) with adjustment for age. Estimates for exclusive perineal

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dusting, powder on sanitary napkins, or genital deodorizing spray were similar (OR range, 1.5–1.8), but diaphragm storage in powder was not associated with increased risk. When analysed by type of powder used, any talcum powder use (OR, 1.6; 95% CI, 0.9–2.8) and any bath or body powder use (OR, 1.5; 95% CI, 0.9–2.4) stood out as possible drivers of the overall positive association. Histological subtype-specific estimates for any genital use of powder were: serous ovarian cancer, OR, 1.7 (95% CI, 1.1–2.5); mucinous, OR, 0.7 (95% CI, 0.4–1.4); endometrioid, OR, 1.2 (95% CI, 0.6–2.3); and other histological subtypes, OR, 1.8 (95% CI, 1.1–2.8). [The Working Group noted as a limitation that this study had minimal confounder adjustment (age only), so residual confounding by body size, reproductive history, and exogenous hormone use may be present. Differential exposure misclassification may also be present.]

In a small, hospital-based case–control study (77 cases, 46 controls) carried out in 1981–1985 by Rosenblatt et al. (1992) (see Section 2.1.5(c)), any genital exposure to fibres (questions about genital exposure to fibres included questions focused on talc, e.g. talcum powder after bathing or applied to genital areas or sanitary napkins or use of talc on diaphragm, together with less specific questions, e.g. use of condom; the prevalence of genital fibre use was 88% in controls) was not associated with ovarian cancer risk (OR, 1.0; 95% CI, 0.2–4.0), matched on age and race, adjusting for number of live births. However, ever use of talc on sanitary napkins (86% of controls) was associated with an increased odds of ovarian cancer (OR, 4.8; 95% CI, 1.3–17.8), with imprecise positive associations also present for ever use of genital talc after bathing (OR, 1.7; 95% CI, 0.7–3.9) and use of talc on a diaphragm (OR, 3.0; 95% CI, 0.8–10.8). [The Working Group noted as a limitation that the lack of adjustment for body size, other reproductive factors, and exogenous hormone use could result in confounding. Differential exposure misclassification may have occurred.]

Chen et al. (1992) conducted a small population-based study (112 cases, 224 controls) in Beijing, China, in 1984–1986 (see Section 2.1.5(b)). Approximately 2% of controls reported ever using dusting powder on the lower abdomen or perineum for ≥ 3 months. The reported OR for this definition of powder exposure and ovarian cancer was 3.9 (95% CI, 0.9–10.6). [The Working Group noted as a limitation that this OR was based on very small numbers (7 exposed cases and 5 exposed controls) but was from one of the few studies conducted outside the USA. Differential exposure misclassification may be present.]

In a large case–control study (824 cases, 855 controls) conducted in Australia between 1990 and 1993, Green et al. (1997) (see Section 2.1.5(c)) reported a positive association between ever (versus never) perineal use of talc and ovarian cancer risk (OR, 1.3; 95% CI, 1.1–1.6), after adjusting for age, place of residence, parity, duration of oral contraceptive use, education, BMI, smoking, and family history of cancer. Cases were identified from gynaecological treatment centres and were matched on age and district to controls identified via electoral roll. Approximately 40% of control participants reported ever use. No association with duration of talc use or reported age when talc was first used in the perineal area was found [ORs not reported]. An elevated OR was observed for talc users with no tubal ligation or hysterectomy relative to women who did not use talc and did not have surgery (OR, 1.3; 95% CI, 1.0–1.7). [The Working Group noted that differential exposure misclassification might be present.]

Shushan et al. (1996) reported results of a population-based case–control study conducted in Israel between 1990 and 1994 (see Section 2.1.5(b)), where 6% of controls reported using talc moderately or "a lot" (relative to never or seldom). In a model unadjusted for covariates, but in which cases (n = 200) and controls

(*n* = 408) were matched on area code, being exposed to "moderate/ a lot" of talc was positively associated with ovarian cancer ([OR, 1.97; 95% CI, 1.06–3.66]), relative to being exposed "never/seldom". [The OR was derived by the Working Group on the basis of the numbers in the frequency table. Talc use was not well defined in this study; it was unclear whether it referred specifically to genital use of talc, and details on what amounts qualified as seldom, moderate, or a lot were not provided. Differential exposure misclassification might be present.]

In a comparison of 462 cases of ovarian cancer and 693 age-matched controls from Roswell Park Cancer Institute, Buffalo, New York, USA, in 1982–1995, Wong et al. (1999) (see Section 2.1.5(c)) found that perineal use of talc was not associated with ovarian cancer; the OR for ever use, relative to never talc use, was 0.92 (95% CI, 0.24–3.62) after controlling for age, parity, oral contraceptive use, smoking history, family history of ovarian cancer, age at menarche, menopausal status, income, education geographical location, history of tubal ligation, and previous hysterectomy. Estimates were similar for sanitary napkin use [only] (OR, 0.9; 95% CI, 0.4–2.0), genital or thigh area use [only] (OR, 1.0; 95% CI, 0.8–1.3), or combined use (OR, 1.1; 95% CI, 0.7–1.7). Ever use of any talc was reported by 45% of controls. All application sites considered, there was no evidence of a trend in risk estimates across duration of talc use. The observed OR for women with no history of genital tract interruption (no tubal ligation or hysterectomy) was 1.2 (95% CI, 0.8–1.6). Some histological subtype-specific evaluations were performed for ever versus never use of talc: serous ovarian cancer, OR, 1.2 (95% CI, 0.7–2.1); mucinous, OR, 1.5, (95% CI, 0.6–4.0); endometrioid, OR, 1.4 (95% CI, 0.7–2.7); and clear cell, OR, 1.6 (95% CI, 0.6–4.3). [The Working Group noted as a limitation that the OR estimates were not adjusted for body size, which could have led to upward bias. Differential exposure misclassification leading to bias away from the null also could not be ruled out.]

Tzonou et al. (1993) reported on a hospital-based case–control study (189 cases, 200 controls) in Athens, Greece, conducted in 1989–1991 (see Section 2.1.5(c)). The OR for the association between talc applied to the perineum (exposure prevalence in controls, 4%) and ovarian cancer was 1.05 (95% CI, 0.28–3.98), adjusted for age, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking, alcohol, coffee, analgesics, tranquillizers, and hair dyes.

Chang and Risch (1997) reported estimated ORs for the associations between several measures of powder use and ovarian cancer, adjusting for age, oral contraceptive use, parity, breastfeeding, tubal ligation, hysterectomy, and family history of breast and ovarian cancer (see Section 2.1.5(b)). The analysis was based on the SON study, which included 450 cases of invasive or borderline ovarian cancer identified via the Ontario cancer registry and 564 population-based controls (1989–1992). Overall, regular use of talc (reported by 36% of controls) was positively associated with ovarian cancer (OR, 1.420; 95% CI, 1.08–1.86). Estimates for application on sanitary napkins (OR, 1.262; 95% CI, 0.81–1.96) and post-bath (OR, 1.312; 95% CI, 1.00–1.73) were similar. ORs did not increase with higher frequency or longer duration of use. The OR for ever versus never talc use was highest for tumours that were of "endometrioid" histological subtypes (non-serous and non-mucinous, OR, 1.671; 95% CI, 1.00–2.79), but all histological subtype-specific ORs were > 1.0. The authors considered cornstarch use separately, but with < 1% of controls reporting any use, estimates were highly imprecise (OR, 0.305; 95% CI, 0.06–1.66). [The Working Group noted as a limitation that the publication did not clearly specify whether "any talc exposure" was limited to the perineal area or could include other body

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parts; it appeared to be a summary variable for ever application to a sanitary napkin or ever application to the perineum after showering or bathing, but the questionnaire wording was not explicitly stated. The Working Group also noted that no adjustment was made for body size, and differential exposure misclassification may have occurred.]

A study including 170 cases of epithelial ovarian cancer and 170 controls, frequency-matched to cases on age and ethnicity, was conducted in Montreal, Canada, in 1995–1996 (Godard et al., 1998) (see Section 2.1.5(c)). The authors reported an OR of 2.49 (95% CI, 0.94–6.58) for ever versus never perineal use of talc, with adjustment for age, ethnicity (through matching), age at last childbirth, age at menarche, age at last oral contraceptive use, tubal ligation or hysterectomy, and alcohol use. Approximately 5% of controls reported ever use. [The Working Group noted as limitations that the duration and frequency of use were not evaluated; the sample size was small with few exposed controls (n = 18); and differential exposure misclassification and lack of adjustment for body size could have inflated effect estimates.]

Cramer et al. (2016) reported on three phases of the NEC study (phase 1, 1992–1997; phase 2, 1998–2002; phase 3, 2003–2008) (see Section 2.1.5(b)). Overall, 26% of the 2100 population-based controls from eastern Massachusetts and New Hampshire, USA, had ever used powder [used interchangeably with "talc"] in the genital area. With 31% of the 2041 cases of invasive or borderline ovarian, fallopian tube, or peritoneal cancer reporting use, the estimated OR was 1.33 (95% CI, 1.16–1.52), after adjusting for the matching factors of referent age, study centre, and study phase. The positive association was consistent across several dose–response measures, including frequency of use (OR for ≥ 30 days per month versus never, 1.46; 95% CI, 1.20–1.78; P for trend, < 0.0001), number of years used (OR for > 35 years versus none, 1.33; 95% CI, 1.03–1.71; P for trend, 0.002), months per year of use (OR for 12 months per year versus none, 1.35; 95% CI, 1.09–1.67; P for trend, 0.006) and total number of applications (OR for > 7200 versus none, 1.49; 95% CI, 1.06–2.10; P for trend, 0.02). Starting use during a woman's twenties was associated with a notably higher risk (OR, 1.71; 95% CI, 1.34–2.17) than other start ages. In analyses that adjusted for a large set of potential confounders, including BMI, parity, reproductive factors, family history, smoking and alcohol (among others), African-American women had a higher OR (5.08; 95% CI, 1.32–19.6) than did women from other racial/ethnic groups (P for heterogeneity, 0.002). There was also statistically significant heterogeneity between groups defined by menopausal status and hormone therapy use, with the strongest ORs seen among users of postmenopausal hormone therapy (OR, 2.21; 95% CI, 1.63–3.00). Histological subtype-specific ORs for ever versus never use were (invasive disease only): serous ovarian cancer, OR, 1.42 (95% CI, 1.19–1.69); mucinous, OR, 0.87 (95% CI, 0.53–1.44); endometrioid, OR, 1.38 (95% CI, 1.06–1.80); and clear cell, OR, 1.01 (95% CI, 0.65–1.57). [The Working Group noted that the *IARC Monographs* Working Group for Volume 93 (Carbon black, titanium dioxide, and talc) met in February 2006, during the third enrolment phase of this study. Differential exposure misclassification is a potential source of bias for all case–control studies with retrospective exposure assessment, but the degree of bias may have changed over time depending on the general public's awareness of the potential carcinogenic effects of talc-based body powders.]

Ness et al. (2000) reported on a case–control study that recruited 767 cases from 39 hospitals in the Delaware Valley, USA, and 1367 population-based controls frequency-matched on age and area code from telephone exchanges (age < 65 years) or on age and county of residence from Health Care Financing Administration lists (age ≥ 65 years) between 1994 and 1998 (see

Section 2.1.5(c)). Of the controls, 47% reported ever using any talc. After adjusting for gravidity, race, family history of ovarian cancer, tubal ligation, hysterectomy, breast feeding, and age, ever use of talc in the genital or rectal area was positively associated with ovarian cancer, (OR, 1.5; 95% CI, 1.1–2.0), compared with women who never used talc in any body area. Talc use on non-genital areas (feet, arms, breasts) (OR, 1.4; 95% CI, 1.1–1.6), sanitary napkin (OR, 1.6; 95% CI, 1.1–2.3) or underwear (OR, 1.7; 95% CI, 1.2–2.4) was also associated with an increased risk of ovarian cancer. There was no increasing trend associated with increased duration of talc use for application directly to the body (non-genital or genital/rectal areas) (e.g. OR for < 1 year of use, 2.0; 95% CI, 1.0–4.0, but OR for ≥ 10 years of use, 1.2; 95% CI, 1.0–1.5). [The Working Group considered it a notable limitation that the authors did not provide an overall estimate of genital use of talc, which included sanitary napkins, underwear, and possibly diaphragms. Women could have contributed to more than one application site category. The duration estimates combined genital/rectal and non-genital use. Effect estimates could have been upwardly biased because of differential exposure misclassification and uncontrolled confounding by body size.]

In a population-based case–control study of ovarian cancer (256 cases, 1122 controls) conducted in central California, USA, in 2000–2001, Mills et al. (2004) reported that 37% of controls had ever used talc in the genital area (see Section 2.1.5(b)). In models adjusted for age, race/ethnicity, duration of oral contraceptive use, and breastfeeding, ever genital use of talc was positively associated with ovarian cancer risk (OR, 1.37; 95% CI, 1.02–1.85). A positive dose–response trend was present for frequency of use (*P* for trend, 0.015, and OR for use 4–7 times/week versus never, 1.74 (95% CI, 1.14–2.64). Non-monotonic but still generally positive trends were also observed for duration of use (*P* for trend, 0.045) and cumulative use (*P* for trend, 0.051). Additional analyses indicated elevated OR estimates (relative to never use) for women first using after 1975 (OR, 1.92; 95% CI, 1.27–2.91), between ages 20 and 24 years (OR, 2.41; 95% CI, 1.43–4.09), after first birth (OR, 2.51; 95% CI, 1.63–3.87) and who had last used in the preceding 1–2 years (excluding current users; OR, 2.40; 95% CI, 1.43–4.05). Histological subtype-specific associations for ever versus never use of perineal talc were: serous invasive ovarian cancer OR, 1.77 (95% CI, 1.12–2.81); mucinous invasive, OR, 2.56 (95% CI, 0.89–7.39); endometrioid, OR, 1.28 (95% CI, 0.62–2.62); and clear cell, OR, 0.63 (95% CI, 0.15–2.64). [The Working Group noted that multivariable models did not include body size, which could upwardly bias effect estimates. Differential exposure misclassification may be present.]

In a population-based study in Los Angeles County, California, USA, in 1992–2008, Wu et al. (2015) included a racially and ethnically diverse sample of 1701 cases and 2391 controls (see Section 2.1.5(b)). Genital use of talc was most common in African-American women (44%), followed by non-Hispanic White women (30%), and then Hispanic women (29%). Effect estimates for ever versus never genital use of talc were similar across groups, with evidence of increasing risk per 5 years of exposure (OR for non-Hispanic White women, 1.14; 95% CI, 1.08–1.21; OR for Hispanic women, 1.18; 95% CI, 1.02–1.36; and OR for African-American women, 1.15; 95% CI, 0.90–1.47). These ORs were adjusted for age, menopausal status, age at menarche, hormone therapy use, BMI, education, income, parity, oral contraceptive use, tubal ligation, endometriosis, and family history of ovarian cancer. [The Working Group noted that differential exposure misclassification may have occurred.]

The DOV study, as described by Rosenblatt et al. (2011), included 812 cases of invasive or borderline epithelial ovarian cancer identified via the SEER registry in western Washington

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state, USA, in 2002–2005, and 1313 controls identified via random-digit dialling and frequency-matched to cases on age, calendar time, and county (see Section 2.1.5(b)). The association between ever perineal use of powder and ovarian cancer was OR, 1.27 (95% CI, 0.97–1.66). ORs did not increase with higher cumulative number of applications or duration of use. There was some indication that starting to use later in life, at age ≥ 30 years (OR, 1.69; 95% CI, 1.08–2.64) or in 1980 or later (OR, 2.03; 95% CI, 1.28–3.24), relative to never use, was associated with higher risk. Models were adjusted for matching factors, parity, and use of hormonal birth control. [The Working Group noted as limitations that the analysis did not adjust for body size, which could result in an upward bias of the effect estimates; and that differential exposure misclassification may have occurred.]

Terry et al. (2013) brought together data from eight ovarian cancer case–control studies contributing to the OCAC (see Section 2.1.5(b)). These included: the SON study, originally published by Chang and Risch (1997); the AUS study, originally published by Merritt et al. (2008); the NCO study, originally published by Moorman et al. (2009); the DOV study, originally published by Rosenblatt et al. (2011); the HOP study, originally published by Kurta et al. (2012); the NEC study, originally published by Cramer et al. (1999) and later with additional participants by Cramer et al. (2016); the HAW study, not previously published; and the USC study, originally published by Wu et al. (2009) and later with additional participants by Wu et al. (2015). Altogether, 8525 cases and 9859 controls were included, all enrolled between 1989–2009. Most were from the USA, but women from Australia and Canada were also represented.

The primary exposure of interest in the study by Terry et al. (2013) was genital use of powder, which was reported by 25% of controls (ranging from 15% in the HAW study to 45% in AUS). Cases were matched to controls on age and study, with all pooled multivariable logistic regression models adjusted for duration of oral contraceptive use, parity, tubal ligation, BMI, and race or ethnicity. Compared with those with no powder use, genital use of powder was positively associated with ovarian cancer risk (OR, 1.24; 95% CI, 1.15–1.33), with no between-study heterogeneity (*P* for heterogeneity, 0.61). The was some evidence of an increasing trend across quartiles of lifetime exposure (ORs for lifetime number of applications in the 1st, 2nd, 3rd, and 4th quartile of use relative to never use were 1.14, 1.23, 1.22, and 1.32, respectively; *P* for trend, 0.17). Patterns were similar after excluding women who only started genital use of powder after tubal ligation or hysterectomy. Neither BMI nor calendar year of first use were strong modifiers of the association. Terry et al. (2013) provided histological subtype-specific estimates for ever versus never genital use of talc: serous invasive ovarian cancer, OR, 1.24 (95% CI, 1.13–1.35); mucinous invasive, OR, 1.06 (95% CI, 0.82–1.36); endometrioid invasive, OR, 1.20 (95% CI, 1.03–1.40); and clear cell invasive, OR, 1.26 (95% CI, 1.04–1.52). [The Working Group noted that a limitation of the pooled analysis was the use of a "common denominator" exposure metric across the included studies. A strength was the examination of risks by histological subtype.]

Phung et al. (2022) also pooled data from case–control studies, including many of those included in Terry et al. (2013) (AUS, DOV, HAW, HOP, NEC, and USC), as well as previously unpublished results from three other USA-based case–control studies with data on talc use: the CON and UCI studies (see Section 2.1.6(b)). In total, 8500 cases and 13 952 controls were included and enrolled between 1992 and 2010 (see Section 2.1.5(b)). Overall, there were 7996 cases and 12 039 controls included in the estimation of the association between ovarian cancer and talc use. Overall associations between genital use of talc and ovarian cancer were not reported, but the authors found that, relative to never users

of talc, the association for genital use of talc was similarly elevated for those with (OR, 1.38; 95% CI, 1.04–1.84) and without (OR, 1.12; 95% CI, 1.01–1.25) a history of endometriosis (*P* for heterogeneity, 0.65).

As reported by Schildkraut et al. (2016), a total of 584 cases and 745 controls were included in the AACES, a case–control study of invasive epithelial ovarian cancer among African-American women recruited from 11 sites throughout the USA in 2010–2015 (see Section 2.1.5(b)). Of 351 cases and 591 controls interviewed before 2014, 37% of cases and 34% of controls reported ever genital use of powder, with a corresponding covariate-adjusted OR for any genital use of powder versus never body powder use of 1.19 (95% CI, 0.87–1.63). However, of 233 cases and 154 controls interviewed in 2014 or later, 52% of cases and 34% of controls reported ever genital use of powder (OR, 2.91; 95% CI, 1.70–4.97). The overall combined OR for ever use of body powder (versus never) was 1.39 (95% CI, 1.10–1.76), and the OR for any genital use (versus never use on any area of the body) was 1.44 (95% CI, 1.11–1.86). Among all participants combined, Schildkraut et al. (2016) observed positive dose–response relations between ovarian cancer and dose of talc applied on the genital area (frequency of use, duration of use, and lifetime number of applications). [The marked difference in the prevalence of self-reported genital use of powder in cases diagnosed before versus after 2014 was interpreted by the authors and the Working Group to be an indication that mainstream media coverage of talc-related lawsuits may have influenced reporting for women with ovarian cancer. The Working Group noted that differential misclassification is a potential source of bias in all case–control studies with retrospectively collected exposure data. Although 2014 may be an important marker of increased awareness about the potential harms of body powder use, it is not clear whether there was a meaningful increase in bias at that time, and the Working Group urged caution in assuming that there was a time where this source of bias was not present.]

Davis et al. (2021) published results from a pooled sample of 3420 cases and 7881 controls from studies included in the OCWAA consortium (see Section 2.1.5(b)). This included NCO (Moorman et al., 2009), AACES (published separately by Schildkraut et al., 2016), USC (here referred to as the Los Angeles County Ovarian Cancer Study (LACOCS), published separately first by Wu et al., 2009 and then Wu et al., 2015), the CCCS, published separately by Kim et al., 2010, and a nested case–control sample from WHI-OS (original published by Houghton et al., 2014). Davis et al. (2021) included only participants from AACES who were interviewed before 2014.

Davis et al. (2021) reported that 31.4% of controls ever used powder in the genital area (White women, 31.0%; African-American women, 34.0%) (see Section 2.1.5(b)). In models adjusting for age, education, oral contraceptive use, family history of breast or ovarian cancer, parity, tubal ligation, hysterectomy, year of interview, BMI, menopausal status, smoking, and study site, ever genital use of powder was positively associated with ovarian cancer risk (OR, 1.32; 95% CI, 1.17–1.48), with no between-study heterogeneity (*P* for heterogeneity, 1.0). Estimates were similar for White (OR, 1.36; 95% CI, 1.19–1.57), African-American women (OR, 1.22; 95% CI, 0.97–1.53), and women who had patent (OR, 1.27; 95% CI, 1.09–1.48) and non-patent (OR, 1.42. 95% CI, 1.17–1.72) reproductive tracts. [The Working Group noted that patency here referred to status at the age the participant completed the study questionnaire, not the age(s) at which talc was used, which would have been more informative.] There were no clear dose–response patterns for either frequency or duration of use. Estimates of the effect of ever versus never genital use of powder were similar for high-grade serous ovarian cancer (OR, 1.32;

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95% CI, 1.15–1.51) versus all other histological subtypes (OR, 1.29; 95% CI, 1.10–1.52).

In a population-based case–control study with extensive occupational history data conducted in the greater Montreal area, Canada, in 2010–2016, Leung et al. (2023) observed an OR of 1.51 (95% CI, 0.36–6.30) for occupational exposure to cosmetic talc for ≥ 8 years (see Section 2.1.4(b)) and cancers of the ovary, fallopian tubes, or peritoneum. The association between having had "high" occupational cosmetic talc exposure was OR, 2.25 (95% CI, 0.52–7.41). ORs were adjusted for age, education, ancestry, parity, marital status, oral contraceptive use, endometriosis, and tubal ligation. [The Working Group noted as a limitation that the ORs were based on a very small number of workers with ovarian cancer in the highly exposed categories (8 workers exposed for ≥ 8 years; 12 workers had high cumulative exposure).]

2.2.3 Meta-analyses

Soon after *IARC Monographs* Volume 93 was published, a subset of the Working Group for that volume published a meta-analysis summarizing the state of the literature on talc and ovarian cancer (Langseth et al., 2008; meta-odds ratio, meta-OR, 1.35; 95% CI, 1.26–1.46). Three more recent meta-analyses have provided updated analyses, including most of the non-occupational studies described in the previous sections. Studies published after 2016 (Leung et al., 2023; O'Brien et al., 2024) have not yet been incorporated into any published meta-analyses. Independently published results from studies included in the pooled papers (O'Brien et al., 2020; Terry et al., 2013; Phung et al., 2022; Davis et al., 2021) were eligible for meta-analysis, but estimates from otherwise unpublished studies and updated estimates from established studies were not. A direct comparison of the studies included in the meta-analyses and pooled studies, including histological subtype-specific analyses and analyses stratified by patency was provided by Wentzensen and O'Brien (2021).

Berge et al. (2018) included 24 case–control studies and three cohort studies. The overall meta-relative risk (meta-RR) for ever use of genital talc was 1.22 (95% CI, 1.13–1.30), with differences seen between case–control summary estimates (meta-RR, 1.26; 95% CI, 1.17–1.35) and cohort summary estimates (meta-RR, 1.02; 95% CI, 0.85–1.20). The summary estimate for serous ovarian cancer (all study designs together) was 1.24 (95% CI, 1.15–1.34), with meta-relative risks closer to unity for endometrioid (meta-RR, 1.15; 95% CI, 0.91–1.39), mucinous (meta-RR, 0.96; 95% CI, 0.73–1.18), and clear cell ovarian cancer (meta-RR, 0.98; 95% CI, 0.72–1.23). Among 12 studies with data on duration of use, there was a positive association for every additional 10 years of use (meta-RR, 1.16; 95% CI, 1.07–1.26). The meta-RR for each additional use per week was 1.05 (95% CI, 1.04–1.07; 7 studies). In analyses limited to studies with information on period of exposure, meta-RRs were similar for talc use in the "early" period (before 1970 or 1980) (1.18; 95% CI, 0.99–1.37; 5 studies) compared with talc use in the "late" period (after 1970 or 1980) (1.31; 95% CI, 1.03–1.61; 5 studies).

Penninkilampi and Eslick (2018) reported similar, albeit slightly higher summary estimates for 24 case–control studies (meta-OR, 1.35; 95% CI, 1.27–1.43) and three cohort studies (meta-OR, 1.06; 95% CI, 0.90–1.25) and an overall meta-OR of 1.31 (95% CI, 1.24–1.39). Among 11 case–control studies with data on duration of use, the meta-OR for > 10 years of use was 1.29 (95% CI, 1.13–1.47). Penninkilampi and Eslick (2018) also assessed histological subtype-specific meta-ORs for serous (meta-OR, 1.32; 95% 1.22–1.43), endometrioid (meta-OR, 1.35; 95% CI, 1.14–1.60), mucinous (meta-OR, 1.12; 95% CI, 0.94–1.33), and clear cell (meta-OR, 1.02; 95% CI, 0.75–1.39) ovarian cancer. They additionally evaluated duration of use (the meta-OR for > 10 years of use versus none was 1.25; 95%

CI, 1.10–1.43; 12 studies) and frequency of use (the meta-OR for < 3600 applications versus none was 1.32; 95% CI, 1.15–1.50; the meta-OR for > 3600 applications versus none was 1.42; 95% CI, 1.25–1.61; 5 studies).

Lastly, Kadry Taher et al. (2019) reported a case–control summary estimate of 1.32 (95% CI, 1.24–1.40; based on 24 studies) and a cohort summary estimate of 1.06 (95% CI, 0.90–1.25; based on three studies), and an overall meta-OR of 1.28 (95% CI, 1.20–1.37). The histological subtype-specific meta-OR estimates were 1.38 (95% CI, 1.22–1.56) for serous; 1.39 (95% CI, 1.05–1.82) for endometrioid; 1.05 (95% CI, 0.85–1.29) for mucinous; and 0.63 (95% CI, 0.15–2.65) for clear cell ovarian cancer. The authors meta-analysed the association of genital use of powder and ovarian cancer separately among women with a history of tubal ligation (meta-OR, 0.64; 95% CI, 0.45–0.92), hysterectomy (meta-OR, 0.89; 95% CI, 0.54–1.46), or both (meta-OR, 1.06; 95% CI, 0.78–1.42), but did not consider the effect among women with patent reproductive tracts. Analyses considering the exposure–response relation by duration and frequency of use showed non-monotonically and monotonically increasing trends, respectively, but these were based on small numbers of studies.

[The Working Group noted that all three of these meta-analyses included 27 studies. Although highly consistent with one another, there was incomplete overlap between the three (see Wentzensen and O'Brien, 2021). Although some attempts were made to investigate differences by histological subtype or patency at time of exposure or to look at exposure–response relations, these sub-analyses often had limited power and interpretability compared with the evaluations of ever versus never use owing to heterogeneity in how specific measures were defined. The Working Group did not consider previous meta-analyses on this topic, either because they were published earlier, and thus included fewer studies, or because their focus was narrower in scope (Woolen et al., 2022).]

The Working Group conducted a quantitative bias analysis to assess the potential impacts of exposure misclassification in the findings for ovarian cancer (Annex 2, Quantitative bias analysis for exposure misclassification for the effects of ever versus never use of talc on ovarian cancer, available from: https://publications.iarc.who.int/646). This analysis included published data from the four cohort studies (those included in the pooled analysis of O'Brien et al., 2020) and a selection of 11 case–control studies (those included in the pooled analyses by Terry et al., 2013, and Davis et al., 2021), as these data were readily available and thought to be representative of the literature. Working Group members provided estimates (based on their expert judgement, because such estimates were not available in the literature) of the sensitivity and specificity of talc use as measured in the studies. These estimates, made separately for case and control participants, were used in this analysis (cohort members were presumed to have the same values as control participants). In general, this quantitative bias analysis found that misclassification-adjusted estimates based on ever versus never exposure tended to move slightly away from the null for the cohort studies (relative to the original estimates), whereas the estimates for case–control studies tended to move towards the null. Meta-analyses of study-specific bias-adjusted estimates resulted in pooled estimates ranging from 1.0 to 1.3. Additional analysis based on expert specification of sensitivity and specificity resulted in an effect range of 1.04–1.18. There was little evidence of heterogeneity in the effect estimates. Further details of the analysis are presented in Annex 2 (Quantitative bias analysis for exposure misclassification for the effects of ever versus never use of talc on ovarian cancer, available from: https://publications.iarc.who.int/646).

2.3 Cancers of the respiratory system and mesothelium

See Table 2.3.

2.3.1 Cohort studies

The association between talc exposure and lung cancer has been examined in numerous cohort studies. The most common industrial occupations that have been studied are talc miners and millers, and rubber workers. Cases of mesothelioma have been reported in only a few studies and mostly without expected numbers of cases. The findings from these studies are presented below in chronological order of first publication. Studies excluded from this review because they were uninformative included a PMR study that involved substantial exposure to asbestos (Stern et al., 2001), a nested case–control study in which there was no control for matching variables or smoking (Gamble, 1993), and a small cohort study in which expected numbers of deaths were not provided (Viskum et al., 1989).

Honda et al. (2002) reported results from a study of mortality in a previously studied cohort of talc miners and millers in the Gouverneur District, New York, USA (NIOSH, 1990) (see Section 2.1.1(a)). Workers were included in the study if they had worked for ≥ 1 day between the establishment of the plant in 1948 and 1989. They reported an SMR for lung cancer of [2.32] (95% CI, [1.57–3.29]), which was larger for workers first employed before 1955 (SMR, [2.86]; 95% CI, [1.90–4.14]) and for miners (SMR, [3.94]; 95% CI, [2.33–6.22]). There was weaker evidence of an increased risk among millers (SMR, [1.28]; 95% CI, [0.51–2.63]), which might be explained by the fact that millers had lower cumulative exposures (median, 683 mg/m^3-days) to talc dust than miners (median, 739 mg/m^3-days). There was no evidence of an exposure–response relation between talc dust exposure and lung cancer risk in internal analyses using Poisson regression. Workers in the categories of highest (≥ 987.0 mg/m^3-days) and intermediate (95.1 to < 987.0 mg/m^3-days) exposure had a lower risk than did workers in the category of lowest exposure (0 to < 95.1 mg/m^3-days). [The Working Group noted that the lack of an exposure–response relation might be caused by weaknesses in the assessment of talc exposure. The authors acknowledged that the exposure measurements were limited and that measurements were not available for most of the area and year combinations. The JEM was mostly based on the expert opinion of one engineer who worked at the plant. It might also be explained by a strong HWSB, since there was an excess of NMRD mortality in this study, which may have caused highly exposed workers to retire early. Finally, a limitation of this study was that it did not control for cigarette smoking, although as the authors noted, the increase of fourfold in lung cancer mortality among miners was unlikely to be fully explained by smoking (Blair et al., 1995). Asbestos contamination of the ore was likely in this mine (Table 1.1), which could have led to confounding for lung cancer.

The cohort study by Honda et al. reported 2 deaths from mesothelioma. An estimate of the expected number of cases was not provided, but the authors concluded that these cases were unlikely to be related to talc exposures since the latency was only 15 years for one case, and the other case was in a participant who was only briefly employed at the facility. Finkelstein (2012) identified an additional 5 cases of mesothelioma that occurred after the end of follow-up in 1989 in the study by Honda et al. (see Section 2.1.1(a)). The cases were identified from death certificates and medical records for individuals employed in the New York State talc industry that were made publicly available as part of public response to a draft of NIOSH Bulletin 62 (NIOSH, 2007b; Finkelstein, 2012). Person-years were estimated for the cohort by assuming that none of the 567 men who were alive at the end of 1989 died in

Table 2.3 Epidemiological studies on exposure to talc and cancers of the lung, mesothelioma, and other sites in the respiratory system

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Honda et al. (2002) USA Enrolment, 1948–1989/follow-up, 1950–1989 Cohort	809; White men who worked at a talc mining and milling facility in upstate New York for ≥ 1 day between 1948 and 1989, whose vital status was known in 1950 onwards. (Study was restricted to White men because of low prevalence of other race/ethnicities). Exposure assessment method: See Table 2.1.	Lung, mortality	Year of hire (SMR, regional referent):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: No expected number of deaths from mesothelioma were provided. Despite the longer follow-up, the expected number of lung cancers (13.4) was rather small.
			Before 1955	28	[2.86 (1.9–4.14)]		
			After 1955	3	[0.83 (0.17–2.42)]		
			Total cohort	31	[2.32 (1.57–3.29)]		
		Lung, mortality	Years since hire and years worked (SMR, regional referent):				
			< 20 yr since hire and < 5 yr worked	3	[1.26 (0.26–3.7)]		
			< 20 yr since hire and ≥ 5 yr worked	2	[1.26 (0.15–4.54)]		
			≥ 20 yr since hire and < 5 yr worked	19	[3.31 (1.99–5.16)]		
			≥ 20 yr since hire and ≥ 5 yr worked	7	[1.9 (0.76–3.92)]		
		Lung, mortality	Non-mutually exclusive work areas (SMR, regional referent):				
			Mills	7	[1.28 (0.51–2.63)]		
			Mines	18	[3.94 (2.33–6.22)]		
			Minimal exposure	3	[0.77 (0.15–2.24)]		
			No exposure	3	[2.81 (0.58–8.21)]		
			Unknown area	2	[1.51 (0.18–5.47)]		
		Lung, mortality	Work area (RR):			Age, calendar period, employment in mines	
			All other employees	NR	1		
			Mills	7	0.6 (0.2–1.8)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Honda et al. (2002) (cont.)		Lung, mortality	Work area (RR):			Age, calendar period, employment in mills	
			All other employees	NR	1		
			Mines	18	2.1 (0.8–5.5)		
		Lung, mortality	Cumulative respirable dust exposure (RR):			Age, years since hire	
			0 to < 95.1 mg/m^3-days	11	1		
			95.1 to < 987.0 mg/m^3-days	9	0.8 (0.3–1.9)		
			≥ 987.0 mg/m^3-days	9	0.5 (0.2–1.3)		
		Mesothelioma, mortality	No. of deaths:			NA	
			Total cohort	2	-		
		Larynx, mortality	SMR (regional referent):			Age, calendar period	
			Total cohort	2	[3.16 (0.38–11.42)]		
Finkelstein (2012) USA 1990–2007 Cohort	567 members of the Honda et al. (2002) cohort alive at the end of follow-up in 1989. The cohort was followed from 1990 (end of follow-up by Honda) through 2007 for mesothelioma incidence. The author did not have access to the original data and made the conservative assumption that all 567 were alive at the end of 2007.	Mesothelioma, incidence	IRR:			None	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.
			Total cohort	5	5 (1.6–11.7)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Monson and Fine (1978) Akron, OH, USA Enrolment, early 1940s to 1 July 1971/follow-up, 1940 through 30 June 1976 (mortality) and 1964–1974 (diagnoses) Cohort	13 570 White men, members of local union and employed (≥ 5 yr) in Akron in tyre or rubber manufacture. Follow-up (1940–1976) via death certificates (any cancer listed in the death certificate, even those not listed as underlying cause of death). For the period 1964–1974, incident cancers were identified through tumour registry of four Akron-based hospitals. Exposure assessment method: See Table 2.1.	Lung, mortality	Work area and minimum years in area (SMR):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Strengths*: See Table 2.1. *Limitations*: See Table 2.1.
			Tyre curing, 5+ yr	26	[1.73 (1.13–2.54)]		
			Tyre moulds, 5+ yr	9	[1.58 (0.72–3)]		
			Fuel cells/de-icers, 5+ yr	23	[1.15 (0.73–1.73)]		
			Fuels cells/de-icers, 0–4 yr	20	[1.56 (0.95–2.41)]		
		Lung, mortality and incidence	Work area and minimum years in area (SRR):				
			All other work areas	196	1		
			Tyre curing, 5+ yr	31	2.2		
			Tyre moulds, 5+ yr	10	2		
			Fuel cells/de-icers, 5+ yr	26	1.4		
			Fuel cells/de-icers, 0–4 yr	20	1.9		
Ciocan et al. (2022a) Val Chisone, north Italy Enrolment, 1946–1995/follow-up, through 31 January 2020 Cohort	1749 (1184 miners, 565 millers); men employed for ≥ 1 mo in the talc mine or mill in Val Chisone between 1946 and 1995. Exposure assessment method: See Table 2.1.	Lung, mortality	Department of employment (SMR, regional referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: long (74 yr) follow-up. *Other limitations*: See Table 2.1. *Other comments*: regional rates used for the period 1970–2020, national rates used before 1970.
			Miners	56	1.01 (0.76–1.31)		
			Millers	29	1.06 (0.71–1.52)		
			Total cohort	85	1.02 (0.82–1.27)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciocan et al. (2022a) (cont.)		Lung, mortality	Duration of employment (SMR, regional referent):			Age and calendar period	
			< 15 yr	31	1.03 (0.7–1.46)		
			15–24 yr	18	0.87 (0.52–1.38)		
			≥ 25 yr	36	1.12 (0.78–1.55)		
			Trend-test *P*-value, 0.72				
		Larynx, mortality	Department of employment (SMR, regional referent):				
			Total cohort	8	0.92 (0.4–1.81)		
		Pleura, mortality	SMR (regional referent):				
			Total cohort	0	[0 (0–1.3)]		
Fordyce et al. (2019) Vermont, USA Enrolment, 1940–1969 (initial), 1930–1983 (expanded)/follow-up, 1940–2012 Cohort	427 White male Vermont talc workers who had worked for ≥ 1 yr in 1940–1969 (initial enrolment) or 1930–1940 or 1970–1983 (expanded enrolment). These correspond to all talc workers who participated in the Vermont Health Department radiograph programme (workers were offered annual chest radiographs from 1930 to 1983). Exposure assessment method: See Table 2.1.	Lung, mortality	Job type (SMR, US referent):			NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Lung cancer was specified as "bronchus, trachea, lung". Covariates controlled were not reported but likely included age and calendar period, as a life-table programme and US rates were used to estimate expected numbers of deaths.
			Miller	14	[1.426 (0.779–2.392)]		
			Miner	14	[1.278 (0.699–2.145)]		
			Total cohort	32	[1.439 (0.984–2.031)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fordyce et al. (2019) (cont.)		Lung, mortality	Duration of employment (SMR, US referent):			NR	
			0–4 yr	18	[1.51 (0.895–2.387)]		
			5–14 yr	9	[1.477 (0.675–2.804)]		
			15–29 yr	3	[0.926 (0.191–2.707)]		
			≥ 30 yr	2	[2.024 (0.245–7.311)]		
		Lung, mortality	Time since exposure (hire) (SMR, US referent):			NR	
			0–14 yr	1	[0.876 (0.022–4.88)]		
			15–29 yr	7	[1.706 (0.686–3.515)]		
			≥ 30 yr	24	[1.412 (0.905–2.101)]		
		Mesothelioma, mortality	No. of deaths:			None	
			Total cohort	1	-		
		Larynx, mortality	SMR (US referent):			NR	
			Total cohort	0	[0 (0–4.443)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wild et al. (2002) Austria and France Enrolment, 1945–1994 (French cohort) or 1972–1995 (Austrian cohort)/follow-up, through 1996 (French cohort), or 1995 (Austrian cohort) Cohort	1612 (1070 French, 542 Austrian); male workers employed continuously for ≥ 1 yr during 1945–1994 in a talc mine in the French Pyrenees (French cohort) or 1972–1995 in mine or mills in the Styrian Alps or in the Head office in Graz (Austrian cohort). For the French cohort, cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. A nested case–control study of lung cancer compared estimated talc exposure for 30 cases of lung cancer with 87 controls selected using incidence density sampling and matching on calendar period. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (local referent rates):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: smoking data were available for only 50% of the French cohort. Other limitations listed in Table 2.1 *Other comments*: for the French cohort, local referent rates were used 1968–1996, national referent rates were used for earlier years.
			French cohort	21	1.23 (0.76–1.89)		
		Lung, mortality	SMR (Styria referent rates):				
			Austrian cohort	7	1.06 (0.43–2.19)		
		Lung, mortality	Cumulative talc exposure (OR):				
			Non-exposed	9	1		
			≤ 100 mg/m³-yr	6	0.86		
			100–400 mg/m³-yr	7	1.07		
			400–800 mg/m³-yr	5	0.6		
			> 800 mg/m³-yr	3	0.73		
			Continuous (per 100 mg/m³-yr)	30	0.98 (0.88–1.1)		
		Mesothelioma, mortality	SMR (local referent rates):				
			French cohort	0	[0 (0–12)]		
		Mesothelioma, mortality	SMR (Styria referent rates):				
			Austrian cohort	0	[0 (0–37)]		

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Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Thomas and Stewart (1987) USA Enrolment, 1939–1966/follow-up, 1940 through 1 January 1981 Cohort	2055; White men employed for ≥ 1 yr (1939–1966) at three plants of a single US company producing ceramic plumbing fixtures. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (US referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Total cohort	52	[1.43 (1.07–1.88)]		
		Lung, mortality	Year of hire (SMR, US referent):				
			< 1940	23	[1.17 (0.74–1.76)]		
			1940–1949	22	[1.93 (1.21–2.92)]		
			1950–1965	7	[1.33 (0.53–2.74)]		
		Lung, mortality	Exposure/job category (SMR, US referent):				
			No silica, no talc	1	[0.61 (0.02–3.4)]		
			Low silica, no talc	7	[0.68 (0.27–1.4)]		
			High silica overall	44	[1.81 (1.32–2.43)]		
			High silica, no talc	18	[1.37 (0.81–2.17)]		
			High silica, nonfibrous talc	21	[2.54 (1.57–3.88)]		
			High silica, fibrous talc	5	[1.74 (0.56–4.06)]		
		Lung, mortality	Talc exposure, casting workers (SMR, US referent):				
			No talc exposure	10	1.46 (0.7–2.68)		
			Nonfibrous talc exposure	21	[2.73 (1.69–4.17)]		
		Lung, mortality	Duration of nonfibrous talc exposure (SMR, US referent):				
			< 5 yr	2	[0.95 (0.12–3.43)]		
			5–14 yr	11	[2.76 (1.38–4.94)]		
			≥ 15 yr	8	[3.64 (1.57–7.17)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Thomas and Stewart (1987) (cont.)		Lung, mortality	Years since first nonfibrous talc exposure (SMR, US referent):			Age and calendar period	
			< 5 yr	0	[0 (0–5.27)]		
			5–14 yr	8	[2.81 (1.21–5.54)]		
			≥ 15 yr	13	[2.75 (1.46–4.7)]		
		Mesothelioma, mortality	No. of deaths:			None	
			Total cohort	1	-		
Negri et al. (1989) Italy 1946–1981 Cohort	6629; all men who had worked for ≥ 1 yr between 1946 and 1981 in a rubber tyre factory in Turin district. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (national referent):			Age, calendar period	*Strengths*: See Table 2.1. *Limitations*: Asbestos exposure was considered likely and possibly explained the excess pleural cancer. For other limitations, see Table 2.1.
			Total cohort	64	1.01 (0.79–1.29)		
		Lung, mortality	Period first employed (SMR, national referent):				
			1906–1939	24	[1.27 (0.82–1.9)]		
			1940–1981	40	[0.9 (0.64–1.23)]		
		Lung, mortality	Age at first exposure (SMR, national referent):				
			< 30 yr	28	[1.04 (0.69–1.51)]		
			≥ 30 yr	36	[0.99 (0.69–1.37)]		
		Lung, mortality	Duration of exposure (SMR, national referent):				
			< 10 yr	11	[1.05 (0.52–1.88)]		
			10–19 yr	19	[1.08 (0.65–1.69)]		
			≥ 20 yr	34	[0.97 (0.37–1.35)]		
		Lung, mortality	Period since last exposure (SMR, national referent):				
			During exposure	28	[1.18 (0.79–1.71)]		
			< 5 yr	14	[1.15 (0.63–1.93)]		
			≥ 5 yr	22	[0.8 (0.5–1.22)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Negri et al. (1989) (cont.)		Lung, mortality	Job category with ≥ 1 yr of employment (SMR, national referent):			Age, calendar period	
			Mechanical maintenance	21	[1.56 (0.96–2.38)]		
			Milling	6	[0.57 (0.21–1.25)]		
			Extruding and calendering	11	[1.1 (0.55–1.97)]		
			Tyre building	13	[1.07 (0.57–1.83)]		
			Various services	25	[2.25 (1.45–3.32)]		
		Pleura, mortality	SMR (national referent):				
			Total cohort	9	10.98 (5.23–20.86)		
		Pleura, mortality	Period first employed (SMR, national referent):				
			1906–1939	6	[28.57 (10.5–62.2)]		
			1940–1981	3	[4.92 (1.01–14.4)]		
		Pleura, mortality	Age at first exposure (SMR, national referent):				
			< 30 yr	4	[11.43 (3.1–29.3)]		
			≥ 30 yr	5	[10.64 (3.5–24.8)]		
		Pleura, mortality	Duration of exposure (SMR, national referent):				
			< 10 yr	2	[13.33 (1.6–48.2)]		
			10–19 yr	2	[8.7 (1.1–31.4)]		
			≥ 20 yr	5	[11.36 (3.7–26.5)]		
		Pleura, mortality	Period since last exposure (SMR, national referent):				
			During exposure	4	[14.29 (3.9–36.6)]		
			< 5 yr	3	[21.43 (4.4–62.6)]		
			≥ 5 yr	2	[5.06 (0.6–18.3)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Negri et al. (1989) (cont.)		Pleura, mortality	Job category with ≥ 1 yr of employment (SMR, national referent):			Age, calendar period	
			Mechanical maintenance	4	[23.53 (6.41–60.2)]		
			Milling	1	[7.49 (0.19–41.7)]		
			Extruding and calendering	2	[15.38 (1.86–55.6)]		
			Tyre building	0	[0 (0–23.1)]		
			Various services	3	16.66 (3.44–48.7)		
		Larynx, mortality	SMR (national referent):				
			Total cohort	13	1.26 (0.67–2.16)		
Wergeland et al. (2017) Norway Enrolment 1944–1972 (miners), 1935–1972 (millers)/follow-up, 1953–2011 Cohort	390 (94 miners, 296 millers); men employed in the mine for ≥ 1 yr (1944–1972) or in the mill for ≥ 2 yr (1935–1972). Exposure assessment method: See Table 2.1.	Lung, incidence	Job type (SIR, general population referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Miners	4	1.04 (0.28–2.65)		
			Millers	17	1.21 (0.7–1.94)		
			Total cohort	21	1.17 (0.73–1.79)		
		Lung, mortality	Duration of employment and years since first employment (SMR, general population referent):				
			< 10 yr employed and < 20 yr since first employment	1	2.04 (0.05–11.4)		
			< 10 yr employed and > 20 yr since first employment	6	1.35 (0.49–2.93)		
			≥ 10 yr employed and < 20 yr since first employment	1	0.95 (0.02–5.27)		
			≥ 10 yr employed and > 20 yr since first employment	7	0.87 (0.35–1.8)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wergeland et al. (2017) (cont.)		Mesothelioma, incidence	No. of deaths:			None	
			Total cohort	0	-		
		Pleura, incidence	No. of deaths:			None	
			Total cohort	0	-		
Ierardi et al. (2022) Austria, France, Italy, Norway, and USA (pooled study) Enrolment/follow-up varies by study Cohort	4178; pooled analysis of five cohorts of talc miners and millers. Included cohorts are Italian miners and millers described in Ciocan et al. (2022a); Norwegian miners and millers described in Wergeland et al. (2017); French and Austrian miners and millers described in Wild et al. (2002); and US miners and millers described in Fordyce et al. (2019).	Mesothelioma, mortality	SMR (referent varies by study):			Age and calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.
			Pooled cohort	1	0.242 (0.006115–1.35)		
Zhang et al. (1989) Shanghai, China Enrolment, 1972/follow-up, 1 December 1972 to 30 November 1984 Cohort	1624 (957 men and 667 women); male and female rubber workers working at a rubber plant in the Xuhui district of Shanghai who entered a screening programme for coronary heart disease in 1972. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (local referent, Xuhui district):			Age	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: The authors found that smoking was higher in curing and inner-tube tyre workers and this probably explained the excess lung cancer mortality risk.
			Men	16	[1.32 (0.75–2.14)]		
			Women	4	[1.32 (0.36–3.38)]		
			Total cohort	20	[1.33 (0.81–2.05)]		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zhang et al. (1989) (cont.)		Lung, mortality	Type of job (SMR, local referent, Xuhui district):			Age	
			Curing	6	[2.86 (1.05–6.23)]		
			Inner tyre tube	3	[3.75 (0.77–11)]		
		Lung, mortality	Exposure to curing agents or inner tubes, men (relative risk):			Smoking	
			Never	NR	1		
			Ever	NR	3.2 (1.3–8.2)		
		Lung, mortality	Exposure to curing agents or inner tubes, women (relative risk):				
			Never	NR	1		
			Ever	NR	4.6 (0.8–27.9)		
Fu and Zhang (1992) Haichen talc mine, China Enrolment, January 1974/ follow-up, 1974–1988 Cohort	1357 male workers on the wage employee list in January 1974 with ≥ 1 yr of work history followed until 1988. Workers with work history in chemical industry were excluded. For SMR estimation, age-standardized mortality was calculated relative to a cohort of workers in the iron and steel industry. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (iron and steel worker cohort referent):			Age	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Millers	7	[2.82 (1.13–5.81)]		
			Miners	8	[1.61 (0.7–3.17)]		
			All talc workers	15	[2.22 (1.24–3.66)]		
		Lung, mortality	Latency (SMR, iron and steel worker cohort referent):				
			0–9 yr	0	0		
			10–19 yr	1	[1.4 (0.04–7.8)]		
			20–29 yr	6	[1.57 (0.58–3.42)]		
			≥ 30 yr	8	[2.88 (1.24–5.67)]		

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Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nie et al. (1992) China Enrolment, 1972–1974/follow-up, through 1989 Cohort	12 218 (8654 men, 3564 women); registered employees with more than 1 yr of employment in seven porcelain factories.	Lung, mortality	SMR (national referent comprised of small and medium-sized cities): Total cohort Talc-exposed workers	 62 7	 [0.94 (0.72–1.21)] [2.62 (1.05–5.4)]	Age	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.
Chiazze et al. (1993) USA 1940–1982 Nested case–control	Source cohort: See Table 2.1. Cases: 144; cases are those that died from a malignant respiratory disease. In the source cohort study vital status had been determined through the US Social Security Administration and other sources; death certificates had been requested from state health departments and the underlying cause of death coded according to the ICD revision in effect at the time of death (Enterline et al., 1987).	Lung, mortality Lung, mortality	Year of hire (OR): 1945 or later Before 1945 Cumulative exposure to talc (OR): 0 fibres/mL-day 10–999 fibres/mL-day ≥ 1000 fibres/mL-day	 NR NR NR NR NR	 1 2.177 (1.386–3.421) 1 0.551 (0.293–1.038) 0.678 (0.314–1.466)	Year of birth, survival at the end of follow-up/death	*Exposure assessment critique*: See Table 2.1. Strengths: See Table 2.1. Limitations: See Table 2.1.

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chiazze et al. (1993) (cont.)	Controls: 260; included cohort members who had not died from malignant or non-malignant respiratory disease but also excluded those who died from suicide or homicide. Controls matched on year of birth, survival at the end of follow-up/ death. Exposure assessment method: See Table 2.1.	Lung, mortality	Cumulative exposure to talc (OR):			Year of birth, survival at the end of follow-up/ death, smoking, education, year of hire, age at first hire, and cumulative exposure to respirable fibres, asbestos, formaldehyde, respirable silica, and asphalt fumes	
			0 fibres/mL-day	NR	1		
			10–999 fibres/ mL-day	NR	0.657 (0.246–1.751)		
			≥ 1000 fibres/ mL-day	NR	1.355 (0.407–4.515)		
Li and Yu (2002) Shanghai, China Enrolment, 1973/follow-up, 1973–1997 Cohort	1598 (934 men, 664 women); employees of a rubber factory. Outcome ascertained through death certificates.	Lung, mortality	Department (SMR, Shanghai referent):			Age, sex, calendar period	*Strengths*: See Table 2.1. *Limitations*: The exposure is defined by the primary process of employment. No quantitative assessment of talc exposure. *Other comments*: Unclear overlap with Zhang et al. (1989).
			Tyre curing and vulcanizing	17	[2.24 (1.3–3.58)]		
			Tube curing	4	[1.48 (0.4–3.79)]		
			Total cohort	51	1.25 (0.93–1.64)		
		Lung, mortality	Department, men (SMR, Shanghai referent):			Age, calendar period	
			Tyre curing and vulcanizing	16	[2.39 (1.36–3.88)]		
			Tube curing	3	[1.67 (0.34–4.87)]		
			Total cohort	32	1.13 (0.77–1.6)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bulbulyan et al. (1999) Russian Federation 1979–1993 Cohort	3473 women with ≥ 2-yr employment in two printing plants as of December 1978. Exposure assessment method: See Table 2.1.	Lung, mortality	Primary employment process (SMR, Moscow referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Compositors	0	[0 (0–3.1)]		
			Press operators	3	1.9 (0.4–5.3)		
			Bookbinders	3	0.7 (0.1–2)		
			Total cohort	9	0.8 (0.4–1.5)		
		Mesothelioma (peritoneal), mortality	No. of deaths:			None	
			Total cohort	1	-		
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	4274; cohort of 4247 women who worked for ≥ 1 yr between 1920 and 1993 in a pulp and paper mill in Norway. Exposure assessment method: See Table 2.1.	Lung, incidence	Length of employment (SIR, national referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			< 3 yr	8	3 (1.29–5.89)		
			≥ 3 yr	14	1.4 (0.7–2.16)		
		Pleura, incidence	Length of employment (SIR, national referent):				
			< 3 yr	0	0		
			≥ 3 yr	0	[0 (0–37)]		
Straif et al. (2000) Germany Enrolment, 1950–1981/follow-up, 1981–1991 Cohort	8933; all male German blue collar workers hired during or after 1950 in five rubber plants and who had worked for ≥ 1 yr. They needed to be still alive and actively employed or retired on 1 January 1981. Exposure assessment method: See Table 2.1.	Lung, mortality	SMR (national referent, western Germany):			NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Lung specified as "trachea or bronchus or lung". Covariates controlled not reported for SMR but likely were age and calendar period. Smoking not adjusted for, but this was an internal analysis, and authors proposed that smoking was similar between exposure groups.
			Total cohort	154	[1.23 (1.04–1.44)]		
		Lung, mortality	Talc exposure category, 10-yr lag period (HRR):			Age	
			Low (< 1 yr at medium and high levels (combined))	88	1		
			Medium	30	1.3 (0.8–2)		
			High (≥ 1 yr at high level)	30	1.6 (1.1–2.4)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Straif et al. (2000) (cont.)		Lung, mortality	Talc exposure category, 10-yr lag period (HRR):			Age	
			Low (< 0.5 yr at medium and high levels (combined))	87	1		
			Medium	41	1.1 (0.8–1.6)		
			High (≥ 10 yr at high)	21	1.9 (1.1–3.1)		
		Mesothelioma, mortality	No. of deaths:			None	
			Total cohort	0	-		
		Larynx, mortality	SMR (national referent, western Germany):			NR	
			Total cohort	8	[1.17 (0.5–2.3)]		
		Larynx, mortality	Talc exposure category, 10-yr lag period (HRR):			Age	
			Low (< 1 yr at medium and high levels, combined)	3	1		
			Medium	2	2.8 (0.5–16.7)		
			High (≥ 1 yr at high level)	3	5.4 (1.1–27)		
Boffetta and Colin (2001) (publicly available since 2023) 15 countries Enrolment, varies/follow-up, between 1943 and 1985 through the mid-1990s Cohort	103 773 for mortality; 73 775 for incidence; workers employed for ≥ 1 yr in pulp and paper companies with complete data. Exposure assessment method: See Table 2.1.	Lung, mortality	Talc exposure (SMR):			Age, sex, period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Ever-exposed to talc	286	0.97 (0.86–1.09)		
			Ever highly exposed to talc	59	0.96 (0.73–1.24)		
		Lung, mortality	Talc exposure, men (SMR):			Age, period, country	
			Ever-exposed to talc	265	0.95 (0.84–1.07)		
			Ever highly exposed to talc	45	0.79 (0.58–1.06)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Lung, mortality	Talc exposure, women (SMR):			Age, period, country	
			Ever-exposed to talc	21	1.42 (0.88–2.18)		
			Ever highly exposed to talc	14	3.02 (1.65–5.07)		
		Lung, mortality	Years since first exposure to talc (SMR):			Age, sex, period, country	
			0–15 yr	64	0.91 (0.7–1.16)		
			16–25 yr	80	1.05 (0.83–1.3)		
			26–34 yr	73	1.05 (0.82–1.32)		
			≥ 35 yr	69	0.88 (0.68–1.11)		
			Trend-test *P*-value, 0.799				
		Lung, mortality	Duration of talc exposure (SMR):				
			0–2 yr	73	1.05 (0.82–1.32)		
			3–8 yr	65	1.13 (0.87–1.44)		
			9–19 yr	79	1.01 (0.8–1.26)		
			≥ 20 yr	69	0.77 (0.6–0.98)		
			Trend-test *P*-value, 0.051				
		Lung, mortality	Duration of high talc exposure (SMR):				
			0–1 yr	16	1.32 (0.75–2.14)		
			3–6 yr	16	1.33 (0.76–2.16)		
			7–17 yr	15	0.88 (0.49–1.45)		
			≥ 18 yr	12	0.59 (0.3–1.03)		
			Trend-test *P*-value, 0.016				
		Lung, mortality	Cumulative talc exposure (SMR):				
			0–3 ppm-yr	16	1.33 (0.76–2.16)		
			4–10 ppm-yr	14	1.17 (0.64–1.96)		
			11–26 ppm-yr	16	0.92 (0.53–1.49)		
			≥ 27 ppm-yr	13	0.65 (0.34–1.1)		
			Trend-test *P*-value, 0.038				

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Lung, incidence	Talc exposure (SIR):			Age, sex, period, country	
			Ever-exposed to talc	198	1.02 (0.88–1.17)		
			Ever highly exposed to talc	28	1.06 (0.7–1.53)		
		Lung, incidence	Talc exposure, men (SIR):			Age, period, country	
			Ever-exposed to talc	186	1.01 (0.87–1.17)		
			Ever highly exposed to talc	20	0.86 (0.52–1.32)		
		Lung, incidence	Talc exposure, women (SIR):				
			Ever-exposed to talc	12	1.09 (0.56–1.91)		
			Ever highly exposed to talc	8	2.57 (1.11–5.06)		
		Pleura, mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed to talc	5	1.01 (0.33–2.37)		
			Ever highly exposed to talc	0	0 (0–3.27)		
		Pleura, mortality	Talc exposure, men (SMR):			Age, period, country	
			Ever-exposed to talc	4	0.86 (0.24–2.21)		
			Ever highly exposed to talc	0	0 (0–3.44)		
		Pleura, mortality	Talc exposure, women (SMR):				
			Ever-exposed to talc	1	3.32 (0.08–18.5)		
			Ever highly exposed to talc	0	0 (0–67.4)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Other respiratory organs (ICD-9, 164–165), mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	4	1.25 (0.34–3.2)		
			Ever highly exposed	3	3.38 (0.7–9.89)		
		Larynx, mortality	Talc exposure (SMR):				
			Ever-exposed	18	0.96 (0.57–1.52)		
			Ever highly exposed	11	1.58 (0.79–2.82)		
Ramanakumar et al. (2008) Montreal, Canada; hospital-based Study I, 1979–1986; study II, 1996–2001 Case–control	Cases: 1829 (study I, 857; study II, 1236); Canadian citizens with lung cancer ascertained in the 18 largest Montreal hospitals. Study I was restricted to men aged 35–70 yr living in Montreal metropolitan area (79% response rate); study II included women and men aged 35–75 yr (response rate, 86%).	Lung, incidence	Industrial talc exposure, study I (men only), using population controls (OR):			Age, family income, ethnicity, respondent status, years of schooling, smoking, other occupational hazards exposure (asbestos, silica, or cadmium compounds)	*Exposure assessment critique*: This was a high-quality semiquantitative exposure assessment. A key strength was the evaluation of industrial and cosmetic talc by an experienced team using case-by-case assessment. A key limitation was the lack of information on the purity of talc being used. Like most population-based case–control studies on occupational hazards, the exposure assessment was based on questionnaires that collected work histories: this might lead to recall bias or (nondifferential) exposure misclassification.
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	736	1		
			Any	35	0.9 (0.5–1.7)		
			Non-substantial	28	0.9 (0.6–1.8)		
			Substantial	7	0.6 (0.2–2.7)		
		Lung, incidence	Industrial talc exposure, study I (men only), using cancer controls (OR):				
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	736	1		
			Any	35	1.1 (0.6–2)		
			Non-substantial	28	1.1 (0.6–1.8)		
			Substantial	7	0.7 (0.3–1.7)		

Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ramanakumar et al. (2008) (cont.)	Controls: 2969 (study I: 533 population, 1349 other cancers; study II: 1512); sampled from electoral lists, stratified by sex and age to the distribution of cases (response rate, 70%, for both studies). In study I, an additional control group was selected among cancer cases (from 14 different sites). Exposure assessment method: Very detailed work histories collected through interviews. A team of chemists and industrial hygienists assessed potential exposure to 294 substances.	Lung, incidence	Industrial talc exposure, pooled (studies I and II) (OR):			Age, family income, ethnicity, respondent status, years of schooling, smoking, other occupational hazards exposure (asbestos, silica, or cadmium compounds), sex, study population	*Other strengths*: Large numbers of cases and controls, a good control of confounders (including asbestos) and an expert exposure assessment blind to the case/control status. Analysis adjusted for asbestos co-exposure in work history.
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	1829	1		
			Any	67	1 (0.6–1.5)		
			Non-substantial	49	1 (0.7–1.4)		
			Substantial	18	0.9 (0.6–1.8)		
		Lung, incidence	Occupational exposure to cosmetic talc, study I (men only), using population controls (OR):			Age, family income, ethnicity, respondent status, years of schooling, smoking, other occupational hazards exposure (asbestos, silica, or cadmium compounds)	
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	736	1		
			Any	15	1.3 (0.5–3.1)		
			Non-substantial	11	2.1 (0.5–11.4)		
			Substantial	4	0.3 (0.1–2)		

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Table 2.3 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ramanakumar et al. (2008) (cont.)		Lung, incidence	Occupational exposure to cosmetic talc, study I (men only), using cancer controls (OR):			Age, family income, ethnicity, respondent status, years of schooling, smoking, other occupational hazards exposure (asbestos, silica, or cadmium compounds)	
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	736	1		
			Any	15	0.8 (0.4–1.6)		
			Non-substantial	11	1.2 (0.4–2.2)		
			Substantial	4	0.4 (0.3–3.6)		
		Lung, incidence	Occupational exposure to cosmetic talc, pooled (study I and study II) (OR):			Age, family income, ethnicity, respondent status, years of schooling, smoking, other occupational hazards exposure (asbestos, silica, or cadmium compounds), sex, study population	
			Not exposed to titanium dioxide, carbon black, industrial talc, or cosmetic talc	1829	1		
			Any	53	0.9 (0.5–1.3)		
			Non-substantial	47	1 (0.7–1.5)		
			Substantial	6	0.7 (0.3–1.8)		

CI, confidence interval; HRR, hazard rate ratio; ICD, International Classification of Diseases; IRR, incidence rate ratio; NR, not reported; OH, Ohio; OR, odds ratio; RR, rate ratio; SIR, standardized incidence ratio; SMR, standard mortality ratio; US, United States; USA, United States of America; yr, year(s).

the period between 1990 and the end of 2007. Rates for US White men aged 65–74 years were used to estimate the expected number of cases. On the basis of this approach, an incidence rate ratio of 5 (95% CI, 1.6–11.7) for mesothelioma was observed among the New York State talc miners when compared with the USA population. [The Working Group noted that while the approach used to estimate the person-years and the expected number of deaths was crude, it most probably resulted in an underestimate of the rate ratio. Contamination of the mine ore by asbestos has been documented (see Table 1.1).]

Monson and Fine (1978) (see Section 2.1.2) reported results from the most recent update of a retrospective cohort mortality study among rubber workers in the USA. An excess of lung cancer was observed among workers who had worked for ≥ 5 years in the tyre-curing (SMR, [1.73]; 95% CI, [1.13–2.54]), and tyre moulds (SMR, [1.58]; 95% CI, [0.72–3.00]) departments. An increased risk of lung cancer was also observed among workers in the fuel cells/de-icers department, being strongest among workers with < 5 years of employment in this department [SMR, 1.56; 95% CI, 0.95–2.41]. The paper did not mention talc exposure; however, talc was mentioned as an exposure in the curing department in an earlier publication on this cohort (Peters et al., 1976). No cases of mesothelioma or pleural cancer have been reported in the rubber-workers cohort mortality study in the USA. [The Working Group noted that there was no ICD code for mesothelioma during the time period that the studies on rubber workers were conducted, which would have hampered its inclusion. Additional limitations of the study included the lack of exposure estimates for talc, and the lack of control for potentially confounding lung carcinogens (e.g. smoking, occupational carcinogens).]

Ciocan et al. (2022a) reported findings from an update of a cohort study of workers employed in talc mining and milling in northern Italy for ≥ 1 month between 1946 and 1995 with follow-up through 31 January 2020 (see Section 2.1.1(b)). Overall, there was no evidence of an increased risk of lung cancer (SMR, 1.02; 95% CI, 0.82–1.27) in this cohort. Lung cancer risk was not increased in either talc miners (SMR, 1.01; 95% CI, 0.76–1.31) or millers (SMR, 1.06; 95% CI, 0.71–1.52), and there was no evidence of a trend with duration of exposure (P = 0.72). A large excess of pneumoconiosis (SMR, 9.55 95% CI, 7.43–12.08) was observed, which increased with duration of exposure (P < 0.0001). [The Working Group noted that the large excess of pneumoconiosis possibly caused by silica exposure may have resulted in a strong HWSB, since workers with high exposure may have left employment early if they had pneumoconiosis.] There were no cases of pleural cancer reported in this study (2.8 cases expected). [The Working Group noted that the strengths of this study included the long period of follow-up (74 years) and documentation of the absence of asbestos contamination of the talc (see Table 1.1). A limitation was the lack of an analysis of duration by department and of quantitative assessment of talc exposure, and lack of control for silica exposure.]

Fordyce et al. (2019) performed an update and expansion of a cohort of talc miners and millers in Vermont, USA, that had previously been studied by Selevan et al. (1979) (see Section 2.1.1(c)). All workers employed for ≥ 1 year in the Vermont talc industry between 1930 and 1983 were included in this study. Overall, an excess of lung cancer mortality (SMR, [1.439]; 95% CI, [0.984–2.031]) was observed in this study. The results for lung cancer were slightly stronger for millers (SMR, [1.426]; 95% CI, [0.779–2.392]) than for miners (SMR, [1.278]; 95% CI, [0.699–2.145]). Lung cancer risk was also increased among workers with 15–29 years (SMR, [1.706]; 95% CI, [0.686–3.515]) and ≥ 30 years of latency (SMR, [1.412]; 95% CI, [0.905–2.101]). The excess of lung cancer was the largest in the group with the longest duration of employment (SMR, for

≥ 30 years, [2.024]; 95% CI, [0.245–7.311]), but this result was based on only two cases, and there was no evidence of a trend with duration of employment or time since first exposure. Only one case of mesothelioma was reported in this study, although a second case was reported in another publication (Egilman et al., 2020). [The Working Group noted that the limitations of the study included the small sample size (particularly for mesothelioma), the lack of talc exposure estimates and exposure–response analyses, and that results based on comparison with the US population may be prone to HWE. There is also strong potential bias because of HWSB since there were findings of a high excess risk of NMRD, which may have caused highly exposed workers to leave employment early. There was asbestos contamination of ore from this mine (Table 1.1).]

Wild et al. (2002) reported findings from a cohort mortality study of talc miners and millers in France and Austria (see Section 2.1.1(c)). A small excess of lung cancer was observed in the French cohort (SMR, 1.23; 95% CI, 0.76–1.89) and a very small, imprecise excess was observed in the Austrian cohort (SMR, 1.06; 95% CI, 0.43–2.19).

There was no evidence of a trend in increasing lung cancer risk with cumulative exposure to talc in a nested case–control study in the publication by Wild et al. (2002). Compared with the non-exposed, three of the four cumulative exposure categories had an OR < 1, and the highest category (> 800 mg/m^3-years) had an OR of 0.73. There was also no evidence of an exposure–response relation in a model that included cumulative talc exposure as a continuous variable (OR per 100 mg/m^3-years, 0.98; 95% CI, 0.88–1.10). Controlling for smoking and quartz exposure did not alter the fact that there was no evidence of an exposure–response trend (results not shown). No cases of mesothelioma were identified in this study (0.3 cases expected in the French cohort; 0.1 expected in the Austrian cohort). [The Working Group noted that the long follow-up of the cohort, the quantification of talc exposures, the lack of asbestos contamination of the ore (Table 1.1), and the ability to control for smoking and quartz exposure were strengths of this study. Limitations included the small cohort size, the lack of data on smoking for 50% of the cohort, and potential bias from HWSB in the lung cancer exposure–response analysis since there was a strong trend for increased risk from NMRDs, which might have caused highly exposed workers to terminate employment early.]

Thomas and Stewart (1987) reported findings from a cohort mortality study of workers employed in three plants owned by the same company that produced ceramic plumbing fixtures in the USA (see Section 2.1.3). Overall, an excess of lung cancer mortality was observed in this study (SMR, 1.43; 95% CI, [1.07–1.88]). This excess was primarily among workers first employed between 1940 and 1949 (SMR, 1.93; 95% CI, [1.21–2.92]) and among workers with high exposure to silica and exposure to "nonfibrous" talc (SMR, 2.54; 95% CI, [1.57–3.88]). The authors described "nonfibrous talc" as Montana steatite talc and stated that it appeared to contain no "asbestiform fibres" and was used almost exclusively in the cast shop. The authors also stated that what they described as "tremolite (fibrous) talc" was used in some glazes until its use was discontinued in 1976. Lung cancer mortality was increased among workers with > 15 years of exposure (SMR, 3.64; 95% CI, [1.57–7.17]), and with 5–14 years (SMR, 2.81; 95% CI, [1.21–5.54]) or ≥ 15 years (SMR, 2.75; 95% CI, [1.46–4.70]) since first exposure to nonfibrous talc. All the 21 cases of lung cancer in workers exposed to nonfibrous talc had worked as casters (SMR, 2.73; 95% CI, [1.69–4.17]). Only 1 death from mesothelioma was observed, and an expected number of deaths was not provided. [The Working Group noted that this study had many strengths, including the study size, long follow-up, and estimation of exposures to silica and to fibrous and nonfibrous talc. A limitation of the study was the difficulty in separating the effects of silica and talc, as all

jobs with talc exposure had high exposure to silica. There was also evidence of a potential bias because of the HWSB, since there was strong evidence of an increased risk of NMRDs, which would be expected to cause highly exposed workers to terminate employment early.]

Negri et al. (1989) (see Section 2.1.2) reported findings from a cohort mortality study of workers in a rubber-tyre factory in Turin, Italy. The authors stated that "fibre containing talc" was used as an anti-tacking agent in tyre manufacture and storage in "earlier periods", although the nature of the fibres and the dates were not specified. Overall, there was little evidence of an increased risk of lung cancer in this study (SMR, 1.01; 95% CI, 0.79–1.29; 64 deaths). An excess of lung cancer was observed among workers in mechanical maintenance (SMR, 1.56; 95% CI, [0.96–2.38]) and various services (SMR, 2.25; 95% CI, [1.45–3.32]). There was no evidence of an increase in lung cancer mortality with age at first exposure, duration of exposure, or time since last exposure.

There was strong evidence of an increased risk of pleural cancer (SMR, 10.98; 95% CI, 5.23–20.86; 9 cases) in the study by Negri et al. (1989). The results for pleural cancer were stronger (SMR, 28.57; [95% CI, 10.5–62.2]) among those first employed in the earliest study period (1906–1939) with < 5 years since last exposures (SMR, 21.43; 95% CI, [4.40–62.6]). There was little variation in the findings for pleural cancer by age at first exposure or for duration of exposure. Being employed in the earliest period (before 1940) was the only variable found to be significant in a multiplicative model (not defined) for pleural cancer, which simultaneously included these temporal variables. In an analysis of 27 job categories, the highest risk of pleural cancer was observed among those who worked in mechanical maintenance (SMR, 23.53; 95% CI, [6.41–60.2]), extruding and calendaring (SMR, 15.38; 95% CI, [1.86–55.6]), and various services (SMR, 16.66; 95% CI, [3.44–48.7]). The authors suggested that the excess of pleural cancer may have been caused by the use of "fibre containing talc". [The Working Group noted that there was evidence of asbestos contamination of talc in this cohort, as described in Chang et al. (2020b). This was supported by the very high excess risk of pleural cancer in this cohort.] The authors did not provide any further information on the type of fibre or the source of the talc. [A limitation of the study for lung cancer was the lack of control for exposure to other carcinogens. However, this was unlikely to be an issue that could explain the large excess of pleural cancer in this study, since there are few known risk factors for pleural cancer other than asbestos.]

Zhang et al. (1989) (see Section 2.1.2) reported findings from a retrospective cohort mortality study of workers at a rubber factory in Shanghai, China. Overall, an increased risk of lung cancer was observed in this study (SMR, 1.33; 95% CI, [0.81–2.02]). The risk was particularly high among workers in curing (SMR, 2.86; 95% CI, [1.05–6.23]) and tyre inner tubing (SMR, 3.75; 95% CI, [0.77–11.0]). The RR among workers in either curing agent or inner-tube jobs was 3.2 (95% CI, 1.3–8.2) in men, and 4.6 (95% CI, 0.8–27.9) in women, when smoking was controlled for using Mantel–Haenszel methods. [The Working Group noted that a strength of this study was its ability to control for smoking. Limitations were the relatively short follow-up (maximum, 12 years), lack of estimates of talc exposure, and lack of control for exposure to other potential workplace carcinogens, including possible contamination of the talc by asbestos.]

Fu and Zhang (1992) reported findings from a cohort mortality study of miners and millers in a talc mine in Haichen, China (see Section 2.1.1(c)). Overall, the number of lung cancer deaths among all talc workers was more than twice that expected (SMR, 2.22; 95% CI, [1.34–3.66]). The increase in lung cancer mortality was greater among millers (SMR, 2.82; 95% CI, [1.13–5.81]) than among miners (SMR, 1.61; 95%

CI, 0.70–3.17). Lung cancer mortality increased with time since first exposure; for example, the SMR in the group with the highest latency (> 30 years) was 2.88. No information on pleural cancer was reported in the paper.

[The Working Group noted that smoking or exposure to other respiratory carcinogens was not controlled for in the analysis. The maximum follow-up of this cohort was 15 years, which is short, particularly for mesothelioma. A strength of this paper was that it used another working population as the referent rather than the general population. The Working Group concluded that there was probable contamination of the talc by chrysotile asbestos (Table 1.1) but noted that the talc in this study was considered to be not contaminated by asbestos in the meta-analysis by Chang et al. (2017).]

Wergeland et al. (2017) reported findings from a cohort study of cancer incidence and mortality among workers in Norway who were employed for ≥ 1 year between 1944 and 1972 as a talc miner, or for ≥ 2 years between 1935 and 1972 (as reported in Wergeland et al., 1990) as a miller (see Section 2.1.1(c)). Overall, a small excess of lung cancer (SIR, 1.17; 95% CI, 0.73–1.79) was observed. The lung cancer excess was higher among millers (SIR, 1.21; 95% CI, 0.70–1.94) than among miners (SIR, 1.04; 95% CI, 0.28–2.65). Lung cancer mortality was not increased among workers with long length of employment (≥ 10 years) and time since first employment (> 20 years). There were no cases of mesothelioma, or of cancers of pleura or peritoneum in this study. The expected number of pleural cancers was 0.1 for miners and 0.5 for millers. [The Working Group noted that this study was of limited informativeness because of its small cohort size and lack of control for smoking. As the authors noted, there seemed to be a downward bias because of the HWE. A strength of the study was its use of cancer incidence data. The Working Group concluded that there was contamination of the ore by anthophyllite asbestos (Table 1.1).]

Ierardi et al. (2022) reported results from a pooled analysis of mesothelioma mortality in four studies of cosmetic-talc miners and millers (see Section 2.1.1(c)). This study was an update of previous pooled analyses of these cohorts (Marsh et al., 2019; Marsh and Ierardi, 2020). Only one case of mesothelioma was observed in the cohorts, whereas 4.14 were expected. This case occurred in a cohort (Fordyce et al., 2019) for which the Working Group concluded chrysotile was a contaminant of the ore (Table 1.1). The authors conducted an analysis to determine the statistical power of the pooled analysis to detect an increased risk of mesothelioma, which was 59% and 78% for relative risks of 2.5 and 3.0, respectively. [The Working Group noted that post hoc analyses of statistical power are not very informative, and in general it is more appropriate to consider the confidence interval, which was quite wide (SMR, 0.242; 95% CI, 0.006115–1.35). Concerns have been raised that the expected number of cases was inflated because of the use of regional rates, particularly in the Italian study (see critique in Finkelstein, 2019). However, the Working Group considered that this concern did not materially change the interpretation of the results.]

Nie et al. (1992) reported findings from a cohort mortality study of 12 218 workers employed for > 1 year in seven porcelain factories from 1972 to 1974 (see Section 2.1.3). Overall lung cancer mortality was less than expected (SMR, 0.94 [95% CI, 0.72–1.21]). However, lung cancer mortality among workers exposed to talc was substantially increased (SMR, 2.62 [1.05–5.40]) when compared with age-specific mortality rates of residents from small and medium-sized cities across the country in 1987. [The talc dust exposure in these factories was reported to be fibre-free; however, the Working Group noted that the talc in these factories might have been contaminated with asbestos. The Working

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Group noted, as did the authors, that it was not possible to separate the effects of talc and silica in this study. The informativeness of the study was also limited by its small sample size, lack of adjustment for calendar time and smoking, and lack of quantitative estimates of exposure.]

Chiazze et al. (1993) reported findings from a case–control study nested in a cohort of workers in the fibreglass-manufacturing industry (see Section 2.1.3). The study included an extensive effort to quantify exposures to talc, fibreglass, asbestos, silica, formaldehyde, asphalt fumes, and total particulates. An increase in lung cancer was observed among workers who were hired before 1945 compared with workers first employed in 1945 or later (OR, 2.177; 95% CI, 1.386–3.421). An imprecise deficit in lung cancer was observed in the highest category (≥ 1000 fibres/mL) of talc exposure (OR, 0.678; 95% CI, 0.314–1.466) in analyses that did not control for smoking or other workplace exposures. However, a weak and highly imprecise association (OR, 1.355; 95% CI, 0.407–4.515) was observed for this category in analyses that controlled for smoking and the other workplace exposures. [The Working Group noted that a strength of this paper was the study's ability to control for other occupational exposures and personal risk factors (i.e. smoking and education). However, they did not appear to account for asbestos contamination within the talc. The use of an exposure metric of fibres/mL for talc was considered unusual by the Working Group.]

Li and Yu (2002) reported findings from a cohort mortality study of workers in a rubber factory in Shanghai, China, who were included in a general survey of ischaemic heart disease in 1972, with follow-up to 1995 (see Section 2.1.2). An excess of lung cancer was observed in this cohort (SMR, 1.25; 95% CI, 0.93–1.64). [The Working Group noted that the informativeness of this study was extremely limited by there being no mention of talc exposure, the small cohort size, and the lack of control for smoking and exposure to other carcinogens, including possible asbestos contamination of the talc. It was also noted that this study may overlap with the study by Zhang et al. (1989).]

Bulbulyan et al. (1999) reported findings from a cohort mortality study of women in the printing industry in the Russian Federation (see Section 2.1.4(a)). Overall, an excess in mortality from lung cancer was not observed in this study (SMR, 0.8; 95% CI, 0.4–1.5). An excess was observed among press operators, but it was based on only 3 deaths and was statistically imprecise (SMR, 1.9; 95% CI, 0.4–5.3). One death from mesothelioma of the peritoneum was reported. [The Working Group noted that the informativeness of this study was limited by its relatively short follow-up (maximum, 14 years) and no documentation on levels of exposure to talc, asbestos, or cigarette smoking.]

Langseth and Andersen (1999) published findings for lung cancer incidence from a cohort study of women employed in the pulp and paper industry in Norway (see Section 2.1.4(a)). An increase in lung cancer incidence was observed among women employed for < 3 years in the industry (SIR, 3.0; 95% CI, 1.29–5.89). An SIR of 1.4 (95% CI, 0.70–2.16) was observed among workers employed for ≥ 3 years. No cases of pleural cancer were reported, but only 0.1 was expected. [The Working Group noted that this study was of limited informativeness because of its lack of quantitative estimates of talc and asbestos exposure, and information on smoking. Asbestos has been widely used in this industry and might also be a contaminant of the talc used.]

Straif et al. (2000) (see Section 2.1.2) reported findings from a cohort mortality study of workers in the rubber industry in Germany. Overall, an increased risk of mortality from lung cancer (SMR, [1.23]; 95% CI, [1.04–1.44]) was observed. The study included semiquantitative estimates (high, medium, and low) of exposure to talc, asbestos, carbon black, and nitrosamines. An increased rate of lung cancer

mortality was observed in bivariate models that did not control for asbestos, carbon black, or nitrosamines among workers who had high exposure to talc for ≥ 1 year (hazard rate ratio, HRR, 1.6; 95% CI, 1.1–2.4), and in an alternative assessment in which high exposure was defined as having worked for ≥ 10 years in a high-exposure area (HRR, 1.9; 95% CI, 1.1–3.1) compared with workers with low exposure. No cases of mesothelioma were reported in this study. [The Working Group noted that a strength of this study was that it developed a semiquantitative assessment of exposure to talc and other substances in the rubber industry. A limitation was the lack of data on smoking; however, the internal comparisons that were made in the Cox model analyses were unlikely to be confounded by smoking. A serious concern was potential confounding from exposure to multiple substances in the rubber industry, such as carbon black, nitrosamines, and asbestos, including contamination of asbestos in the talc.]

Boffetta and Colin (2001) reported findings from a study coordinated by IARC of the pooled results from 15 cohort studies on mortality among 103 773 workers in the pulp and paper industry (see Section 2.1.4(a)). Increased mortality from lung cancer was observed among women ever exposed to talc (SMR, 1.42; 95% CI, 0.88–2.18), but not among men (SMR, 0.95; 95% CI, 0.84–1.07). The risk of lung cancer decreased with increasing duration of high exposure to talc ($P = 0.016$). Increased mortality from lung cancer was observed among female workers who were ever highly exposed to talc (SMR, 3.02; 95% CI, 1.65–5.07). There was no evidence of an increased risk of lung cancer mortality among women who were ever-exposed to asbestos (SMR, 0.67; 95% CI, 0.14–1.96). A slight excess based on only 1 case was observed among women who were highly exposed to asbestos (SMR, 2.03; 95% CI, 0.05–11.3). Boffetta and Colin (2001) also reported findings for cancer incidence among 73 775 workers from five countries. Ever being highly exposed to talc was associated with an increased risk of lung cancer incidence among women (SIR, 2.57; 95% CI, 1.11–5.06), but not among men (SIR, 0.86; 95% CI, 0.52–1.32). [The Working Group noted that a strength of this study was the large cohort size, extensive exposure characterization, and analysis of duration, latency, and cumulative exposure. Limitations included the lack of control for exposures to other carcinogens in the talc analyses, and the potential for contamination of the talc by asbestos.]

2.3.2 Case–control studies

Ramanakumar et al. (2008) reported findings on incident lung cancer and occupational exposure to industrial and cosmetic talc from two population-based case–control studies in Montreal, Canada (see Section 2.1.4(b)). There was no evidence of an association between lung cancer and either industrial talc (OR, 1.0; 95% CI, 0.6–1.5) or occupational exposure to cosmetic talc (OR, 0.9; 95% CI, 0.5–1.3). There was also no evidence of an association among workers with substantial exposure to industrial (OR, 0.9; 95% CI, 0.6–1.8) or cosmetic (OR, 0.7; 95% CI, 0.3–1.8) talc in a pooled analysis of the studies. [The Working Group noted that the strengths of this study included the control of smoking and the use of lifetime work history information. Limitations included the lack of quantitative measures of exposure, the reliance on expert opinion to estimate potential for exposure, and the potential for contamination of the talc by asbestos. The concentrations and duration of talc exposures in this study were mostly low and short, which limited the power of the study.]

2.3.3 Meta-analyses

The association between talc with lung cancer and/or mesothelioma has been examined in several meta-analyses (Wild, 2006; Chang et al., 2017; Ciocan et al., 2022b; Mundt et al., 2022).

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Most recently, Ciocan et al. (2022b) reported findings from a meta-analysis of studies on talc miners and millers and lung cancer mortality published between 1980 and 2022. Results from six cohort studies and one nested case–control study were identified for inclusion in the analyses. The studies were judged to be of high quality on the basis of a US National Institutes of Health tool. An increased risk of lung cancer mortality was observed in the meta-analysis (SMR, 1.42; 95% CI, 1.07–1.89). The increase in lung cancer mortality was larger in miners (SMR, 1.55; 95% CI, 0.75–3.19) than in millers (SMR, 1.18; 95% CI, 0.91–1.52). [The Working Group noted that there was substantial overlap in the studies by Dement et al. (1980) and Honda et al. (2002), which were both included in the analyses. The Working Group also noted that the analysis was based on a small number of studies and did not control for potential confounding from exposure to other carcinogens.]

[The Working Group noted that the meta-analysis by Ciocan et al. (2022b) contained several mistakes, including, for example, the inclusion of overlapping cohorts, and did not consider it further. The Working Group also did not concur with the authors' assessment of which cohorts were exposed to talc contaminated with asbestos.]

Chang et al. (2017) conducted a meta-analysis of cohort studies that examined the risk of lung cancer and occupational exposure to talc. The literature search included cohort studies that were published as of March 2017. Of the 14 cohorts from 13 publications that were included in the analyses, seven cohorts were from studies of talc mines or mills and seven were from talc-using industries. Seven of the cohorts were exposed to talc that, according to the authors, did not contain asbestos. Pooling results from all the studies resulted in an SMR of 1.45 (95% CI, 1.22–1.72). Subgroup analyses did not show any difference ($P = 0.87$) between cohort studies assessing "asbestiform talc" (SMR, 1.45; 95% CI, 1.18–1.78) and those assessing "non-asbestiform talc" (SMR, 1.51; 95% CI, 1.02–2.22). [The Working Group noted that the meaning of "asbestiform" was unclear, although it seemed that the authors were indicating contamination by asbestos.] There was also little difference ($P = 0.87$) in the results from the industries producing talc (SMR, 1.47; 95% CI, 1.02–2.11) or using talc (SMR, 1.41; 95% CI, 1.14–1.76).

There was significant evidence of heterogeneity in the findings of the study by Chang et al. ($I^2 = 72.9\%$; $P < 0.0001$). There was stronger evidence of increased lung cancer mortality ($P = 0.01$) in studies from Asia (SMR, 1.98; 95% CI, 1.11–3.51) and North America (SMR, 2.01; 95% CI, 1.34–3.00) than in those from Europe (SMR, 1.16; 95% CI, 1.02–1.31). The results were also stronger ($P < 0.01$) for studies with a medium quality score (SMR, 2.54; 95% CI, 1.11–1.56) than for studies with a high-quality score (SMR, 1.32; 95% CI, 1.74–3.71) based on the Newcastle–Ottawa scale (NOS). [The Working Group noted that this analysis included industries that were not included in the more recent meta-analyses by Ciocan et al. (2022b). Findings were stratified by whether or not the talc to which the workers were exposed contained asbestiform fibres, and by talc-using and talc-producing industries. The Working Group did not always concur with the authors' appraisal of which cohorts were exposed to talc that was potentially contaminated by asbestos. A limitation of the study was that there were no analyses that controlled for potential confounding by exposure to other carcinogens (i.e. smoking, silica, diesel, or radon).]

Mundt et al. (2022) conducted an analysis combining the SMRs for lung cancer from five cohort studies of talc miners and millers (Wergeland et al., 2017; Fordyce et al., 2019; Ciocan et al., 2022b; and Wild et al., 2002, which includes two cohorts) that were "reportedly not contaminated with asbestos". Observed and expected deaths from the studies were combined, and the observed number was divided by the

expected number to develop a pooled estimate. The pooled SMR for lung cancer was 1.13 (95% CI, 0.97–1.31). [The Working Group noted that this analysis did not include a cohort study by Fu and Zhang (1992), which was included in the meta-analysis by Chang et al. (2017) who also considered this mine to be asbestos-free, although this was contradicted by the appraisal of the Working Group (Table 1.1). The methods used to estimate the pooled SMRs and confidence intervals were not described, but it seemed that the authors did not account for heterogeneity in the study estimates by using a random effects model. Results were not presented separately for talc millers and miners.

The Working Group performed a meta-analysis of the results of six cohort studies in miners and millers (Fu and Zhang, 1992; Wergeland et al., 2017; Fordyce et al., 2019; Ciocan et al., 2022a; and Wild et al., 2002, which includes two cohorts). The meta-analysis conducted by Chang et al. (2017) included four of these six studies, although for the Vermont talc miners and the Val Chisone talc miners they used an earlier publication (with shorter follow-up) than that used by the Working Group. The meta-analysis by Mundt et al. (2022) did not include the study by Fu and Zhang (1992). On the basis of the information reported in Table 1.1, the Working Group stratified these studies by asbestos contamination of the ore: those conducted among workers in asbestos-free mines (Ciocan et al., 2022a; Wild et al., 2002, in Austria and France) and those conducted among workers in mines definitely, probably, or possibly containing asbestos (Fu and Zhang, 1992; Wergeland et al., 2017; Fordyce et al., 2019). In all six studies, the ore of the mines contained quartz (Table 1.1). SMRs and 95% confidence intervals were taken from the original papers; confidence intervals for Fu and Zhang (1992) were taken from Fig. 2 in the meta-analysis by Chang et al., 2017). Stratified and overall meta-SMRs were calculated with random effects (DerSimonian and Laird) formulae (DerSimonian and Laird, 1986). The overall meta-SMR was 1.28 (95% CI, 1.02–1.60) (Fig. 2.1), with a lower meta-SMR for the three cohorts in asbestos-free mines (meta-SMR, 1.06; 95% CI, 0.87–1.28) than in the three cohorts in mines with asbestos-contaminated ore (meta-RR, 1.52; 95% CI, 1.09–2.12). [The Working Group considered the estimate calculated among the cohorts in asbestos-free mines to be more relevant for the evaluation of talc.]

2.4 Cancers of the digestive system

See Table 2.4.

There were 18 cohort studies (including one nested case–control and one case–cohort study) (Monson and Fine, 1978; Blum et al., 1979; Thomas and Stewart, 1987; Negri et al., 1989; Fu and Zhang, 1992; Nie et al., 1992; Bulbulyan et al., 1999; Li and Yu, 1999, 2002; Langseth and Andersen, 1999; Straif et al., 2000; Boffetta and Colin, 2001; Honda et al., 2002; Wild et al., 2002; Wergeland et al., 2017; Chang et al., 2019; Fordyce et al., 2019; Ciocan et al., 2022a), one case–control study (Siemiatycki, 1991), and one meta-analysis (Chang et al., 2020a) that examined the association between talc exposure and any cancer of the digestive system.

The PMR study by Stern et al. (2001) was considered uninformative because the plasterers clearly had substantial exposure to asbestos and silica, they experienced a significant increase in asbestosis, and 4 cases of mesothelioma were observed. The study by Katsnelson and Mokronosova (1979) was considered uninformative because of methodological weaknesses (sample size and number of deaths were not reported, and the description of the statistical methods was unclear). The study by Zhang et al. (1989) was not considered relevant for the evaluation of cancer of the digestive system, because estimates for stomach, colon, and oesophageal cancer were given for the entire cohort and not

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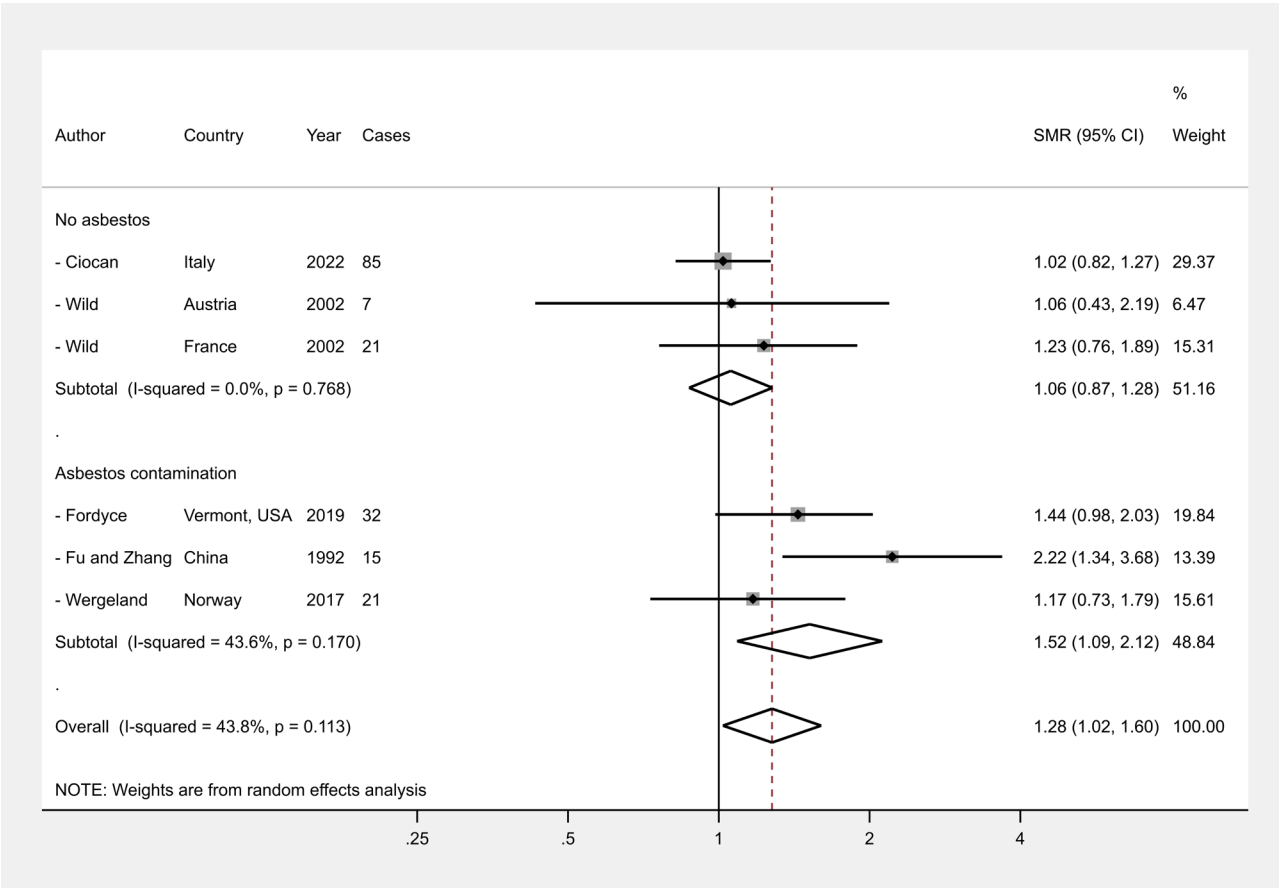
Fig. 2.1 Meta-analysis of lung cancer results from six cohort studies in miners and millers, stratified by asbestos contamination of the ore



CI, confidence interval; SMR, standardized mortality ratio; USA, United States of America.
Created by the Working Group.

stratified by department; hence, it was difficult to identify the workers with exposure to talc.

A cohort of workers at a talc mining and milling facility in the Gouverneur District, New York State, USA, was followed for mortality (see Section 2.1.1(a)). In the latest follow-up available (1950–1989) for that cohort (Honda et al., 2002), no increased risk of death from cancers of the digestive system and peritoneum combined or of the colon and rectum was found among 809 White men. The SMR of [1.44] (95% CI, [0.17–5.20]) for stomach cancer was based on only 2 deaths and thus was very imprecise. [The Working Group noted that this study only analysed the total cohort, without considering proxies of exposure, such as duration of exposure. Moreover, the study was probably affected by downwards bias because of the HWE, since it was based on comparison with the general population. Also, adjustment for potential confounders (e.g. alcohol, diet, and smoking) was lacking.]

In a cohort study of rubber factory workers, Monson and Fine (1978) reported SRRs for working ≥ 5 years in some departments for stomach cancer (SRR for the rubber making department, 2.2; SRR for the solid tyre or track department, 1.4) and other digestive system cancers (see Section 2.1.2). [The Working

Table 2.4 Epidemiological studies on exposure to talc and cancers of the digestive system

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Honda et al. (2002) USA Enrolment, 1948–1989/follow-up, 1950–1989 Cohort	809 White men who worked at a talc mining and milling facility in upstate New York for ≥ 1 day between 1948 and 1989, whose vital status was known in 1950 onwards. (Study was restricted to White men because of the low prevalence of other race/ethnicities). Exposure assessment method: Quantitative measurements; individual cumulative respirable dust concentration estimation for individual subjects from a JEM based on work area and calendar year combinations throughout the study period (Oestenstad et al., 2002).	Digestive organs and peritoneum, mortality Stomach, mortality Colon and rectum, mortality	SMR (regional referent): Total cohort SMR (regional referent): Total cohort SMR (regional referent): Total cohort	10 2 2	[1.02 (0.49–1.87)] [1.44 (0.17–5.2)] [0.42 (0.05–1.5)]	Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Monson and Fine (1978) Akron (OH), USA Enrolment, early 1940s to 1 July 1971/ follow-up, 1940 through 30 June 1976 (mortality) and 1964–1974 (diagnoses) Cohort	13 570 White men, members of local union and employed (≥ 5 yr) in Akron in tyres or rubber manufacturing. Follow-up (1940–1976) through death certificates (any cancer listed in the death certificate, even those not listed as underlying cause of death). For the period 1964–1974, incident cancers were identified through the tumour registry of four Akron-based hospitals. Exposure assessment method: See Table 2.1.	Stomach, mortality and incidence	Work area and minimum years in area (SRR):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			All other departments	92	1		
			Rubber making, 5+ yr	13	2.2		
			Solid tyres/ track, 5+ yr	4	1.4		
		Intestine, mortality and incidence	Work area and minimum years in area (SRR):				
			All other departments	122	1		
			Rubber making, 5+ yr	17	2		
			Solid tyres/ track, 5+ yr	9	2.3		
		Pancreas, mortality and incidence	Work area and minimum years in area (SRR):				
			All other departments	52	1		
			Elevators, 5+ yr	6	3		
			Tyre curing, 5+ yr	8	2.5		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciocan et al. (2022a) Val Chisone, north Italy Enrolment, 1946–1995/follow-up, through 31 January 2020 Cohort	1749 (1184 miners, 565 millers); men employed for ≥ 1 mo in the talc mine or mill in Val Chisone between 1946 and 1995. Exposure assessment method: Quantitative measurements; see Table 2.1.	Oral/pharyngeal combined, mortality	Department of employment (SMR, national referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: For oral and pharyngeal and oesophageal cancers, only national rates were available; for others, regional rates were used for the period 1970–2020, national rates were used before 1970.
			Miners	25	4.06 (2.62–5.99)		
			Millers	9	2.86 (1.31–5.43)		
			Total cohort	34	3.65 (2.53–5.1)		
		Oral/pharyngeal combined, mortality	Duration of employment (SMR, national referent):				
			< 15 yr	15	4.44 (2.48–7.32)		
			15–24 yr	6	2.42 (0.89–5.27)		
			≥ 25 yr	13	3.76 (2–6.44)		
			Trend-test *P*-value, 0.65				
		Oesophagus, mortality	Department of employment (SMR, national referent)				
			Miners	11	2.3 (1.14–4.11)		
			Millers	3	1.2 (0.25–3.49)		
			Total cohort	14	1.92 (1.05–3.22)		
		Oesophagus, mortality	Duration of employment (SMR, national referent)				
			< 15 yr	8	3.14 (1.35–6.18)		
			15–24 yr	4	2.04 (0.55–5.21)		
			≥ 25 yr	2	0.72 (0.09–2.59)		
			Trend-test *P*-value, 0.044				
		Stomach, mortality	SMR (regional referent):				
			Total cohort	37	1.15 (0.81–1.59)		
		Colon and rectum, mortality	SMR (regional referent):				
			Total cohort	31	0.95 (0.65–1.35)		
		Liver and bile ducts (ICD-9, 155), mortality	SMR (regional referent):				
			Total cohort	18	1.34 (0.8–2.12)		
		Pancreas, mortality	SMR (regional referent):				
			Total cohort	11	0.93 (0.46–1.66)		
		Peritoneum, mortality	SMR (regional referent):				
			Total cohort	2	1.43 (0.17–5.15)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Blum et al. (1979) USA 1964–1973 Nested case–control	Source cohort: See Table 2.1. Cases: 100 workers from two rubber plants whose death certificates indicated stomach cancer (as underlying cause of death or anywhere on the death certificate). Controls: 400; controls selected from the same worker cohort and matched for age (± 3 yr), race, sex, and company; 50% of controls were additionally matched on total duration of employment in the industry, but this was found to be similar for cases and controls. Exposure assessment method: See Table 2.1.	Stomach, mortality	Potential talc exposure ≥ 2 yr, company A (OR) (90% CI):			Age, race, sex, company	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			No exposure	NR	1		
			Moderate	8	1.97 (0.95–4.09)		
			High	9	1.7 (0.79–3.68)		
			High or moderate	16	2.48 (1.28–4.81)		
		Stomach, mortality	Potential talc exposure ≥ 2 yr, company B (OR) (90% CI):				
			No exposure	NR	1		
			Moderate	19	1.49 (0.85–2.6)		
			High	9	0.56 (0.29–1.08)		
			High or moderate	26	1.27 (0.68–2.35)		
Fordyce et al. (2019) Vermont, USA Enrolment, 1940–1969 (initial), 1930–1983 (expanded)/ follow-up, 1940–2012 Cohort	427 White male Vermont talc workers who had worked ≥ 1 yr from 1940–1969 (initial enrolment) or 1930–1940 or 1970–1983 (expanded enrolment). These corresponded to all talc workers who participated in the Vermont Health Department radiograph programme (workers were offered annual chest radiographs from 1930 to 1983). Exposure assessment method: See Table 2.1	Oral/pharyngeal combined, mortality	SMR (US referent): Total cohort	0	[0 (0–2.336)]	NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Covariates controlled not reported but likely included age and calendar period, as a life-table programme and US rates were used to estimate expected numbers of deaths.
		Oesophagus, mortality	SMR (US referent): Total cohort	2	[1.082 (0.131–3.91)]	NR	

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Fordyce et al. (2019) (cont.)		Stomach, mortality	SMR (US referent): Total cohort	2	[0.749 (0.091–2.705)]	NR	
		Colon, mortality	SMR (US referent): Total cohort	4	[0.67 (0.183–1.717)]	NR	
		Rectum, mortality	SMR (US referent): Total cohort	3	[1.98 (0.409–5.786)]	NR	
		Liver and bile ducts, mortality	SMR (US referent): Total cohort	1	[0.628 (0.016–3.497)]	NR	
		Pancreas, mortality	SMR (US referent): Total cohort	2	[0.563 (0.068–2.035)]	NR	
Wild et al. (2002) Austria and France Enrolment, 1945–1994 (French cohort) or 1972–1995 (Austrian cohort)/follow-up, through 1996 (French cohort), or 1995 (Austrian cohort) Cohort	1612 (1070 French, 542 Austrian); male workers employed continuously for ≥ 1 yr during 1945–1994 in a talc mine in the French Pyrenees (French cohort) or 1972–1995 in mine or mills in the Styrian Alps or in the Head office in Graz (Austrian cohort). For the French cohort, cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. Exposure assessment method: See Table 2.1. Of note, JEM were used only for the lung cancer case–control component.	Stomach, mortality	SMR (local referent rates): French cohort	5	1.18 (0.38–2.75)	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Long follow-up. *Other limitations*: Smoking data not available for the cohort analysis. Small sample size. For other strengths and limitations, see Table 2.1. *Other comments*: For the French cohort, local referent rates were used for 1968–1996, national referent rates were used for earlier years.
		Stomach, mortality	SMR (Styria referent rates): Austrian cohort	1	0.4 (0.01–2.25)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wild (2000) France Enrolment, 1945–1994/follow-up, 1968–1996 Cohort	1070; men employed continuously for ≥ 1 yr during 1945–1994 in a talc mine in the French Pyrenees (this is the French cohort in Wild et al. (2002), see Table 2.1). Cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. Results were limited to 1070 men and excluded 90 women described in the report. Exposure assessment method: See Wild et al. (2002) in Table 2.1.	Oesophagus, mortality Colon, intestine, mortality Rectum, mortality Liver, mortality Pancreas, mortality	SMR (regional reference): French cohort SMR (regional reference): French cohort SMR (regional reference): French cohort SMR (regional reference): French cohort SMR (regional reference): French cohort	3 5 2 4 3	 0.95 (0.19–2.77) 0.78 (0.25–1.81) 0.69 (0.08–2.5) 1.9 (0.51–4.85) 1.01 (0.2–2.94)	Age, calendar period	*Strengths*: Long follow-up. *Limitations*: Smoking data not available for the cohort analysis. Small sample size. *Other comments*: In Wild et al. (2002), only cancers of the stomach, mesothelioma, and lung are reported; data on other outcomes has been extracted from this INRS report.
Thomas and Stewart (1987) USA Enrolment, 1939–1966/follow-up, 1940 through 1 January 1981 Cohort	2055 White men employed for ≥ 1 yr (1939–1966) in three plants of a single US company producing ceramic plumbing fixtures. Exposure assessment method: See Table 2.1.	Digestive cancers (ICD-8, 150–159), mortality	SMR (US referent): Total cohort	 19	 [0.52 (0.31–0.81)]	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
Negri et al. (1989) Italy 1946–1981 Cohort	6629; all men who worked for ≥ 1 yr between 1946 and 1981 in a rubber tyre factory in Turin district. Exposure assessment method: See Table 2.1.	Oesophagus, mortality Stomach, mortality Liver, mortality Pancreas, mortality	SMR (national referent): Total cohort SMR (national referent): Total cohort SMR (national referent): Total cohort SMR (national referent): Total cohort	 7 35 3 2	 1.02 (0.42–2.1) 0.78 (0.54–1.08) 0.54 (0.11–1.56) 0.26 (0.03–0.96)	Age, calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wergeland et al. (2017) Norway Enrolment, 1944–1972 (miners), 1935–1972 (millers)/follow-up, 1953–2011 Cohort	390 (94 miners, 296 millers); men employed in the mine for ≥ 1 yr (1944–1972) or in the mill for ≥ 2yr (1935–1972). Exposure assessment method: See Table 2.1.	Stomach, incidence	Job type (SIR, general population referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Miners	3	1.69 (0.35–4.94)		
			Millers	7	1.09 (0.44–2.25)		
			Total cohort	10	1.22 (0.59–2.25)		
		Colon and rectum, incidence	Job type (SIR, general population referent):				
			Miners	6	1.47 (0.54–3.2)		
			Millers	24	1.62 (1.04–2.41)		
			Total cohort	30	1.59 (1.07–2.26)		
		Colon and rectum, incidence	Job type (SIR, general population referent, considering only one cancer case per individual in the numerator):				
			Millers	21	[1.42 (0.88–2.17)]		
Fu and Zhang (1992) Haichen talc mine, China Enrolment, January 1974/ follow-up, 1974–1988 Cohort	1357 male workers on the wage employee list in January 1974 with ≥ 1 yr of work history followed until 1988. Workers with work history in the chemical industry were excluded. For SRR estimation, age-standardized mortality was calculated relative to a cohort of workers in the iron and steel industry. Exposure assessment method: See Table 2.1.	Oesophagus, mortality	No. of deaths:			None	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			All talc workers	0	-		
		Stomach, mortality	SMR (iron and steel worker cohort referent):			Age	
			All talc workers	11	[1.72 (0.86–3.08)]		
		Colon, mortality	SMR (iron and steel worker cohort referent):				
			All talc workers	2	[1.41 (0.17–5.09)]		
		Liver and bile ducts, mortality	SMR (iron and steel worker cohort referent):				
			All talc workers	12	[1.58 (0.82–2.76)]		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nie et al. (1992) China Enrolment, 1972–1974/follow-up, through 1989 Cohort	12 218 (8654 men, 3564 women); Registered employees with > 1 yr of employment in seven porcelain factories. Exposure assessment method: See Table 2.1.	Stomach, mortality	SMR (national referent comprised of small and medium-sized cities):			Age	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.
			Total cohort	63	[1.3 (1–1.67)]		
			Talc-exposed workers	2	[1.03 (0.12–3.72)]		
		Liver, mortality	SMR (national referent comprised of small and medium-sized cities):				
			Total cohort	72	[1.06 (0.83–1.33)]		
Bulbulyan et al. (1999) Russian Federation 1979–1993 Cohort	3473 women with ≥ 2-yr employment in two printing plants as of December 1978. Exposure assessment method: See Table 2.1.	Oesophagus, mortality	Primary employment process (SMR, Moscow referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Compositors	1	[3.3 (0.1–19)]		
			Press operators	1	[3.3 (0.1–19)]		
			Bookbinders	4	4.1 (1–10.4)		
			Total cohort	7	2.6 (1.1–5.4)		
		Stomach, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	3	0.9 (0.2–2.7)		
			Press operators	9	2.2 (1–4.2)		
			Bookbinders	12	1 (0.5–1.8)		
			Total cohort	29	0.9 (0.6–1.3)		
		Colon, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	2	1.2 (0.1–4.2)		
			Press operators	2	0.9 (0.1–3.1)		
			Bookbinders	8	1.3 (0.6–2.6)		
			Total cohort	17	1 (0.6–1.7)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bulbulyan et al. (1999) (cont.)		Rectum, mortality	Primary employment process (SMR, Moscow referent):			Age and calendar period	
			Compositors	1	[0.9 (0–5.1)]		
			Press operators	0	[0 (0–2.6)]		
			Bookbinders	5	1.3 (0.4–3.1)		
			Total cohort	12	1.2 (0.6–2.1)		
		Liver and bile ducts, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	1	[3.3 (0.1–19)]		
			Press operators	0	[0 (0–9.2)]		
			Bookbinders	1	[0.8 (0–4.6)]		
			Total cohort	3	0.9 (0.2–2.7)		
		Pancreas, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	0	[0 (0–4.6)]		
			Press operators	2	2 (0.3–7.4)		
			Bookbinders	3	1.1 (0.2–3.3)		
			Total cohort	6	0.8 (0.3–1.8)		
Li and Yu (2002) Shanghai, China Enrolment, 1972/follow-up, 1973–1997 Cohort	1598 (934 men, 664 women); employees of a rubber factory. Exposure assessment method: See Table 2.1.	Oesophagus	Department (SMR, Shanghai referent):			Age, sex, calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1. *Other comments*: Unclear follow-up with Zhang et al. (1989).
			Tyre curing and vulcanizing	0	[0 (0–1.6)]		
			Tube curing	0	[0 (0–4.1)]		
			Total cohort	9	0.67 (0.3–1.27)		
		Liver, mortality	Department (SMR, Shanghai referent):				
			Tyre curing and vulcanizing	2	[0.48 (0.1–1.5)]		
			Tube curing	1	[0.67 (0–3.7)]		
			Total cohort	18	0.8 (0.47–1.26)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li and Yu (1999) Shanghai, China 1973–1995 Case–cohort	Cohort size was 1598 (934 men, 664 women). Workers with ≥ 1 yr of employment in a rubber manufacturing plant in Shanghai between 1973 and 1995. Analyses used the case–cohort study design. Cases included 36 deaths from stomach cancer observed in the cohort. A subcohort (comparison cohort, randomly sampled) consisted of 175 workers. Exposure assessment method: See Table 2.1.	Stomach, mortality	Duration of employment in the inner tyre tube department (relative risk): < 1 yr 1–19 yr 20–45 yr	 34 1 1	 1 1.54 (0.17–14.3) 1.64 (0.17–15.6)	Sex, average annual income	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: The "inner tyre tube" workshop was considered by author to have the highest talc exposure, but no analysis by talc exposure was provided.
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	Cohort of 4247 women who worked for ≥ 1 yr during 1920–1993 in a pulp and paper mill in Norway. Exposure assessment method: See Table 2.1.	Stomach, incidence	Length of employment (SIR, national referent): < 3 yr ≥ 3 yr	 2 16	 0.9 (0.11–3.41) 1.4 (0.82–2.33)	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. In this industry, asbestos was used.
		Colon, incidence	Length of employment (SIR, national referent): < 3 yr ≥ 3 yr	 6 23	 1.3 (0.48–2.86) 1.1 (0.68–1.6)		
		Rectum, incidence	Length of employment (SIR, national referent): < 3 yr ≥ 3 yr	 2 12	 0.9 (0.11–3.26) 1.2 (0.61–2.05)		

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Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Straif et al. (2000) Germany Enrolment, 1950–1981/Follow-up:1981–1991 Cohort	8933; all male German blue collar workers hired during or after 1950 in five study rubber plants and who were alive and actively employed or retired on 1 January 1981. Exposure assessment method: See Table 2.1	Stomach, mortality	SMR (national referent, western Germany):			NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: covariates controlled not reported for SMR but probably age and calendar period.
			Total cohort	44	[1.17 (0.85–1.57)]		
		Stomach, mortality	Talc exposure category, 10-yr lag period (HRR):			Age	
			Low (< 1 yr at medium and high levels, combined)	22	1		
			Medium	9	1.4 (0.6–3.2)		
			High (≥ 1 yr at high level)	13	2.4 (1.2–4.9)		
		Stomach, mortality	Talc exposure category, 10-yr lag period (HRR):				
			Low (< 0.5 yr at medium and high levels, combined)	21	1		
			Medium	12	1.2 (0.6–2.4)		
			High (≥ 10 yr at high level)	11	4.3 (2.1–9)		
Boffetta and Colin (2001) (publicly available since 2023) 15 countries Enrolment, varies/follow-up, between 1943 and 1985 through the mid-1990s Cohort	103 773 workers employed for ≥ 1 yr in pulp and paper companies with complete data. Exposure assessment method: See Table 2.1	Oral/pharyngeal combined, mortality	Talc exposure (SMR):			Age, sex, period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Ever-exposed	16	0.51 (0.29–0.82)		
			Ever highly exposed	5	0.47 (0.15–1.09)		
		Oesophagus, mortality	Talc exposure (SMR):				
			Ever-exposed	25	0.7 (0.45–1.04)		
			Ever highly exposed	7	0.69 (0.28–1.41)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Stomach, mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	104	0.92 (0.75–1.11)		
			Ever highly exposed	24	1.28 (0.82–1.91)		
		Colon, mortality	Talc exposure (SMR):				
			Ever-exposed	65	0.93 (0.72–1.18)		
			Ever highly exposed	12	0.76 (0.39–1.32)		
		Rectum, mortality	Talc exposure (SMR):				
			Ever-exposed	34	0.74 (0.52–1.04)		
			Ever highly exposed	6	0.64 (0.24–1.4)		
		Liver, mortality	Talc exposure (SMR):				
			Ever-exposed	22	0.81 (0.51–1.23)		
			Ever highly exposed	9	1.2 (0.55–2.28)		
		Gallbladder, mortality	Talc exposure (SMR):				
			Ever-exposed	8	0.72 (0.31–1.42)		
			Ever highly exposed	4	1.94 (0.53–4.98)		
		Pancreas, mortality	Talc exposure (SMR):				
			Ever-exposed	50	0.88 (0.65–1.15)		
			Ever highly exposed	7	0.65 (0.26–1.33)		

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Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang et al. (2019) Taiwan, China Enrolment, 2005/follow-up, 1997–2013 Cohort	605 652; the study used data from the Longitudinal Health Insurance Database established in 2005, which includes claims data from 1 million beneficiaries randomly sampled from the NHIRD, Taiwan, China (includes 99.6% of Taiwanese people), which includes a drug prescription file. Patients aged < 20 yr in 1997, with a diagnosis of cancer in 1997, or with gastric ulcer, duodenal ulcer, peptic ulcer, gastritis, duodenitis, *H. pylori*, in or before 1997 were excluded. Exposure assessment method: See Table 2.1.	Stomach, incidence	Oral intake of talc without asbestos indicated on medical records (HR):			Age, sex, Charlson comorbidity index excluding malignancies	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Asbestos exposure can be ruled out after 2005. Adjustment for potential confounders such as age and comorbidities. *Other limitations*: Diet and personal lifestyle factors not considered. Possible residual confounding because of diet and other lifestyle factors. Additional limitations in Table 2.1.
			Unexposed period	1804	1		
			Talc-exposed period	45	2.13 (1.54–2.94)		
		Stomach, incidence	Cumulative oral intake of talc without asbestos (HR):				
			Low to none (≤ 6 g)	1816	1		
			Medium (6–21 g)	23	2.3 (1.48–3.57)		
			High (> 21 g)	10	1.58 (0.79–3.17)		

Table 2.4 (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Siemiatycki (1991) Montreal, Canada September 1979 to June 1985 Case–control	Cases: cancers of the oesophagus, 99; stomach, 251; colon, 497; rectum, 257; pancreas, 116; in men aged 35–70 yr, residents in the Montreal area, with histologically confirmed cancer diagnosis (1979–1985). Cases ascertained through hospital records. Controls: Two controls per case (other cancer controls); men aged 35–70 yr, residents in Montreal area, with other cancers. Cases of cancer at other sites served as controls for cases at a specific cancer site.	Oesophagus, incidence	Industrial talc exposure, OR (90% CI):			Age, family income, cigarette index, alcohol index	*Strengths*: Large case–control study with an exposure assessment to many substances blind to the case–control status. *Limitations*: The fact that the controls of the case–control studies were cancer cases may have biased the results towards the null for any substance, which may have an effect on several cancer sites. Given the several thousand tests performed, the number of false positive tests is expected to be large. Like most population-based case–control studies on occupational hazards, the exposure assessment was based on questionnaires that collect work histories: this might lead to recall bias or (nondifferential) exposure misclassification. Furthermore, no assessment of the type of talc was possible with this approach.
			Never	NR	1		
			Ever	7	1.4 (0.7–2.7)		
			Ever substantial	1	0.8 (0.1–4.3)		
		Stomach, incidence	Industrial talc exposure OR (90% CI):				
			Never	NR	1		
			Ever	11	1 (0.6–1.7)		
			Ever substantial	3	1.1 (0.4–3.1)		
		Colon, incidence	Industrial talc exposure OR (90% CI):			Age, family income, cigarette index, ethnic origin, beer index	
			Never	NR	1		
			Ever	21	0.9 (0.6–1.3)		
			Ever substantial	5	0.9 (0.4–2)		
		Rectum, incidence	Industrial talc exposure OR (90% CI):				
			Never	NR	1		
			Ever	10	0.8 (0.4–1.4)		
			Ever substantial	5	1.9 (0.8–4.6)		
		Pancreas, incidence	Industrial talc exposure OR (90% CI):				
			Never	NR	1		
			Ever	2	0.4 (0.1–1.4)		
			Ever substantial	0	0 (0–2.8)		

CI, confidence interval; HR, hazard ratio; HRR, hazard rate ratio; JEM, job-exposure matrix, ICD, International Classification of Diseases; INRS, Institut National de Recherche et de Sécurité; NHIRD, National Health Insurance Research Database; NR, not reported; OR, odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; RR, rate ratio; USA, United States of America; yr, year(s).

Group considered that this study was less informative for the evaluation because it considered only work areas, not exposure to talc, although talc exposure in this cohort was documented in a previous update (Peters et al., 1976).]

A mortality study was conducted among 1749 male talc miners and millers in Val Chisone, in the Piedmont region of Italy (see Section 2.1.1(b)). In the last follow-up update for 1946 through 31 January 2020 (Ciocan et al., 2022a), mortality from oesophageal cancer was increased in the 1184 miners (SMR, 2.3; 95% CI, 1.14-4.11) and slightly but imprecisely increased in the 565 millers (SMR, 1.2; 95% CI, 0.25–3.49), compared with the national population. In the full cohort, there was an inverse trend across duration categories. Small-to-moderate increases were observed for cancers of the stomach (SMR, 1.15; 95% CI, 0.81–1.59), liver and bile ducts, and peritoneum, whereas no increase was observed for colorectal or pancreatic cancers. [The Working Group noted that liver cirrhosis mortality was increased, suggesting potential confounding by alcohol consumption for some cancers.]

A nested case–control study (100 workers who died from or with stomach cancer and 400 controls) was conducted within a cohort of about 17 000 workers at two US rubber-processing companies who were followed up in 1964–1973 (see Section 2.1.2) (Blum et al., 1979). Although no clear exposure–response relations were found for either company, there was an elevated risk for high or moderate exposure combined (exposed to talc for ≥ 2 years) (OR, 2.48; 90% CI, 1.28–4.81) in one company, and the OR for high or moderate exposure was 1.27 (90% CI, 0.68–2.35) in the other company. [The Working Group noted that no information on talc composition or purity was provided. The authors stated that they were investigating whether talc in the first company contained asbestiform or other fibres, but no subsequently published information was available to the Working Group. Moreover, the company-specific ORs for talc exposure were adjusted (using matched controls) only for age, sex, and race, and not for other occupational co-exposures (PAHs, nitrosamines, or carbon black) or other potential confounders for stomach cancer.]

Mortality in a cohort of 427 talc miners and millers in Vermont, USA, was updated and followed up for the period 1940–2012 (see Section 2.1.1(c)) (Fordyce et al., 2019). The results of this study were very imprecise, being based on few deaths from digestive system cancers (15 deaths in total, including only 2 deaths from stomach cancer). No excess risk for stomach cancer was found. [The Working Group noted this study may be downwardly biased by the HWE. Moreover, this study was considered minimally informative for the evaluation of digestive system cancers because of the small numbers of observed deaths for each organ.]

A mortality study was conducted in two cohorts of workers in talc mines and mills in France (1945–1994) and Austria (1972–1995) (see Section 2.1.1(c)) (Wild, 2000; Wild et al., 2002). The number of deaths from stomach cancer was small in each cohort (5 in the French cohort; SMR, 1.18; 95% CI, 0.38–2.75; and 1 in the Austrian cohort; SMR, 0.40; 95% CI, 0.01–2.25). [The Working Group noted this study may be downwardly biased by the HWE. The study was considered minimally informative for the evaluation of digestive system cancers because of the small numbers of observed deaths and the lack of exposure–response analyses and of accounting for possible confounders.]

A cohort mortality study (follow-up, 1940 through 1 January 1981) included 2055 White men employed in a company manufacturing ceramic plumbing fixtures in the USA (see Section 2.1.3) (Thomas and Stewart, 1987). Mortality from the 19 cancers of the digestive system was lower than expected (SMR, 0.52; 95% CI, [0.31–0.81]). No findings for cancer in specific digestive organs were presented. [The Working Group noted that this study may be biased downwards by the HWE. This study was considered

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uninformative for the evaluation of digestive system cancer because results by specific digestive organ were not reported.]

A cohort of 6629 male workers in a rubber-tyre factory in Italy was followed for mortality over the period 1946–1981 (see Section 2.1.2) (Negri et al., 1989). No increased mortality was found for deaths from cancer of the stomach, oesophagus, liver, or pancreas. [The Working Group noted that no quantitative or proxy estimates of exposure to talc were performed and no specification of talc type was provided. The low SMR for non-malignant causes of death raised concern about downward bias from the HWE. The > 10-fold excess of pleural cancer raised the possibility of contamination of the talc with asbestos.]

A study on mortality and cancer incidence in 94 talc miners and 296 millers (all men) in Norway was performed (see Section 2.1.1(c)). In the last update (1953–2011) (Wergeland et al., 2017), few cases and very imprecise SIR estimates were found for stomach cancer in the whole cohort and for colorectal cancer among miners, whereas 24 cases of colorectal cancer were observed in millers (SIR, 1.62; 96% CI, 1.04–2.41). For stomach cancer in the whole cohort, the SIR was 1.22 (95% CI, 0.59–2.25). [The Working Group noted that the exposure assessment to talc was not used in the analysis. Also, adjustment for potential confounders (e.g. alcohol and smoking) was lacking. Moreover, multiple cancers in the same individual were counted: one participant was registered with 4 cases of adenocarcinoma in the colon. Assuming 21 observed cases instead of 24 (and that the duplicates were observed for a miller rather than a miner) and that the effect of removing duplicates from the referent rate file would be negligible, the Working Group calculated that the SIR for colon cancer in millers would be [1.42] (95% CI, [0.88–2.17], using the exact Poisson method).]

Fu and Zhang (1992) described a cohort of 1357 workers in the Haichen talc mine in China (see Section 2.1.1(c)). Mortality was elevated for stomach cancer (SMR, 1.72; 95% CI, [0.86–3.08]; 11 deaths), colon cancer (SMR, 1.41; 95% CI, [0.17–5.09]; 2 deaths), and liver and bile duct cancer (SMR, 1.58; 95% CI, [0.82–2.76]; 12 deaths). [The Working Group noted that no information on talc type was provided. Analysis by time since first exposure was performed only for deaths from all digestive system cancers combined.]

Nie et al. (1992) analysed mortality in 12 218 workers (8654 men and 3564 women) who were employed for ≥ 1 year between 1972 and 1974 in seven porcelain factories and followed through 1989 (see Section 2.1.3). In the period 1972–1989, mortality from stomach cancer was slightly increased, but there were only 2 deaths, and no increased risk was found in the group exposed to dust and talc. No increased risk of death from liver cancer was observed.

A cancer mortality study (with follow-up through 1979–1993) was conducted in a cohort of 3473 women working in two large printing plants in Moscow, Russian Federation (see Section 2.1.4) (Bulbulyan et al., 1999). Oesophageal cancer mortality was increased in the total cohort (SMR, 2.6; 95% CI, 1.1–5.4; 7 deaths) and in bookbinders in particular (SMR, 4.1; 95% CI, 1.0–10.4; 4 deaths). Stomach cancer deaths were increased among press operators (SMR, 2.2; 95% CI, 1.0–4.2; 9 deaths), but there was no increase for bookbinders. For other cancers (colon, rectum, liver and bile ducts, and pancreas), SMRs were not or were modestly increased and/or were based on only a few deaths. [The Working Group noted this study did not assess exposure to talc, but only analysed job groups. The authors noted that bookbinders probably had some exposure to asbestos and that one death from mesothelioma of the abdomen was observed (no expected death given). There was potential exposure to other known and suspected carcinogens including lead, benzene, benzo[*a*]pyrene and other PAHs,

benzidine-based dyes, and carbon black. SMRs may be biased downwards by the HWE. Also, adjustment for potential confounders (e.g. alcohol, diet, and smoking) was lacking.]

Li and Yu (2002) described a cohort mortality study of workers in a rubber factory in Shanghai, China (1972–1995) (see Section 2.1.2). No increased SMRs for cancers of the oesophagus and liver were observed in the total cohort, or in the tube- or tyre-curing department. [The Working Group considered that this study was minimally informative for the evaluation of digestive system cancers because of the small numbers of observed deaths. It was also noted that this study may overlap with the study by Zhang et al. (1989).]

Within this cohort, a case–cohort study of stomach cancer mortality (32 men, 4 women; 1973–1995) was performed (see Section 2.1.2) (Li and Yu, 1999). The high risks in the two categories with ≥ 1 year of employment in the tyre inner-tube production department, believed to be the department with the highest exposure to talc, were based on only 1 death in each category. [In the absence of a quantitative exposure assessment for talc, the Working Group considered the results for tyre inner-tube production to be most relevant to exposure to talc. However, this study was minimally informative for the evaluation of digestive system cancers because of the small numbers of observed deaths.]

An incidence study was performed in a cohort of 4247 female workers in the pulp and paper mill industry in Norway who were followed in the period 1953–1993 (see Section 2.1.4) (Langseth and Andersen, 1999). In women employed for ≥ 3 years, a moderate excess of stomach cancer (SIR, 1.4; 95% CI, 0.82–2.33; 16 cases) and small excesses of colon and rectum cancer were found. [The Working Group noted that there was no assessment of quantitative exposure to talc (only analysis by length of employment was performed) and that asbestos was used in this industry. SIRs may be biased downwards by the HWE (although incidence data were used, so the bias would be less than with mortality data). Also, adjustment for potential confounders (e.g. alcohol, diet, and smoking) was lacking. This cohort was included in the pulp and paper industry pooled cohort study coordinated by IARC (Boffetta and Colin, 2001).]

A cohort of 8933 male rubber workers from five rubber plants in Germany was followed for mortality in the period 1981–1991 (see Section 2.1.2) (Straif et al., 2000). A slightly elevated stomach cancer risk was found in the whole cohort (SMR, [1.17]; 95% CI [0.85–1.57]). In internal Cox analyses unadjusted for asbestos exposure, a positive trend with exposure category (low, medium, high) and particularly elevated risks for the high category defined as either ≥ 1 year (HRR, 2.4; 95% CI, 1.2–4.9; 13 deaths) or ≥ 10 years (HRR, 4.3; 95% CI, 2.1–9.0; 11 deaths) at the high talc exposure level were found. [The Working Group noted that no information on the type of talc used in this study was provided. In some analyses, talc and asbestos were combined, and analyses for talc adjusted for asbestos exposure were not performed.]

The IARC Multicentric International Study of Workers in the Pulp and Paper Industry (Boffetta and Colin, 2001) examined mortality and cancer incidence in 15 countries (see Section 2.1.4(a)). For many digestive organs, there was no increased SMR, except for stomach cancer among workers (in both men and women) ever highly exposed to talc (SMR, 1.28; 95% CI, 0.82–1.91; 24 deaths), but there was no increase for those only ever-exposed to talc (SMR, 0.92; 95% CI, 0.75–1.11). [The Working Group noted that for digestive system cancers there was no analysis of cancer incidence nor of cumulative or duration of exposure to talc and that in this industry asbestos and several other chemicals were used. SMRs may have been biased downwards by the HWE. Also, adjustment for potential confounders (e.g. alcohol and smoking) was lacking.]

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A large, population-based incidence study (1997–2013) was performed in Taiwan, China, in 605 652 individuals included in the Longitudinal Health Insurance Database (see Section 2.1.6) (Chang et al., 2019). An elevated incidence of stomach cancer was found for those taking oral talc powder without asbestos via Chinese herbal medicine. No positive trend was found with cumulative oral intake: risk was markedly elevated for low cumulative oral intake (6–21 g) and moderately elevated for high (> 21 g). Although asbestos contamination can be reasonably excluded from 2005 onwards because it was prohibited by law, the authors acknowledged that no information was available on the presence of asbestos in talc for medical use during 1997–2005. [The Working Group noted that there may have been downwards survival bias: as only those alive in 2005 were followed, and those with incident stomach cancer who died before 2005 were not included. Data were not available on the possible confounders, smoking, diet, and alcohol use. The reasons for prescription of the medicine containing talc were not specified and could potentially be for condition(s) related to the later development of stomach cancer.]

Siemiatycki (1991) reported multiple case–control studies conducted in the Montreal area, Canada (1979–1985) (see Section 2.1.4(b)). Occupational exposure to talc was estimated from worker history. ORs for industrial talc exposure (ever versus never, or ever substantial versus never) were reported for several digestive system cancers (oesophagus, stomach, colon, rectum, pancreas); however, the estimates were highly imprecise, given the wide confidence intervals. For example, the OR for stomach cancer for ever-exposed to talc was 1 (95% CI, 0.6–1.7). [The Working Group noted that the main limitation was that no assessment of the type of talc was possible with this approach. Differential exposure misclassification was probably not an issue here because cancer controls were used; however, some nondifferential exposure misclassification (with bias generally towards the null) was expected. A strength was the adjustment for potential lifestyle confounders.]

Chang et al. (2020a) reported a meta-analysis of risk of stomach cancer in relation to occupational exposure to talc. The eligibility criteria included having a cohort with occupational talc exposure and having results (SMR, SIR, PMR) on stomach cancer, published either in English or Chinese. Studies with major exposure to asbestos or silica were excluded, as were case–control studies. The literature search included two major Chinese bibliographic databases. Quality assessment was based on the NOS. The statistical analysis was standard and included assessment of heterogeneity using I^2, assessment of publication bias using funnel plots, and subgroup analyses. The quantitative synthesis "meta-RR" was based on a random effect analysis. Starting from more than 3000 entries in first bibliographic searches, 13 cohorts in 12 publications were identified. According to the NOS, all studies were either of high or medium quality. The authors did not include a funnel plot but stated that there was no evidence of publication bias. The overall summary meta-RR was 1.21 (95% CI, 1.03–1.42). Subgroup analyses showed little difference between talc-using industries (meta-RR, 1.18; 95% CI, 0.93–1.50) and talc-producing industries (meta-RR, 1.23; 95% CI, 0.95–1.60), or between studies with asbestos contamination of the talc (meta-RR, 1.17; 95% CI, 0.93–1.46) or without asbestos contamination (meta-RR, 1.26; 95% CI, 0.97–1.63). A difference was found between geographical locations, with studies in Europe having a lower summary meta-RR than those in Asia or North America. The between-study heterogeneity was rather low (I^2 = 30%). [The Working Group noted that this meta-analysis was nearly identical to the meta-analysis on lung cancer and had the same strengths and weaknesses. The PMR study by Stern et al. (2001), which was considered uninformative by the Working Group, had a large influence on the

meta-RR; after omitting this study, the meta-RR was 1.11 (95% CI, 0.96–1.29). Chang et al. (2020a) also reported results for cohorts exposed to talc not containing asbestos (for the six studies not including Stern et al., 2001, the meta-RR was 1.26; 95% CI, 0.97–1.63), but the forest plot was missing in the paper (the authors erroneously wrote that the plot was in Fig. 3, which in fact was a forest plot of sensitivity analyses).]

The Working Group performed a meta-analysis of the results of six cohort studies in miners and millers (Ciocan et al., 2022a; Wild et al., 2002, which includes two cohorts; Fu and Zhang, 1992; Wergeland et al., 2017; Fordyce et al., 2019). The published meta-analysis by Chang et al. (2020a) included four of these six studies, although for the Vermont talc miners and the Val Chisone talc miners the Working Group used a more updated analysis than that included by Chang et al. (2020a). On the basis of the information reported in Table 1.1, these studies were stratified by asbestos contamination of the ore: those conducted in asbestos-free mines (Ciocan et al., 2022a; Wild et al., 2002 in Austria and France) and those conducted in mines definitely, probably, or possibly containing asbestos (Fu and Zhang, 1992; Wergeland et al., 2017; Fordyce et al., 2019). SMRs and 95% confidence intervals were taken from the original papers; confidence intervals for Fu and Zhang (1992) were taken from Fig. 2 in the meta-analysis by Chang et al., 2020a). [The Working Group noted that the way Chang et al. (2020a) obtained 95% confidence intervals for the study by Fu and Zhang (1992) was unspecified; probably the Boice–Monson method was used).] Stratified and overall meta-SMRs were calculated with random effects (DerSimonian and Laird) formulae (DerSimonian and Laird 1986). The overall meta-SMR was 1.23 (95% CI, 0.95–1.59) (Fig. 2.2), with a lower meta-SMR for the three cohort studies on workers in mines with no contamination of the ore (1.14; 95% CI, 0.83–1.56) than for studies in mines shown to contain asbestos (1.42; 95% CI, 0.92–2.17). The Working Group considered that the meta-estimate from the asbestos-free mines was more informative for the present evaluation. However, the Working Group also noted that informativeness was limited by the small number of cases, especially in the Austrian and French cohorts.]

2.5 Cancers of the cervix and corpus uteri

See Table 2.2.

The Working Group reviewed three cohort studies on uterine and cervical cancer, all from the USA (Karageorgi et al., 2010; Crawford et al., 2012; O'Brien et al., 2019, 2021b), one pooled study of uterine cancer in four cohorts from the USA (O'Brien et al., 2021a), and three occupational cohort studies of printing or paper industry workers (Bulbulyan et al., 1999; Langseth and Andersen, 1999; Boffetta and Colin, 2001) that addressed the relation between talc body powder or occupational exposure and risk of cancer of the uterine cervix or corpus. The WHI-OS (Crawford et al., 2012), the NHS-I (Karageorgi et al., 2010), and the Sister Study (O'Brien et al., 2019) each evaluated the risk of endometrial cancer, including self-reported cancers. The association between talc and cervical cancer was addressed in the Sister Study (O'Brien et al., 2021b). Bulbulyan et al. (1999) evaluated cervical and endometrial cancer mortality in workers from two large printing plants in Moscow, Russian Federation. Boffetta and Colin (2001) published a report on the Multicentric International Cohort Study of Workers in the Pulp and Paper Industry in 15 countries, which also included the Norwegian pulp and paper cohorts reported separately by Langseth and Andersen (1999). There was one case–control study (Neill et al., 2012) that assessed the risk between talc and pathologically confirmed endometrial cancer.

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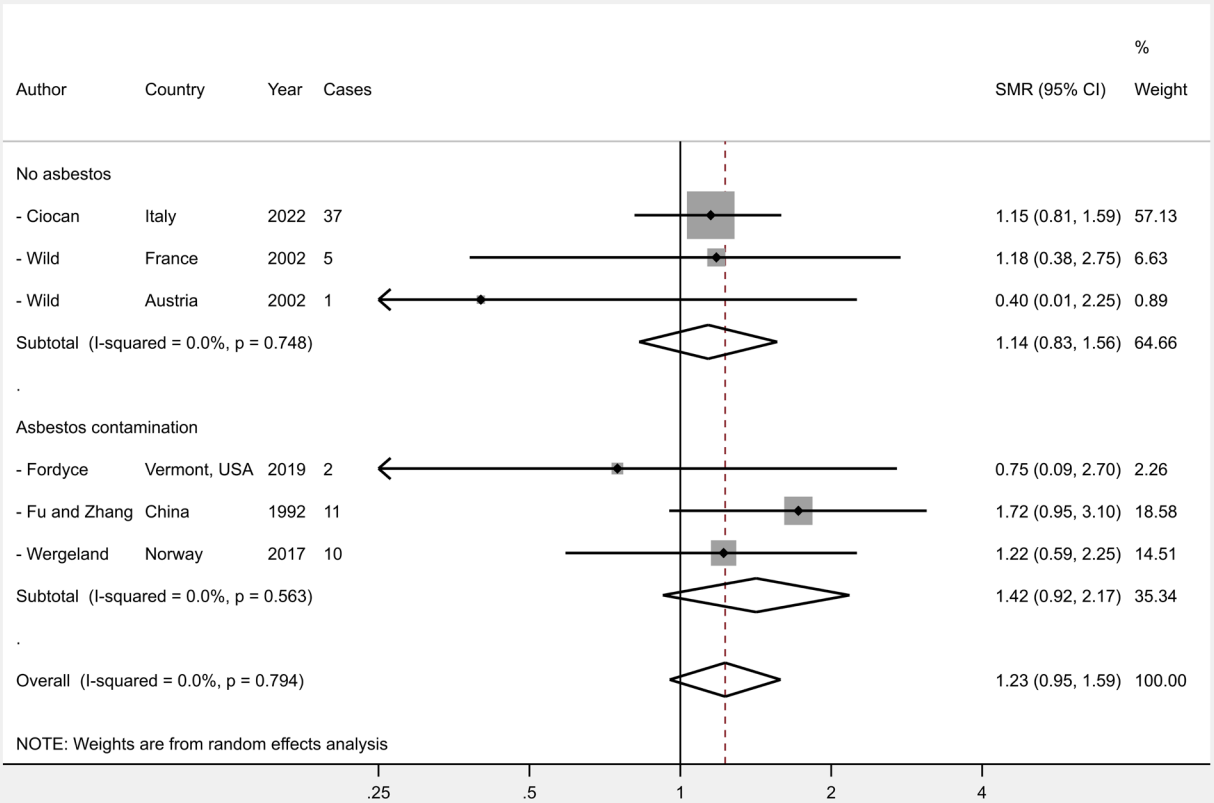
Fig. 2.2 Meta-analysis of stomach cancer results from six cohort studies in miners and millers, stratified by asbestos contamination of the ore



CI, confidence interval; SMR, standardized mortality ratio; USA, United States of America.
Created by the Working Group.

2.5.1 Cohort studies

Bulbulyan et al. (1999) evaluated cancer mortality rates among 3473 women who worked in two large printing plants in Moscow, Russian Federation, as of December 1978 (see Section 2.1.4(a)). The 1271 women working in bookbinding were likely to be exposed to talc contaminated asbestos. For cervical or endometrial cancer, no increased risk was reported, and few cases (6 cervical and 5 uterine corpus cancers in the overall cohort) were observed. [The Working Group noted that the bookbinders were exposed to solvents, adhesive, and paper dust and have probable exposure to asbestos as a contaminant of talc fillers used in paper. Exposure to talc was not directly measured, and the study lacked detailed exposure information. The number of deaths by cancer site was small. Asbestos exposure was not directly measured; however, workers were exposed to talc that was likely to be contaminated with asbestos.]

Langseth and Andersen (1999) conducted a follow-up study to investigate cancer risk among women in the pulp and paper industry in Norway (see Section 2.1.4(a)). The cohort consisted of 4247 women who worked for ≥ 1 year in a pulp and paper mill between 1920 and 1993. Cancer incidence was determined through the National Cancer Registry. Death and emigration status

was determined through Statistics Norway. Exposure was determined according to the department in which the woman worked, and it was noted that talc was used as a filler in the packaging and wrapping of paper. Separate analyses were conducted for short-term (< 3 years) and long-term (≥ 3 years) workers and accounted for variations in exposure levels over time and in time since first exposure. Information on exposure measurements was not documented. The study found 380 new cases of cancer, including 29 incident cancers of the cervix, in the cohort. Compared with a national referent, SIRs were 0.8 (95% CI, 0.25–1.79) for short-term and 1.2 (95% CI, 0.75–1.74) for long-term workers. [The Working Group noted as limitations that potential confounders were not considered in the analysis, no assessment of genital use of talc was available, and the type of exposure could not be determined.]

Boffetta and Colin (2001) reported the results of a multicentric international cohort study to assess associations of various agents used in the pulp and paper industry with cancer in male and female workers (see Section 2.1.4(a)). The study included 18 241 women from 15 countries who had ≥ 1 year of employment in the industry. The years of employment ranged from 1943 up through the 1980s and 1990s. Exposure to various chemicals, including talc, was based on occupational history and the department in which the individual was employed. Exposure was assessed as being none, low, medium, or high, as well as probable or unknown. SMRs and SIRs and 95% CIs were calculated. Analyses included people who worked in only one department and, for each participant, the department of the longest employment. Person-years were based on duration of employment. For those ever highly exposed, the SMRs for cervical and uterine cancer were 0.45 (95% CI, 0.01–2.49; 1 case) and 1.85 (95% CI, 0.22–6.69; 2 cases), respectively. [The Working Group noted that the exposure assessment was imprecise for talc and that individual exposure was not assessed.]

Karageorgi et al. (2010) reported results from the prospective NHS-I cohort for the association between perineal use of talcum powder and endometrial cancer (invasive type I endometrial adenocarcinoma of the uterus) (see Section 2.1.5(a)). Exposure was assessed at a single time point, at baseline in 1982. Participants were asked if they had ever applied talcum powder, baby powder, or deodorizing power to the perineal area or to sanitary napkins and, if so, the number of times per week. Diagnoses were confirmed through medical records. Statistical analysis adjusted for potential confounders, including BMI. The relative risk for ever use was 1.21 (95% CI, 1.02–1.44) among postmenopausal women. Also, among postmenopausal women, the relative risk of endometrial cancer among users, compared with never users, was 1.28 (95% CI, 1.00–1.63) for one to six times per week and 1.24 (95% CI, 0.98–1.56) for daily use. Duration of exposure was not assessed. [The Working Group noted that the exposure assessment did not reflect use after the baseline survey.]

Crawford et al. (2012) reported results from an analysis of the relation between long-term perineal use of powder directly on the genital area, diaphragm, sanitary napkin, or pad, and risk of endometrial cancer, using data from the prospective WHI-OS cohort study (see Section 2.1.5(a)). There were 447 cases diagnosed with endometrial cancer and 52% of the population reported ever use of powder. The HR for ever use of all forms of perineal use of powder was 1.06 (95% CI, 0.87–1.28). Use of powder on a diaphragm for ≥ 20 years was associated with a rate of endometrial cancer that was three times as high (HR, 3.06; 95% CI, 2.00–4.70) as that in women who had never used powder on a diaphragm (*P* for trend, < 0.001, for duration of diaphragm powder use). [The Working Group noted that the data were of good quality and that the magnitude of the HR was high. The

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association with a long duration (≥ 20 years) of diaphragm powder use was based on 23 cases of endometrial cancer and suggested that the exposure may reflect talc contaminated with asbestos because use started before 1976. Self-report could contribute to nondifferential misclassification of the exposure and did not distinguish between powders containing talc. Endometrial cancer subtypes were not considered. The strengths of this study were prospectively collected data, avoiding differential exposure misclassification, the large sample size, and adjustments for covariates, including BMI. This study was considered informative for the evaluation.]

O'Brien et al. (2019) conducted a large prospective study using the Sister Study cohort (2003–2009) (see Section 2.1.5(a)). A baseline questionnaire obtained information on perineal use of talc in the 12 months before enrolment and also assessed frequency of use. There were 271 cases of uterine cancer identified through self-report, and 207 cases were confirmed as invasive uterine cancer. Talc use at age 10–13 years and histological subtype for 188 cases of invasive cancer were also evaluated. Data analysis used Cox proportional hazard regression, controlling for covariates that included age, race/ethnicity, education, BMI, menopausal status, parity, duration of oral contraceptive use, ever use of hormones, smoking, and age at menarche. The prevalence of ever talc use (in the 12 months before enrolment and/or at age 10–13 years) in the full cohort was 26% and was low compared with other observational studies. The adjusted HR for the association of ever talc use (defined as use in the 12 months before baseline and/or use at age 10–13 years) with uterine cancer was 1.2 (95% CI, 0.94–1.6). The estimate for the association with ever use of talc among invasive cancer cases (HR, 1.2; 95% CI, 0.84–1.6) was the same in magnitude as the estimate for use at age 10–13 years (HR, 1.2; 95% CI, 0.90–1.6). A positive trend ($P = 0.07$) for frequency of talc use and uterine cancer was reported (HR for frequent versus never users, 1.4; 95% CI, 0.99–2.0). [The Working Group noted that exposure misclassification was probably nondifferential.]

O'Brien et al. (2021b) examined the association between douching or genital use of talc and the risk of prevalent and incident cervical cancer, using data from the prospective Sister Study cohort (see Section 2.1.5(a)). Data were analysed for 523 pre-enrolment prevalent cervical cancers and 23 incident cervical cancers. Talc use was determined at two time points, between the ages of 10 and 13 years and in the 12 months before enrolment. Frequency of use was also obtained. The identification of pre-baseline cervical cancer was mostly based on self-report. Cox proportional hazards models were used to estimate HRs and were adjusted for potential confounders. For incident cervical cancers, the HR for the association with any genital use of talc (between the ages of 10 and 13 years and/or in the 12 months before enrolment) was 1.38 (95% CI, 0.66–2.86) and for any recent genital use of talc was 1.79 (95% CI, 0.78–4.11). [The Working Group noted as a limitation that this study included very few new confirmed cases that were prospectively identified ($n = 23$), since the inclusion of prevalent cases could reflect determinants of survival as well as incidence. Determinants of cervical cancer screening could also affect results.]

O'Brien et al. (2021a) pooled data from four cohort studies, the Sister Study, NHS-I, NHS-II, and WHI-OS, to determine the relation between genital use of powder and uterine cancer (see Section 2.1.5(a)). Across the four cohorts, 37% of women reported ever use. Using Cox proportional hazards models stratified by study and adjusted for many uterine cancer risk factors, including BMI, there was no overall association between ever genital use of powder and invasive uterine cancer (3162 cases). Of the self-reported cases, 2646 were medically confirmed. Most cohort members were non-Hispanic White women. For uterine cancer overall, adjusting for BMI reduced the HR for ever genital use of

powder from 1.13 (95% CI, 1.05–1.21) to 1.03 (95% CI, 0.95–1.10). Regarding long-term use, in the fully adjusted model (including BMI and reproductive factors), long-term (> 20 years) genital use of powder was associated with a slightly increased overall risk of cancer of the corpus uterus (HR, 1.12; 95% CI, 0.96–1.31). An elevated risk was found among long-term users (> 20 years) for non-endometrioid cancer (HR, 1.46; 95% CI, 1.00–2.11). Most cases of uterine cancer were endometrioid. Additional analyses did not find an association among the medically confirmed cases or among the endometrioid versus non-endometroid subtypes. No association was seen in older participants who may have had higher exposure to asbestos-contaminated powder. [The Working Group noted that this was a large study. A limitation was that powder use was assessed only at baseline, and changes over time were not accounted for. Results were not consistent with asbestos contamination, and it was not possible to differentiate between types of powder used or to identify what chemicals the powders contained. Given the similarity in molecular characteristics and possible common cell of origin between high-grade serous ovarian cancer and high-grade serous uterine cancer (Kandoth et al., 2013), the Working Group considered the association between long-term use of body powder and increased risk of non-endometrioid uterine cancers to be consistent with the increased risk of high-grade serous ovarian cancer.]

In the updated Sister Study cohort, O'Brien et al. (2024) re-analysed the association between talc and uterine cancer using additional cases and updated data on talc use across the life-course, which were collected in a follow-up survey administered in 2017–2019 (see Section 2.1.5(a)). Because the follow-up questionnaire was administered after many of the cancer cases had been diagnosed, the authors used multiple imputation and quantitative bias analysis approaches to account for contradictory or missing data. The incidence of uterine cancer was not associated with ever use or frequency of genital use of talc.

2.5.2 Case–control studies

Neill et al. (2012) conducted the Australian National Endometrial Cancer Study (ANECS), a population-based case–control study on endometrial cancer risk (see Section 2.1.5(c)). There were 1399 histologically confirmed cases in women aged 18–79 years, and 740 controls sampled through the national electoral roll were included in the analysis. The cases were diagnosed between 2005 and 2007, and the controls were frequency-matched to cases on state and 5-year age categories. Telephone interviews were conducted, and the association with talcum powder use in the perineal area (i.e. underwear, sanitary pads, or diaphragm) was evaluated. Those who said they had ever used talcum powder were asked age at first use, times per week, and number of years of use. Participants were also asked if they used talcum powder on the upper body. Potential confounders, including age, age at menarche, parity, oral contraceptive use, hormone replacement therapy, BMI, and smoking status, were considered. The proportion of perineal users of talc among controls was 40%. Multiple logistic regression analysis controlled for confounders that had an impact on the point estimates of > 10%. The OR for ever use of talc in the perineal area was 0.88 (95% CI, 0.68–1.14), and there were no substantive findings for frequency and duration of use. [The Working Group noted that although the sample size was large, no increased risk of endometrial cancer was detected. Because of the retrospective nature of the exposure assessment, there was a possibility of differential exposure misclassification.]

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2.6 Cancers of the urinary tract, lymphatic and haematopoietic tissue, and other sites

2.6.1 Cancers of the urinary tract

See Table 2.5.

Associations between occupational talc exposure and cancers of the urinary tract have been investigated in nine occupational cohort studies.

Monson and Fine (1978) found in their retrospective study on mortality and nonfatal cancer in male rubber-industry workers that those who had worked in the tyre-building department for ≥ 5 years had an SRR for urinary bladder cancer of 1.5, compared with those in all other work areas (see Section 2.1.2). Talc exposure was possible in that department, but no estimates of talc exposure were included in the analyses. [The Working Group noted that the rubber industry involves exposure to many other substances, including those associated with bladder cancer, such as *N*-nitrosamine and aromatic amines, reducing the informativeness of these results for the present evaluation.]

Ciocan et al. (2022a) (see Section 2.1.1(b)) found in a mortality study in a cohort of talc miners and millers in Italy that there was a reduced SMR for bladder cancer of 0.23 (95% CI, 0.05–0.66), compared with the regional population referent, but this was based on only 3 deaths. For kidney cancer, the SMR was 0.80 (95% CI, 0.26–1.87), based on only 5 deaths. For these two cancers, no analyses were conducted based on talc exposure levels or duration of exposure. Talc samples collected between 2017 and 2020 confirmed that the talc from this plant was pure talc with no detectable level of asbestos (see also Table 1.1). [The Working Group found this study to be not very informative for the evaluation of urinary tract cancers because of the small number of cases and the lack of exposure–response analyses.]

Fordyce et al. (2019) (see Section 2.1.1(c)) found in a mortality study in a cohort of US (Vermont) talc miners and millers that the SMR for cancer of the bladder and other urinary organs was [0.894] (95% CI, [0.108–3.231]), based on only 2 deaths. For kidney cancer, the SMR was [1.764] (95% CI, [0.364–5.155]), based on only 3 deaths. For these two cancers, no analyses were conducted based on talc exposure levels. [The Working Group considered that the additional analyses presented by duration of exposure and latency were uninformative because of the small sample sizes.]

Wild (2000) (see Section 2.1.1(c)) found in a mortality study of talc miners in France that there was no excess of bladder cancer for the whole cohort (SMR, 0.85; 95% CI, 0.17–2.48). No subgroup analyses based on talc exposure were reported for urinary tract cancers. Negri et al. (1989) (see Section 2.1.2) found in a mortality study in a cohort of rubber factory workers in Italy that the SMR for bladder cancer was 1.83 (95% CI, 1.05–2.96). The SMR for cancers of the kidney and other urinary organs was 1.33 (95% CI, 0.43–3.09), based on only 5 deaths. There was an analysis by duration of exposure, which indicated an inverse exposure–response relation for bladder cancer. [The Working Group noted that the rubber industry involves exposure to many other substances, including those associated with bladder cancer, such as *N*-nitrosamine and aromatic amines, reducing the informativeness of these results to the present evaluation. Also, no analyses based on talc exposure levels were conducted.]

Wergeland et al. (2017) (Section 2.1.1(c)) found in their cancer incidence study in a small cohort of talc miners and millers in Norway that the SIR for bladder cancer was 1.35 (95% CI, 0.72–2.30), based on 13 cases. For kidney cancer, the SIR was 0.87 (95% CI, 0.24–2.22), based on only 4 cases. Findings for each cancer type were very imprecise when the cohort was divided into miners and millers, because of the small numbers in each

Table 2.5 Epidemiological studies on exposure to talc and cancer of the urinary tract and other solid organs

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Monson and Fine (1978) Akron (OH), USA Enrolment, early 1940s to 1 July 1971/follow-up, 1940 through 30 June 1976 (mortality) and 1964–1974 (diagnoses) Cohort	13 570 White men, members of local union and employed (≥ 5 yr) in Akron in tyre or rubber manufacture. Follow-up (1940–1976) through death certificates (any cancer listed in the death certificate, even those not listed as underlying cause of death). For the period 1964–1974, incident cancers were identified through the tumour registry of four Akron-based hospitals. Exposure assessment method: See Table 2.1.	Urinary bladder, mortality and incidence	Work area and minimum years in area (SRR):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			All other work areas	64	1		
			Chemical, 0+ yr	6	2.5		
			Tyre building, 5+ yr	16	1.5		
			Raw material warehouse/ shipping, 0+ yr	4	1.1		
			Finished good warehouse, 0+ yr	5	1.5		
		Prostate, mortality and incidence	Work area and minimum years in area (SRR):				
			All other work areas	111	1		
			Material conservation, 25+ yr	4	7.6		
			Final finish, 25+ yr	4	2.4		
			Machine maintenance, 5+ yr	15	1.6		
			Machine maintenance 0–4 yr	7	2.1		
		Brain, mortality and incidence	Work area and minimum years in area (SRR):				
			All other work areas	17	1		
			Tyre assembly, 5+ yr	8	4.1		

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciocan et al. (2022a) Val Chisone, north Italy Enrolment, 1946–1995/ follow-up, through 31 January 2020 Cohort	1749 (1184 miners, 565 millers); Men employed for ≥ 1 mo in the talc mine or mill in Val Chisone between 1946 and 1995. Exposure assessment method: See Table 2.1.	Kidney, mortality	SMR (regional referent) Total cohort	5	0.8 (0.26–1.87)	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: regional rates used for the period 1970–2020, national rates used before 1970
		Urinary bladder, mortality	SMR (regional referent): Total cohort	3	0.23 (0.05–0.66)		
		Prostate, mortality	SMR (regional referent): Total cohort	15	0.8 (0.45–1.32)		
		Brain and other CNS (ICD-9, 191–192), mortality	SMR (regional referent): Total cohort	5	0.7 (0.23–1.64)		
Fordyce et al. (2019) Vermont, USA Enrolment, 1940–1969 (initial), 1930–1983 (expanded)/follow-up, 1940–2012 Cohort	427 White male Vermont talc workers who had worked ≥ 1 yr from 1940–1969 (initial enrolment) or 1930–1940 or 1970–1983 (expanded enrolment). Those correspond to all talc workers who participated in the Vermont Health Department radiograph programme (workers were offered annual chest radiographs from 1930 to 1983). Exposure assessment method: See Table 2.1.	Kidney, mortality	SMR (US referent): Total cohort	3	[1.764 (0.364–5.155)]	NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Covariates controlled were not reported but probably included age and calendar period, as a life-table programme and US rates were used to estimate expected numbers of deaths.
		Urinary bladder, mortality	SMR (US referent): Total cohort	2	[0.894 (0.108–3.231)]	NR	
		Prostate, mortality	SMR (US referent): Total cohort	6	[0.908 (0.333–1.977)]	NR	
		CNS, mortality	SMR (US referent): Total cohort	3	[1.809 (0.373–5.285)]	NR	
		Breast, mortality	SMR (US referent): Total cohort	1	[11.098 (0.277–61.836)]	NR	

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wild (2000) France Enrolment, 1945–1994/follow-up, 1968–1996 Cohort	1070 men employed continuously for ≥ 1 yr between 1945 and 1994 in a talc mine in the French Pyrenees (this is the French cohort in Wild et al., 2002). Cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. Results were limited to 1070 men and excluded 90 women described in the report. Exposure assessment method: See Wild et al. (2002) in Table 2.1.	Urinary bladder, mortality Prostate, mortality Brain, mortality	SMR (regional reference): French cohort SMR (regional reference): French cohort SMR (regional reference): French cohort	3 8 0	 0.85 (0.17–2.48) 0.94 (0.4–1.85) 0 (0–3.22)	Age, calendar period	*Exposure assessment critique*: See Wild et al. (2002) in Table 2.1. *Other strengths*: Long follow-up. *Other limitations*: Smoking data not available for the cohort analysis. Small sample size. *Other comments*: In Wild et al. (2002), only stomach, mesothelioma and lung are reported; other data has been extracted from this INRS report.
Negri et al. (1989) Italy 1946–1981 Cohort	6629; all men who worked for ≥ 1 yr between 1946 and 1981 in a rubber tyre factory in Turin district. Exposure assessment method: See Table 2.1.	Kidney and other urinary organs, mortality Urinary bladder, mortality Urinary bladder, mortality Brain	SMR (national referent): Total cohort SMR (national referent): Total cohort Duration of exposure (SMR, national referent): < 10 yr 10–19 yr ≥ 20 yr SMR (national referent): Total cohort	5 16 3 4 9 9	 1.33 (0.43–3.09) 1.83 (1.05–2.96) [2.73 (0.56–7.97)] [1.97 (0.54–5.05)] [1.6 (0.73–3.04)] 0.88 (0.4–1.67)	Age, calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wergeland et al. (2017) Norway Enrolment 1944–1972 (miners), 1935–1972 (millers)/follow-up, 1953–2011 Cohort	390 (94 talc miners, 296 millers); men employed in the mine for ≥ 1 yr (1944–1972) or in the mill for ≥ 2 yr (1935–1972). Exposure assessment method: See Table 2.1.	Kidney, incidence	Job type (SIR, general population referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: lack of exposure estimates and exposure–response analyses. Additional limitations in Table 2.1.
			Miners	0	0 (0–3.61)		
			Millers	4	1.11 (0.3–2.85)		
			Total cohort	4	0.87 (0.24–2.22)		
		Urinary bladder, incidence	Job type (SIR, general population referent):				
			Miners	1	0.49 (0.01–2.74)		
			Millers	12	1.58 (0.81–2.75)		
			Total cohort	13	1.35 (0.72–2.3)		
		Urinary bladder, incidence	Job type (SIR, general population referent):				
			Among workers first employed 1960–1964: Millers	7	5.38 (2.16–11.08)		
		Urinary bladder, incidence	Job type (SIR, general population referent):				
			Among workers ever employed 1960–1964: Millers	10	1.77 (0.85–3.26)		
		Prostate, incidence	Job type (SIR, general population referent):				
			Miners	9	1.27 (0.58–2.4)		
			Millers	25	1 (0.64–1.47)		
			Total cohort	34	1.06 (0.73–1.48)		
Li and Yu (2002) Shanghai, China Enrolment, 1972/follow-up, 1973–1997 Cohort	1598 (934 men, 664 women); employees of a rubber factory. Exposure assessment method: See Table 2.1.	Urinary bladder, mortality	Department (SMR, Shanghai referent):			Age, sex, calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1. *Other comments*: Unclear follow-up with Zhang et al. (1989).
			Tyre curing and vulcanizing	0	[0 (0–7.4)]		
			Tube curing	1	[5 (0.1–27.9)]		
			Total cohort	1	1.56 (0.5–3.65)		

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bulbulyan et al. (1999) Russian Federation 1979–1993 Cohort	3473 women with ≥ 2-yr employment in two printing plants as of December 1978. Exposure assessment method: See Table 2.1.	Kidney, mortality	Primary employment process (SMR, Moscow referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Compositors	2	4.4 (0.5–15.7)		
			Press operators	1	[1.7 (0–9.3)]		
			Bookbinders	3	1.9 (0.4–5.6)		
			Total cohort	6	1.4 (0.5–3.1)		
		Urinary bladder, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	0	[0 (0–37)]		
			Press operators	2	12.5 (1.5–45.1)		
			Bookbinders	1	[2 (0.1–11.1)]		
			Total cohort	3	2.2 (0.5–6.3)		
		Brain (ICD-9, 191–192), mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	0	[0 (0–9.2)]		
			Press operators	1	[2 (0.1–11.1)]		
			Book binders	3	2.6 (0.5–4.6)		
			Total cohort	4	1.4 (0.5–3.1)		
		Breast, mortality	Primary employment process (SMR, Moscow referent):				
			Compositors	1	[0.3 (0–1.8)]		
			Press operators	3	0.7 (0.2–2.1)		
			Bookbinders	10	1 (0.5–1.9)		
			Total cohort	19	0.7 (0.4–1.1)		

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	Cohort of 4247 women who worked for ≥ 1 yr between 1920 and 1993in a pulp and paper mill in Norway. Exposure assessment method: See Table 2.1.	Kidney, incidence	Duration of employment (SIR, national referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			< 3 yr	2	1.6 (0.19–2.82)		
			≥ 3 yr	8	1.4 (0.61–2.79)		
		Urinary bladder, incidence	Duration of employment (SIR, national referent):				
			< 3 yr	4	3.7 (1–9.38)		
			≥ 3 yr	1	0.2 (0–1.04)		
		Breast, incidence	Duration of employment (SIR, national referent):				
			< 3 yr	22	1.4 (0.86–2.08)		
			≥ 3 yr	70	1.2 (0.91–1.47)		
Boffetta and Colin (2001) (publicly available since 2023) 15 countries Enrolment, varies/follow-up, between 1943 and 1985 through the mid-1990s Cohort	103 773 workers employed for ≥ 1 yr in pulp and paper companies, with complete data. Exposure assessment method: See Table 2.1.	Kidney, mortality	Talc exposure (SMR):			Age, sex, period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Ever-exposed	27	0.87 (0.58–1.27)		
			Ever highly exposed	4	0.68 (0.18–1.73)		
		Urinary bladder, mortality	Talc exposure (SMR):				
			Ever-exposed	34	1.03 (0.71–1.44)		
			Ever highly exposed	4	0.53 (0.15–1.37)		
		Prostate, mortality	Talc exposure (SMR):			Age, period, country	
			Ever-exposed	63	0.83 (0.64–1.06)		
			Ever highly exposed	17	1.3 (0.76–2.08)		
		Testis, mortality	Talc exposure (SMR):				
			Ever-exposed	4	0.78 (0.21–2)		
			Ever highly exposed	0	0 (0–3.33)		

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Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Brain, mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	29	0.88 (0.59–1.26)		
			Ever highly exposed	7	1.02 (0.41–2.1)		
		Thyroid, mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	1	0.29 (0.01–1.59)		
			Ever highly exposed	0	0 (0–5.82)		
		Breast, mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	28	0.86 (0.57–1.24)		
			Ever highly exposed	9	1.04 (0.47–1.97)		
Goldberg et al. (2024) USA Enrolment, 2009–2009/ follow-up, through 30 September 2019 Cohort	45 465 (4049 Black, 2104 Latina, 39 312 White); Prospective SIS cohort of women aged 35–74 yr in the USA or Puerto Rico without breast cancer, but with a sister (or half-sister) with a breast cancer diagnosis. Women missing race/ethnicity or use of personal care products were excluded. Exposure assessment method: See Table 2.1.	Breast, incidence	Use of talcum powder on the genital area at age 10–13 yr, Black or African-American women (HR):			Age, birth cohort, family income level growing up, maximum household education level at age 13 yr	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Did not use	177	1		
			Sometimes	72	0.91 (0.69–1.19)		
			Frequently	25	1.13 (0.74–1.73)		
		Breast, incidence	Use of talcum powder on the genital area at age 10–13 yr, non-Black Hispanic/Latina women (HR):				
			Did not use	111	1		
			Sometimes or frequently	16	0.79 (0.47–1.32)		
		Breast, incidence	Use of talcum powder on the genital area at age 10–13 yr, White women (HR):				
			Did not use	2511	1		
			Sometimes	429	0.92 (0.83–1.02)		
			Frequently	73	1.01 (0.8–1.27)		

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
O'Brien et al. (2024) USA Enrolment, 2003–2009/ follow-up, through September 2021 Cohort	49 806; SIS prospective cohort of women aged 35–74 yr who had a sister previously diagnosed with breast cancer, but who did not have breast cancer themselves at enrolment. Exposure assessment method: See Table 2.1.	Breast (premenopausal), incidence	Genital use of talc (bias corrected) (HR):			Age, race/ ethnicity, attained education, measured BMI at enrolment, self-reported BMI ages 30–39 yr, age at menarche, hormonal birth control use, menopausal status, hormone therapy use, smoking status, alcohol use, geographical region	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Never	NR	1		
			Ever	NR	0.98 (0.81–1.19)		
		Breast (premenopausal), incidence	Frequency of genital use of talc (bias corrected) (HR):				
			Never	NR	1		
			Sometimes	NR	0.89 (0.69–1.14)		
			Frequent	NR	1.1 (0.87–1.39)		
			Trend-test *P*-value, 0.68				
		Breast (postmenopausal), incidence	Genital use of talc (bias corrected) (HR):				
			Never	NR	1		
			Ever	NR	0.96 (0.9–1.03)		
		Breast (postmenopausal), incidence	Frequency of genital use of talc (bias corrected) (HR):				
			Never	NR	1		
			Sometimes	NR	0.97 (0.88–1.06)		
			Frequent	NR	0.96 (0.88–1.05)		
			Trend-test *P*-value, 0.35				
Siemiatycki (1991) Montreal, Canada September 1979 to June 1985 Case–control	Cases: Cancers of the prostate, 449; urinary bladder, 484; kidney, 177; men aged 35–70 yr, residents in Montreal area, with histologically confirmed prostate cancer diagnosis (1979–1985). Cases ascertained through hospital records.	Prostate, incidence	Industrial talc exposure (OR) (90% CI):			Age, family income, cigarette index, ethnic origin, Quetelet index (weight/ height^2), respondent type	*Strengths*: Large case–control study with an exposure assessment for many substances, blinded to the case–control status.
			Never	NR	1		
			Ever	29	1.4 (1–2.1)		
			Ever substantial	7	1.1 (0.5–2.3)		

Table 2.5 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Siemiatycki (1991) (cont.)	Controls: Two controls per case (other cancer controls); men aged 35–70 yr, residents in Montreal area, with cancers other than prostate. This was a case–control study with cases from different cancer sites, so cancer cases could serve as controls for a specific cancer site. Exposure assessment method: Questionnaire.	Urinary bladder, incidence	Industrial talc exposure (OR) (90% CI):			Age, family income, cigarette index, coffee index, respondent type	*Limitations*: The fact that the controls of the case–control studies were cancer cases may have biased the results towards the null for any substance that may have had an effect on several cancer sites. Given the several thousand tests performed, the number of false positive tests is expected to be large. Like most population-based case–control studies on occupational hazards, the exposure assessment is based on questionnaires that collect work histories: this might lead to differential or nondifferential exposure misclassification. Furthermore, no assessment of the type of talc was possible with this approach.
			Never	NR	1		
			Ever	24	1 (0.7–1.5)		
			Ever substantial	4	0.5 (0.2–1.3)		
		Kidney, incidence	Industrial talc exposure (OR) (90% CI):			Age, family income, cigarette index, ethnic origin	
			Never	NR	1		
			Ever	8	1 (0.6–1.9)		
			Ever substantial	1	0.5 (0.1–2.7)		

BMI, body mass index; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; ICD, International Classification of Diseases; INRS, Institut national de recherche et de sécurité; mo, month(s); NR, not reported; OH, Ohio; OR, odds ratio; SIR, standardized incidence ratio; SIS, Sister Study; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States; USA, United States of America; yr, year(s).

subgroup. An excess of bladder cancer was found among millers first employed in 1960–1964, with an SIR of 5.38 (95% CI, 2.16–11.08), based on 7 cases, but not among all millers ever employed in this period. [The Working Group did not have a clear explanation of why an excess risk would be confined to those first employed during that short period of 5 years.] No analyses based on talc exposure levels or by duration of exposure were conducted.

[The Working Group noted that workers in the five cohorts of talc miners (Ciocan et al., 2022a; Fordyce et al., 2019; Wergeland et al., 2017; and Wild, 2000) would be expected to have higher exposures to talc than would workers in the other industries studied, such as paper processing and printing.]

Li and Yu (2002) (Section 2.1.2) found in a mortality study in a cohort of rubber factory workers in China that the SMR for bladder cancer among tube-curing workers was 5.0 (95% CI, 0.1–27.9), but this was based on only 1 death. [The Working Group noted that, although no analyses based on talc exposure were performed in this paper, in other rubber-industry publications the inner-tube workshop has been identified as having talc exposure.]

Bulbulyan et al. (1999) (described in Section 2.1.4(a)) found in a mortality study in a cohort of female printing workers in the Russian Federation that the SMR for bladder cancer was 2.2 (95% CI, 0.5–6.3), based on only 3 deaths. The SMR for kidney cancer was 1.4 (95% CI, 0.5–3.1), based on only 6 deaths. In subgroup analyses conducted for compositors, press operators and bookbinders, no significant excesses were found for kidney cancer. For bladder cancer, an increased SMR was reported for press operators (SMR, 12.5; 95% CI, 1.5–45.1). [The Working Group considered that the numbers for each type of cancer death in each subgroup were too small for meaningful interpretation.] No analyses based on talc exposure levels or duration of exposure were conducted, although the authors noted that talc was used as a filler pigment. [The Working Group noted that occupational exposure in printing processes has been classified by IARC as *possibly carcinogenic to humans* (Group 2B) (IARC, 1996), with *limited* evidence for bladder cancer, but the authors were not able to adjust for carcinogenic exposures in this industry.]

Langseth and Andersen (1999) (see Section 2.1.4(a)) found in a mortality study in a cohort of female pulp and paper mill workers in Norway that the SMR for bladder cancer was 3.7 (95% CI, 1.00–9.38) for those employed for < 3 years, based on 4 deaths. No excess for bladder cancer mortality was found for those employed for ≥ 3 years, but this was based on only 1 death from bladder cancer. The SMRs for death from kidney cancer were not in excess for either employment duration subgroup. No analyses were conducted based on talc exposure levels, although the authors commented that talc was used as a filler in paper production.

Boffetta and Colin (2001), in a pooled study of workers in the pulp and paper industry from 15 countries, found no excess of bladder or kidney cancer among workers ever-exposed to talc or ever highly exposed to talc (see Section 2.1.4(a)).

In a report on several case–control studies, including one on occupational talc exposure in relation to cancers of the urinary bladder and kidney, Siemiatycki (1991) (see Section 2.1.4(b)) found that participants with ever occupational exposure to talc had an OR for urinary bladder of 1.0 (90% CI, 0.7–1.5; 24 cases), and for kidney of 1 (90% CI, 0.6–1.9; 8 cases). [The Working Group noted the several limitations of this study, including small numbers with imprecise estimates, the use of cancer cases as controls (which could cause bias towards the null), the large number of analyses in the study because a very large number of exposures were investigated, and possible recall bias because work histories were collected by questionnaire.]

[The Working Group noted that the studies commonly had small numbers of cases, and no

studies included analyses based on talc exposure levels.]

2.6.2 Other solid cancer sites

See Table 2.5.

The other main solid cancer sites of interest in the studies of talc worker cohorts were prostate, brain, and breast (including two studies in female workers). A single case–control study investigated industrial exposure to talc and prostate cancer.

Monson and Fine (1978) (Section 2.1.2) found in their retrospective study on mortality and nonfatal cancer in male rubber-industry workers that those who had worked in the tyre-building department for ≥ 5 years had an SRR for brain cancer of 4.1, based on only 8 cases, and compared with those in all other work areas. For prostate cancer, the SRR was 2.4 for ≥ 25 years in the final finish work area compared with all other work areas, based on only 4 cases. The authors considered that talc exposure was possible in these departments, but no estimates of talc exposure were included in the analyses.

Ciocan et al. (2022a) (Section 2.1.1(b)) found in a mortality study in a cohort of talc miners and millers in Italy that the SMR for prostate cancer was 0.8 (95% CI, 0.45–1.32; 15 deaths). The SMR for brain and nervous system cancer was 0.7 (95% CI, 0.23–1.64; 5 deaths).

Fordyce et al. (2019) (Section 2.1.1(c)) found in a mortality study in a cohort of US talc miners and millers that the SMR for prostate cancer was [0.908] (95% CI, [0.333–1.977]; 6 deaths). The SMR for central nervous system cancers was [1.809] (95% CI, [0.373–5.285]; 3 deaths). The SMR for breast cancer was [11.098] (95% CI, [0.277–61.836]), based on 1 death.

Wild (2000) (Section 2.1.1(c)) found in a mortality study of talc miners in France that there was no excess of prostate cancer for the whole cohort; the SMR was 0.94 (95% CI, 0.40–1.85). There were no brain cancer deaths. No subgroup analyses for prostate cancer based on talc exposure were reported.

Negri et al. (1989) (Section 2.1.2) found in a mortality study in a cohort of rubber-tyre factory workers that the SMR for brain cancer was 0.88 (95% CI, 0.40–1.67).

Wergeland et al. (2017) (Section 2.1.1(c)) found in their cancer incidence study of a small cohort of talc miners and millers in Norway that the SIR for prostate cancer for the full cohort was 1.06 (95% CI, 0.73–1.48; 34 cancers). When divided into miller and miner subgroups, no increased SIRs were found. No analyses based on talc exposure level were conducted in this study.

Bulbulyan et al. (1999) (Section 2.1.4(a)) found in a mortality study in a cohort of female printing workers in the Russian Federation that the SMR for brain cancer was 1.4 (95% CI, 0.5–3.1; 4 deaths). The SMR for breast cancer was 0.7 (95% CI, 0.4–1.1; 19 deaths). The only worker subgroup in which the number of breast cancer deaths reached double digits was the bookbinder subgroup, for which the SMR was 1.0 (95% CI, 0.5–1.9; 10 deaths). [The Working Group considered that numbers of deaths in other worker subgroups were too small for meaningful analysis.]

Langseth and Andersen (1999) (Section 2.1.4(a)) found in a mortality study in a cohort of female pulp and paper mill workers in Norway that the SMR for breast cancer for those employed for < 3 years was 1.4 (95% CI, 0.86–2.08; 22 deaths) and for the group employed for ≥ 3 years it was 1.2 (95% CI, 0.91–1.47; 70 deaths). [The Working Group noted the similar findings in both employment duration subgroups and the wide confidence intervals.]

In a pooled study of workers in the pulp and paper industry from 15 countries, Boffetta and Colin (2001) (Section 2.1.4(a)) reported an SMR for prostate cancer of 0.83 (95% CI, 0.64–1.06) for those ever-exposed to talc and an SMR of 1.30 (95% CI, 0.76–2.08) for those ever highly exposed to talc. For brain cancer, they reported an SMR of

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0.88 (95% CI, 0.59–1.26) for those ever-exposed to talc and an SMR of 1.02 (95% CI, 0.41–2.10) for those ever highly exposed to talc. For breast cancer, the SMR was 0.86 (95% CI, 0.57–1.24) for those ever-exposed to talc and 1.04 (95% CI, 0.47–1.97) for those ever highly exposed to talc. For testis and thyroid cancer, the SMRs for ever-exposed were 0.78 (95% CI, 0.21–2.00; 4 deaths) and 0.29 (95% CI, 0.01–1.59; 1 death), respectively.

Goldberg et al. (2024) (Section 2.1.5(a)) reported HRs for breast cancer incidence from the Sister Study cohort, for sometimes and frequent use of talcum powder on the genital area, compared with never users, separately by race/ethnicity. For White women, breast cancer risk was not elevated for sometimes users (HR, 0.92; 95% CI, 0.83–1.02) or frequent users (HR, 1.01; 95% CI, 0.80–1.27). For Black or African-American women, breast cancer risk was not elevated for sometimes users (HR, 0.91; 95% CI, 0.69–1.19), but was for frequent users (HR, 1.13; 95% CI, 0.74–1.73). For non-Black Hispanic women, sometimes or frequent use was not associated with increased risk (HR, 0.79; 95% CI, 0.47–1.32). The analysis by O'Brien et al. (2024) (Section 2.1.5(a)), also within the Sister Study cohort, found no association for genital use of talc and pre- or postmenopausal breast cancer risk.

In a case–control study on prostate cancer and industrial exposure to talc, Siemiatycki (1991) (Section 2.1.4 (b)) found that men with ever industrial exposure to talc had an OR of 1.4 (90% CI, 1.0–2.1; 29 cases), whereas men with substantial industrial exposure to talc had an OR of 1.1 (90% CI, 0.5–2.3; 7 cases only). [The Working Group noted several limitations of this study, including the small numbers with imprecise estimates, the use of cancer cases as controls (which could bias towards the null), the large number of analyses in the study because a very large number of exposures were investigated, and possible recall bias because work histories were collected by questionnaire among men with disease, although this concern was mitigated by the use of workers with other cancers as controls.]

2.6.3 Lymphatic and haematopoietic cancers

See Table 2.6.

In 11 studies (six cohorts, one case–control) on industries with the potential for occupational exposure to talc, results were reported for tumours of lymphatic and haematopoietic tissue.

Honda et al. (2002) (Section 2.1.1(a)) found in a mortality study in a cohort of talc miners and millers in the Gouverneur District, New York State, USA, that the SMR for lymphatic and haemopoietic cancers was [1.92] (95% CI, [0.77–3.95]), but this was based on only 7 deaths.

Monson and Fine (1978) (see Section 2.1.2) found in their retrospective study of mortality and nonfatal cancer in male rubber-industry workers that the workers who had worked in the tyre-building department for ≥ 5 years had an RR of 2.5 for lymphatic cancer, based on 8 cases, and 1.6 for leukaemia, based on 12 cases. The authors considered that talc exposure was possible in that department, but no estimates of talc exposure were included in the analyses. [The Working Group noted that the authors focused their discussion on these findings on exposure to benzene and other solvents.]

Ciocan et al. (2022a) (Section 2.1.1(b)) found in a mortality study in a cohort of talc miners and millers in Italy that the SMR for leukaemia was 1.04 (95% CI, 0.47–1.97), based on 9 deaths. The SMR for lymphoma (type not specified) was 0.49 (95% CI, 0.13–1.27), based on 4 deaths. No deaths from multiple myeloma were observed.

Fordyce et al. (2019) (Section 2.1.1(c)) found in a mortality study in a cohort of talc miners and millers in Vermont, USA, that the SMR for NHL was [0.412] (95% CI, [0.01–2.296]), but this was based on only 1 death. No deaths from leukaemia were reported.

Table 2.6 Epidemiological studies on exposure to talc and cancers of lymphatic and haematopoietic tissue

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Honda et al. (2002) USA Enrolment, 1948–1989/follow-up, 1950–1989 Cohort	809 White men who worked at a talc mining and milling facility in upstate New York for ≥ 1 day between 1948 and 1989, whose vital status was known in 1950 onwards. (Study was restricted to White men because of low prevalence of other race/ethnicities.) Exposure assessment method: See Table 2.1.	Lymphatic and haematopoietic, mortality	SMR (regional referent): Total cohort	7	[1.92 (0.77–3.95)]	Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
Monson and Fine (1978) Akron (OH), USA Enrolment, early 1940s to 1 July 1971/follow-up, 1940 through 30 June 1976 (mortality) and 1964–1974 (diagnoses) Cohort	13 570; White men, members of local union and employed (≥ 5 yr) in Akron in tyres or rubber manufacturing. Follow-up (1940–1976) through death certificates (any cancer listed in the death certificate, even those not listed as underlying cause of death). For the period 1964–74 incident cancer identified through tumour registry of four Akron-based hospitals. Exposure assessment method: See Table 2.1.	Lymphatic, mortality and incidence	Work area and minimum years in area (SRR): All other work areas Tyre building, 5+ yr	 19 8	 1 2.5	Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
		Leukaemia, mortality and incidence	Work area and minimum years in area (SRR): All other work areas Calendering, 5+ yr Tyre curing, 15+ yr Tyre building, 5+ yr Elevators, 5+ yr Tubes, 5+ yr Rubber fabrics, 0+ yr	 38 8 8 12 4 4 4	 1 3.6 3.1 1.6 2.9 2.5 3.5		

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ciocan et al. (2022a) Val Chisone, north Italy Enrolment, 1946–1995/ follow-up, through 31 January 2020 Cohort	1749 (1184 miners, 565 millers); men employed for ≥ 1 mo in the talc mine or mill in Val Chisone between 1946 and 1995. Exposure assessment method: See Table 2.1.	Lymphoma (type not specified; ICD-9, 200–202), mortality	SMR (regional referent): Total cohort	4	0.49 (0.13–1.27)	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Regional rates were used for the period 1970–2020; national rates were used before 1970.
		Multiple myeloma, mortality	SMR (regional referent): Total cohort	0	[0 (0–1.1)]		
		Leukaemia, mortality	SMR (regional referent): Total cohort	9	1.04 (0.47–1.97)		
Fordyce et al. (2019) Vermont, USA Enrolment, 1940–1969 (initial), 1930–1983 (expanded)/follow-up, 1940–2012 Cohort	427; all White male Vermont talc workers who had worked ≥ 1 yr from 1940–1969 (initial enrolment) or 1930–1940 or 1970–1983 (expanded enrolment). These corresponded to all talc workers who participated in the Vermont Health Department radiograph programme (workers were offered annual chest radiographs from 1930 to 1983). Exposure assessment method: See Table 2.1.	NHL (ICD-10, C82, C83.0–C84.9, C85.1–C85.9), mortality	SMR (US referent): Total cohort	1	[0.412 (0.01–2.296)]	NR	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: Lack of exposure estimates and exposure–response analyses. Additional limitations in Table 2.1. *Other comments*: Covariates controlled were not reported but probably included age and calendar period, as a life-table programme and US rates were used to estimate expected numbers of deaths.
		Leukaemia and aleukaemia (ICD-10, C91-C95), mortality	SMR (US referent): Total cohort	0	[0 (0–1.352)]	NR	

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wild (2000) France Enrolment, 1945–1994/follow-up, 1968–1996 Cohort	1070; men employed continuously for ≥ 1 yr between 1945 and 1994 in a talc mine in the French Pyrenees (this is the French cohort in Wild et al. (2002)). Cause of death from national registry available only from 1968. Cause of death before 1968 was obtained from an earlier report of the cohort. Results were limited to 1070 men and excluded 90 women described in the report. Exposure assessment method: See Wild et al. (2002) in Table 2.1.	Lymphoma (type not specified), mortality Leukaemia, mortality	SMR (regional reference): French cohort SMR (regional reference): French cohort	2 3	0.85 (0.1–3.07) 1.19 (0.24–3.46)	Age, calendar period	*Strengths*: Long follow-up. *Limitations*: Smoking data not available for the cohort analysis. Small sample size. *Other comments*: In Wild et al. (2002), only stomach, mesothelioma, and lung cancers are reported; other data were extracted from this INRS report.
Thomas and Stewart (1987) USA Enrolment, 1939–1966/follow-up, 1940 through 1 January 1981 Cohort	2055 White men employed for ≥ 1 yr (1939–1966) in three plants of a single US company producing ceramic plumbing fixtures. Exposure assessment method: See Table 2.1.	Lymphatic and haematopoietic: ICD-8 200–209, mortality	SMR (US referent): Total cohort	14	[1.19 (0.65–1.99)]	Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
Negri et al. (1989) Italy 1946–1981 Cohort	6629; all men who worked for ≥ 1 yr between 1946 and 1981 in a rubber tyre factory in Turin district. Exposure assessment method: See Table 2.1.	Lymphoma (type not specified), mortality Leukaemia, mortality	SMR (national referent): Total cohort SMR (national referent): Total cohort	7 8	0.74 (0.3–1.53) 0.91 (0.39–1.79)	Age, calendar period	*Strengths*: See Table 2.1. *Limitations*: See Table 2.1.

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bulbulyan et al. (1999) the Russian Federation 1979–1993 Cohort	3473; women with minimum 2-year employment in two printing plants as of December 1978. Exposure assessment method: See Table 2.1.	Leukaemia: (ICD-9, 191–192), mortality	Primary employment process (SMR, Moscow referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Compositors	0	[0 (0–6.1)]		
			Press operators	0	[0 (0–5.3)]		
			Bookbinders	3	1.6 (0.3–4.6)		
			Total cohort	4	0.8 (0.2–2)		
Langseth and Andersen (1999) Norway Enrolment, 1920–1993/follow-up, 1953–1993 Cohort	Cohort of 4247 women who for ≥ 1 yr between 1920 and 1993 worked in a pulp and paper mill in Norway. Exposure assessment method: See Table 2.1.	Hodgkin lymphoma, incidence	Length of employment (SIR, national referent):			Age and calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			< 3 yr	0	[0 (0–7.4)]		
			≥ 3 yr	1	0.6 (0.02–3.59)		
		NHL, incidence	Length of employment (SIR, national referent):				
			< 3 yr	1	0.5 (0.01–2.86)		
			≥ 3 yr	6	0.8 (0.3–1.75)		
		Multiple myeloma, incidence	Length of employment (SIR, national referent):				
			< 3 yr	3	4.4 (0.91–12.86)		
			≥ 3 yr	4	1.1 (0.3–2.82)		
		Leukaemia	Length of employment (SIR, national referent):				
			< 3 yr	0	[0 (0–3.4)]		
			≥ 3 yr	2	0.4 (0.05–1.51)		
Boffetta and Colin (2001) (publicly available since 2023) 15 countries Enrolment, varies/follow-up, between 1943 and 1985 through the mid-1990s Cohort	103 773 workers employed for ≥ 1 yr in pulp and paper companies with complete data Exposure assessment method: See Table 2.1.	Lymphatic and haematopoietic (ICD-9, 200–208), mortality	Talc exposure (SMR):			Age, sex, period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			Ever-exposed	84	0.92 (0.73–1.14)		
			Ever highly exposed	18	1 (0.59–1.58)		
		Lymphatic and haematopoietic (ICD-9, 200–208), mortality	Talc exposure, men (SMR):			Age, period, country	
			Ever-exposed	67	0.86 (0.66–1.09)		
			Ever highly exposed	15	0.98 (0.55–1.62)		

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boffetta and Colin (2001) (publicly available since 2023) (cont.)		Lymphatic and haematopoietic: ICD-9 200–208, mortality	Talc exposure, women (SMR):			Age, period, country	
			Ever-exposed	17	1.27 (0.74–2.04)		
			Ever highly exposed	3	1.08 (0.22–3.17)		
		NHL (ICD-9, 200, 202), mortality	Talc exposure (SMR):			Age, sex, period, country	
			Ever-exposed	19	0.68 (0.41–1.06)		
			Ever highly exposed	3	0.57 (0.12–1.67)		
		Hodgkin lymphoma (ICD-9, 201), mortality	Talc exposure (SMR):				
			Ever-exposed	12	1.26 (0.65–2.19)		
			Ever highly exposed	4	2.12 (0.58–5.44)		
		Multiple myeloma (ICD-9 203), mortality	Talc exposure (SMR):				
			Ever-exposed	16	0.97 (0.56–1.58)		
			Ever highly exposed	2	0.73 (0.09–2.62)		
		Leukaemia and aleukaemia (ICD-9, 204–208), mortality	Talc exposure (SMR):				
			Ever-exposed	37	1 (0.71–1.38)		
			Ever highly exposed	9	1.14 (0.52–2.16)		
		Leukaemia (lymphoid; ICD-9, 204), mortality	Talc exposure (SMR):				
			Ever-exposed	5	0.55 (0.18–1.27)		
			Ever highly exposed	0	0 (0–1.9)		
		Leukaemia (myeloid; ICD-9, 205), mortality	Talc exposure (SMR):				
			Ever-exposed	19	1.17 (0.71–1.83)		
			Ever highly exposed	6	1.74 (0.64–3.78)		

Table 2.6 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Siemiatycki (1991) Montreal, Canada September 1979 to June 1985 Case–control	Cases: NHL, 215; men aged 35–70 yr, residents in Montreal area, with histologically confirmed prostate cancer diagnosis (1979–1985). Cases ascertained through hospital records. Controls: Two controls per case (other cancer controls); men aged 35–70 yr, residents in Montreal area, with cancers other than prostate. This was a case–control study with cases from different cancer sites, so cancer cases could serve as controls for a specific cancer site.	NHL, incidence	Industrial talc exposure (OR) (90% CI):			Age, family income, cigarette index	*Strengths*: Large case–control study with an exposure assessment for many substances, blinded to case–control status. *Limitations*: The fact that the controls of the case–control studies were cancer cases may have biased the results towards the null for any substance that may have an effect on several cancer sites. Given the several thousand tests performed, the number of false positive tests is expected to be large. Like most population-based case–control studies on occupational hazards, the exposure assessment was based on questionnaires that collected work histories: this might have led to differential or nondifferential exposure misclassification. Furthermore, no assessment of the type of talc was possible with this approach.
			Never	NR	1		
			Ever	11	1.2 (0.7–2)		
			Ever substantial	5	2.3 (1–5.2)		
		NHL, incidence	Industrial talc exposure, French-Canadians only (OR) (90% CI):			Age, family income, cigarette index	
			Never	NR	1		
			Ever	9	1.6 (0.9–2.9)		
			Ever substantial	4	2.7 (1.1–6.9)		

CI, confidence interval; ICD, International Classification of Diseases; INRS, Institut National de Recherche et de Sécurité; mo, month(s); NHL, non-Hodgkin lymphoma; NR, not reported; OH, Ohio; OR, odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SRR, standardized rate ratio; US, United States; USA, United States of America; yr, year(s).

Wild (2000) (Section 2.1.1(c)) found in a mortality study of talc miners in France that there was no excess of lymphoma or leukaemia for the whole cohort. No subgroup analyses based on talc exposure were reported for haematopoietic cancers.

Thomas and Stewart (1987) (see Section 2.1.3) found in a mortality study in a cohort of US workers producing ceramic plumbing fixtures that the SMR for lymphatic and haematopoietic tumours was [1.19] (95% CI, [0.65–1.99]; 14 deaths).

Negri et al. (1989) (Section 2.1.2) found in a mortality study in a cohort of rubber-industry workers in Italy that the SMR for lymphoma was 0.74 (95% CI, 0.30–1.53; 7 deaths). For leukaemia, the SMR was 0.91 (95% CI, 0.39–1.97; 8 deaths).

Bulbulyan et al. (1999) (Section 2.1.4(a)) found in a mortality study in a cohort of female printing workers in the Russian Federation that the SMR for leukaemia was 0.8 (95% CI, 0.2–2.0; 4 deaths). While subgroup analyses were conducted for compositors, press operators and bookbinders, no excesses were found. [The Working Group considered that the numbers for each type of death from haematopoietic cancer in each subgroup were too small for meaningful interpretation.]

Langseth and Andersen (1999) (Section 2.1.4(a)) found in their incidence study in a cohort of female pulp and paper mill workers in Norway that the SIR for leukaemia for those who had worked for ≥ 3 years was 0.4 (95% CI, 0.05–1.51; 2deaths). For Hodgkin lymphoma, only 6 deaths (only 1 death in long-term workers) were reported, and the SIR was not elevated. There was no evidence of an increased risk of leukaemia or lymphoma among workers employed for > 3 years.

Boffetta and Colin (2001) (Section 2.1.4(a)) found in a pooled study of workers in the pulp and paper industry from 15 countries that there was no excess of cancers of lymphatic and haematopoietic tissue among workers ever-exposed to talc (SMR, 0.92; 95% CI, 0.73–1.14) or ever highly exposed to talc (SMR, 1.00; 95% CI, 0.59–1.58). When analysed by sex or by subgroups of lymphoma and leukaemia, no excess SMRs were found.

Siemiatycki (1991) (Section 2.1.4(b)) reported the results of a case–control study on several cancer types, including NHL. The OR for ever industrial exposure to talc was 1.2 (90% CI, 0.7–2; 11 NHL cases), while those with substantial industrial talc exposure had an OR of 2.3 (90% CI, 1–5.2; 5 NHL cases only). [The Working Group noted the several limitations of this study, including small numbers with imprecise estimates, the use of cancer cases as controls (which could bias results towards the null), the large number of analyses in the study (because a very large number of exposures were investigated), and possible differential exposure misclassification owing to the collection of work histories by questionnaire after disease occurrence, although this concern was mitigated by the use of workers with other cancers as controls.]

2.7 Evidence synthesis for cancer in humans

2.7.1 Studies evaluated

Associations between talc exposure and human cancer have been investigated in two main groups of epidemiological studies. The first group of studies comprises mainly occupational cohort studies in the following industries: talc mining, milling, and processing (Fu and Zhang, 1992; Honda et al., 2002; Wild et al., 2002; Finkelstein, 2012; Wergeland et al., 2017; Fordyce et al., 2019; Ciocan et al., 2022a; Ierardi et al., 2022), the rubber industry (Monson and Fine, 1978; Blum et al., 1979; Negri et al., 1989; Zhang et al., 1989; Li and Yu, 1999, 2002; Straif et al., 2000), the printing and pulp and paper industries (Bulbulyan et al., 1999; Boffetta and Colin, 2001; Langseth and Andersen, 1999; Langseth and Kjaerheim, 2004),

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and the pottery, ceramic, cement, and fibreglass industries (Thomas and Stewart, 1987; Nie et al., 1992; Chiazze et al., 1993). Some of these cohort studies used a nested case–control study design (Blum et al., 1979; Chiazze et al., 1993; Wild et al., 2002; Langseth and Kjaerheim, 2004). There was one hospital-based case–control study of occupational exposures to industrial talc (Hartge and Stewart, 1994). Three population-based case–control studies in Canada investigated the association between several cancers and occupational exposure to talc, as one of many occupational exposures (Siemiatycki, 1991; Ramanakumar et al., 2008; Leung et al., 2023).

Some of these occupational studies were published before the last evaluation of "talc not containing asbestos fibres" in *IARC Monographs* Volume 93, which took place during the meeting in 2006 (Baan et al., 2006), with publication of the full volume in 2010 (IARC, 2010). Some cohorts have had updates in follow-up for cancer incidence or mortality since the Volume 93 meeting. These occupational studies covered a wide range of cancers, with the prime focus being on cancers of the lung, urinary tract, digestive system, lymphatic and haemopoietic tissues, brain, ovary, breast, and prostate.

The next group of studies investigated the application of talc for perineal and other personal uses and cancer. This group of studies comprised population-based cohort studies (Gertig et al., 2000; Karageorgi et al., 2010; Crawford et al., 2012; Houghton et al., 2014; Gonzalez et al., 2016; O'Brien et al., 2019, 2021b, 2024; Goldberg et al., 2024; O'Brien et al., 2024), pooled cohort studies (O'Brien et al., 2020, 2021a), registry-based case–control studies (Harlow and Weiss, 1989; Chen et al., 1992; Shushan et al., 1996; Chang and Risch, 1997; Cook et al., 1997; Faerstein et al., 2001; Mills et al., 2004; Rosenblatt et al., 2011; Kurta et al., 2012; Neill et al., 2012; Wu et al., 2015; Cramer et al., 2016; Schildkraut et al., 2016), pooled registry-based case–control studies (Terry et al., 2013; Davis et al., 2021; Peres et al., 2021; Phung et al., 2022), and other case–control studies (Hartge et al., 1983; Whittemore et al., 1988; Booth et al., 1989; Rosenblatt et al., 1992; Tzonou et al., 1993; Cramer and Xu, 1995; Green et al., 1997; Godard et al., 1998; Wong et al., 1999; Ness et al., 2000). The cancer types of prime interest were ovary, corpus uteri, cervix, and breast. Three of the four cohort studies were published after the Volume 93 meeting, whereas most of the case–control studies were published before.

Only one study, published after Volume 93, assessed the medical use of talc (Chang et al., 2019), investigating stomach cancer in people from Taiwan, China, who had ingested herbal products containing talc.

The Working Group also noted that "talc containing asbestos" was evaluated in *IARC Monographs* Volume 100C within the evaluation of asbestos (see "General Remarks", p. 38, and "1.1 Identification of the agent", p. 219, of IARC, 2012a). Asbestos was classified as *carcinogenic to humans* (Group 1), on the basis of *sufficient* evidence for several cancer types (lung, mesothelium, larynx, and ovary) in humans. In Volume 100C, asbestos contamination of industrial and cosmetic talc was well documented, and the Working Group concluded that talc containing asbestos should be classified as asbestos. As a result, the Working Group for the present volume considered that occupational studies in talc mining and milling for which the talc ore mined had been shown to be asbestos-free were more informative for an evaluation of talc than studies for which there was evidence of asbestos contamination. For all other studies, the Working Group considered the possible impact of contamination of talc with asbestos as a confounder in any associations identified.

2.7.2 Quality of exposure assessment and bias from exposure misclassification

(a) Occupational studies

Exposure assessment in occupational studies of cancer in workers is a critically important factor in assessing the validity of findings from these studies. Despite this, exposure assessment methods often vary widely. Poorer quality exposure assessment includes methods such as self-report, which is prone to error, especially where information is retrospectively collected and there is a long latency between exposure and the outcome being investigated, such as cancer. In addition, workers often did not know the specifics of the substances they were exposed to, which can add to exposure misclassification. Better-quality exposure assessment is done in studies that rely on estimation of exposures at the job or task level, rather than at the department or site level. Knowing the details of workers' job histories can allow the use of JEMs to overcome the problem of self-report of exposure. Higher quality JEMs are usually those for which the researcher was able to access employment and job records, rather than job histories that were self-reported by the participants. Expert assessment is often used to classify jobs within the JEM. Other higher quality exposure assessment methods are those for which the researcher was able to access quantitative exposure information, such as air monitoring data, for the exposure(s) of interest. Unfortunately, most occupational studies are retrospective, so even these high-quality exposure assessment methods often need to rely on incomplete retrospective exposure data. In such instances, historical modelling can be used.

The occupational studies investigating cancer and talc exposure among workers have used a variety of exposure assessment methods. The studies are from China, Europe, and the USA, and there was large variation in the quality of these methods. The studies on talc mining and milling were considered to have the highest prevalence of talc exposure among the workforce and were best-characterized in terms of possible asbestos exposure (see Section 1.6.1(a)). Of the studies on the talc mining and milling industry, two studies used a JEM for dust exposure (Honda et al., 2002; Wild et al., 2002) and validated this with historical exposure concentrations, although these were not usually available for earlier years of the studies. Most other studies based their analysis on the whole cohort only, using department and/or duration of employment, but these studies provided no analyses based on talc exposure. On the basis of analyses of the ore being mined, some of these talc mining studies have been documented to mine talc that is free of asbestos, some were certain to contain talc, and others were uncertain (see Table 1.1).

There are several downstream industries that have used talc in their production process and that have been the subject of studies of cancer in workers. In studies of workers in these industries, methods of talc exposure assessment have been of variable quality and generally of lower quality than those used in the talc mining and milling industry. There have been several studies of workers in the rubber industry, although no new papers have been published since *IARC Monographs* Volume 93. The exposure assessment in this industry is complicated by the fact that there are many additional exposures, some of which have been found to be carcinogenic in humans, such as 2-naphthylamine (IARC, 2012b). In most of these studies, analyses were based on work area, duration of employment, and year of first employment, but usually no metrics based on talc exposure were used in these analyses. A couple of these studies examined risks among workers in the inner-tube workshop, where jobs were thought to involve talc exposure, but no quantitative metrics for talc were used in the analyses. Straif et al. (2000), in their retrospective study of rubber workers from five rubber plants in Germany, used semiquantitative

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retrospective estimates of exposure to talc and other compounds in their analyses, resulting in the highest quality exposure assessment in the rubber-industry studies. The source of talc used in these downstream industries was rarely documented; therefore, there is uncertainty about the presence and magnitude of asbestos contamination.

Four studies investigated cancer in the printing and pulp and paper industries but, as with other talc-related downstream industries, exposure assessment methods were of varying quality, usually with no quantitative or even qualitative assessment of talc exposure (Bulbulyan et al., 1999; Boffetta and Colin, 2001; Langseth and Andersen, 1999; Langseth and Kjaerheim, 2004). Boffetta and Colin (2001) conducted a large IARC-coordinated pooling study of workers in pulp and paper companies in 15 countries. They developed a specific exposure matrix based on talc data at the department level, using both the prevalence and level of exposure. Data at the job level were not available for all plants, which was a limitation. Studies of talc exposure and cancer in other downstream industries were limited to one or two studies, which had similar limitations in exposure assessment as those for the rubber and pulp and paper industries.

Three studies on talc exposure and human cancer have been published using data from the Montreal occupational case–control study, in which a very large number of workplace exposures and several types of cancer were considered (Siemiatycki, 1991; Ramanakumar et al., 2008; Leung et al., 2023). The authors used a high-quality exposure assessment method based on work history, an interview to obtain a detailed description of each job, and a final coding by experienced industrial hygienists with respect to exposures to a large list of substances, including industrial talc. The main limitation of these studies was that there was a very low prevalence of talc exposure, which reduced the power of the study, leading to imprecise risk estimates. The possibility of multiple correlated exposures was also a concern.

(b) Non-occupational studies

Details on the assessment of non-occupational talc exposure are summarized in Section 1.6.1. Most of the studies focused on perineal and genital application of talc and other body powder products. Other exposure routes were assessed occasionally, including ingestion of talc contained in medical products (Chang et al., 2019), and exposure of talc to other areas of the body, which was primarily evaluated as a comparison to genital application of talc.

In all studies evaluating perineal exposure to talc, self-reported exposure assessment was retrospective from the time of the survey or interview. Depending on the study type and participant age at survey or interview, retrospective exposure assessment often covered a long period in an individual's lifetime. In case–control studies, only a single exposure assessment was conducted at around the time of diagnosis. In cohort studies, repeated assessments of talc or body powder exposure were possible but were rarely conducted. One exception was the Sister Study, in which an additional questionnaire was included during follow-up to assess data on genital exposure to talc more comprehensively (O'Brien et al., 2024).

Examples of the diversity of questions asked in case–control or cohort studies are whether participants "ever commonly used talcum, baby powder or deodorizing powder", whether "talcum powder was applied to a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area", or whether participants "had ever used powder on their "private parts (genital areas)" (O'Brien et al., 2020). Variation in the exposure questions asked made it more difficult to compare results across studies and to perform meta-analyses based on consistent exposure metrics.

Most body powder products included talc, but talc-free alternatives such as cornstarch have existed for four decades. There was some evidence from one study that cornstarch was used in much lower proportions than was talc (Cramer et al., 2016). The presence and concentration of talc can vary from brand to brand and within brands over time (Section 1.4.1(e)). Owing to the possible co-occurrence of talc with asbestos in talc mines, it is important to consider whether cosmetic talc products may have been contaminated with asbestos. In the 1960s, testing of talc products was initiated and showed that fibres comprised 8–30% of all tested talc products, with a not-clearly-quantified subset of these fibres being asbestos fibres (see Section 1.4.1(e)). In the 1970s, testing showed that 40% of tested products in the USA had some level of asbestos contamination (Rosner et al., 2019). In the USA, the J4-1 testing approach was adopted voluntarily by the Cosmetic, Toiletry and Fragrance Association in 1976 (Zazenski et al., 1995) and measures asbestos fibres at an LOD of about 0.5%. This means that users of tested products could be exposed to non-trivial amounts of asbestos fibres even for products classified as having "non-detected" asbestos contamination (Rosner et al., 2019; US FDA, 2020). Various attempts to more strictly regulate the purity of talc products in the USA were not successful and, consequently, some talc products were found to be contaminated with asbestos fibres as recently as 2019 (US FDA, 2019).

The retrospective self-assessment of body powder use, with limited information on duration and dose, poses additional challenges for exposure assessment. Different studies used different minimal exposure thresholds to define "any use", "ever use", or "frequent use", ranging from no minimum duration in most studies to requiring ≥ 1 year of use. Estimates of the prevalence of perineal use of talc or body powder varied widely across studies, which may in part reflect true exposure differences, but also differences in exposure assessment and reporting. Rosenblatt et al. (1998) reported that smoking, alcohol use, and increased BMI were associated with higher talc use. Generally, higher prevalence of talc/body powder use has been reported for African-American versus White women in USA-based studies (Kim et al., 2010; Wu et al., 2015; Schildkraut et al., 2016; Davis et al., 2021).

A further limitation of exposure assessment in observational studies is that exposure over the entire lifetime may not be remembered well. An important concern is that recollection of prior use may differ by case–control status, with cases being more likely to remember use of talc or body powder than are controls, which could lead to differential exposure misclassification referred to as recall bias. Raised awareness about a potential role of talc in ovarian cancer may have further contributed to this since 2009, when court cases related to talc use and ovarian cancer risk were reported in the news. Since there were no studies available to the Working Group with an external referent for talc/body powder use, it is difficult to estimate the possible extent of such a bias. The study by O'Brien et al. (2023) provides some insights. They compared the answers to questions on talc use in the questionnaire used in the Sister Study at baseline and at follow-up several years later after publicity about the possibility that talc causes cancer. Although agreement was about 90% and the kappa was moderate (κ, 0.62), the only subgroup for which the proportion of users increased between enrolment and follow-up were the women who developed ovarian cancer during follow-up and who answered the follow-up question on talc use.

In cohort studies, exposure assessment is typically performed before the outcome occurs, eliminating the risk of differential misclassification. However, in many cohort studies, talc/body powder exposure assessment was conducted only at a single time point and may not have captured the full lifetime exposure, which could lead to incomplete, nondifferential exposure

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misclassification. Additionally, many cohort studies used more limited exposure assessment, affecting the ability to study dose and duration of exposure. This limitation in the exposure data collected also led to challenges when trying to account for latency periods for the development of cancer after exposure.

Estimating exposure dose is difficult for perineal application of talc or body powder, since the amount of powder applied can vary substantially between individuals and between different types of applications (e.g. direct application, application on sanitary napkins, application in conjunction with douching). Dose was typically reported as number of applications per week, whereas duration was assessed in some studies, usually reported as number of years of use. Few studies reported on dose–response relations.

In summary, exposure assessment in non-occupational studies has several important limitations for genital application of talc: First, there is uncertainty about the specific body powder products evaluated in observational studies; such products may have included different concentrations of talc, and possible contamination with asbestos makes assessment of talc exposure difficult. Second, different types of misclassification may occur depending on study type, with differential exposure misclassification observed in case–control studies and nondifferential exposure misclassification in cohort studies. Third, limitations in the exposure assessment and difficulty in assessing specific talc doses because of nonstandardized application reduce the ability to evaluate dose–response relations and account for latency period.

2.7.3 Confounding and selection bias

An important confounding factor for some of the cancers being evaluated, including mesothelioma and cancers of the lung and ovary, is contamination of industrial and cosmetic talc with asbestos. Asbestos is an IARC Group 1 carcinogen and a known cause of mesothelioma and cancers of the lung, larynx, and ovary (Volume 100C; IARC, 2012a), which are cancers of prime interest in this evaluation. Therefore, asbestos is both associated with exposure to talc and a causal factor for some of the outcomes being investigated in the present monograph. It is well documented that contamination of talc with asbestos and other fibres was common in the talc mining industry. Although the talc source and therefore the presence of asbestos contamination is not well documented for the downstream industries, the fact that these industries are likely to have used talc from a variety of sources makes it probable that contamination of talc by asbestos has been present. For mining and milling and industrial uses of talc, Table 1.1 summarizes the available evidence for the detection of asbestos in mineralogical deposits from which talc is mined. This information was used by the Working Group to assess the potential for asbestos contamination of the talc mined by the workers in the cohorts evaluated in the present monograph.

Regarding asbestos contamination of talc in cosmetic products (including body powder), the source of the talc was rarely identified; therefore, asbestos contamination could not be excluded. The J4-1 industry standard for assessing contamination of talc products in the USA was voluntary and had limited sensitivity for ruling out contamination (Rosner et al., 2019). Several studies analysing the contents of cosmetic products, including body powder, since the voluntary standard was introduced, have found asbestos contamination was present as recently as 2019 (see Section 1.4.1(e)) (US FDA, 2019). Since asbestos contamination has been detected in most talc mining industries and mines, in downstream industries, and in body powder, asbestos (through contaminated talc) is likely to be a confounder for many of the studies in this evaluation investigating cancers known to be caused by asbestos.

Smoking is a known risk factor for several cancers, including lung, stomach, ovary, and uterine cervix, and may be more prevalent in workers involved in industries using talc and in women using talcum powder by perineal application, so adjustment for this is important for smoking-related cancers. Asbestos, some dietary factors (e.g. consumption of processed meat), or *H. pylori* infection can also be risk factors for stomach cancer and may act as a confounder for this cancer. Alcohol consumption is a risk factor for several cancers, including several cancers of the digestive system (oesophagus, colorectum, liver) and respiratory tract (larynx), so adjustment for this is important for alcohol-related cancers.

Ovarian cancer has several risk factors, including no pregnancies or later age at first pregnancy, low parity, hormone replacement therapy after menopause, and a family history of ovarian or breast cancer. Fertility treatment is also thought to increase the risk of some types of ovarian cancer, as possibly do some dietary factors. There is some evidence that early age at birth of first child, breastfeeding, having a hysterectomy, and having a tubal ligation can reduce the risk of ovarian cancer (PDQ Screening and Prevention Editorial Board, 2024; Webb and Jordan, 2024). Therefore, adjustment for these factors can be important in reducing potential confounding effects. Lack of excess body fatness has been identified as a protective factor for ovarian cancer (*IARC Handbooks of Cancer Prevention* Volume 16; IARC, 2018), but it is less strongly related to ovarian cancer than to uterine cancer, and emerging evidence suggests that obesity is associated with only certain subtypes of epithelial ovarian cancer (IARC, 2018). In addition to obesity (which is a strong risk factor for uterine cancer, particularly endometrioid), several of the risk factors for ovarian cancer are also risk factors for uterine cancer (IARC, 2018).

The HWE occurs because workers are usually healthier than the general population with which they are compared in external analyses. In this situation, bias can occur whereby healthier workers may be more likely to work in jobs known to have possible adverse impacts on health than are workers with pre-existing health conditions. In workplaces involving exposure to talc and other possible airborne hazards, this may mean that workers with pre-existing respiratory conditions or smokers may be less likely to work in this industry because of irritant and other respiratory hazards and the need to wear respirators. Therefore, the HWE could bias estimates downwards, especially for external analyses using cancer in population data as the reference population to estimate SMRs or SIRs, unless this selection effect is taken into account. To overcome the HWE, occupational cohort studies often include internal analyses comparing subgroups within the cohort that have varying levels of exposure. No HWE bias analyses have been done for any of the occupational studies evaluated.

The HWSB is also an important source of possible bias in occupational studies (Picciotto and Hertz-Picciotto, 2015). This is where participants in a cohort study may leave employment early if they develop a disease that may be related to their work. This may result in the more heavily exposed workers leaving the industry, and therefore having a shorter duration of exposure, and in less heavily exposed workers (who remain healthy) working for longer periods. For studies on talc, this could occur if heavily exposed workers developed a non-malignant respiratory condition, such as talc pneumoconiosis. Therefore, any available data on risks of NMRD can be helpful in gauging the effect of this possible source of downward bias. To address the HWSB, specialized methods (e.g. g-estimation) are usually needed. None of the available studies included in the present evaluation used such methods.

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2.7.4 Ovarian cancer

The available epidemiological literature on the association between talc and ovarian cancer included more than 30 studies on perineal application of talc and 5 studies on occupationally exposed women. There are two major groups of studies: case–control and prospective cohort. Three cohort studies have been published since *IARC Monographs* Volume 93 (IARC, 2010), for which results were available only from the NHS. A large number of case–control studies were published before the Volume 93 meeting, and several more have been published since then.

The case–control studies included women recently diagnosed with ovarian cancer (most often epithelial) and a comparison group of women with similar eligibility criteria but who were thought to be free of ovarian cancer at the time of interview. Some were "hospital-based" case–control studies, in which controls were selected from the same clinic(s) as where the cases were diagnosed, but most were "registry-based" case–control studies, meaning that the cases were identified via cancer registries, and controls were women in the same geographical region with no history of ovarian cancer. A key component of the case–control studies was that the case participants were interviewed after the diagnosis of ovarian cancer. This means that women with rapidly fatal disease were less likely to be included and allowed for the possibility of differential exposure misclassification because of differences in reporting for cases relative to controls. It is generally assumed that differential exposure misclassification would result in women with ovarian cancer overreporting their talc use, a trend that would produce an upwardly biased effect estimate.

Of the more than two dozen case–control studies on the association between perineal use of talc or powder and ovarian cancer that have been published to date, most reported positive associations (ORs of approximately 1.3). Two recent examples of large and informative registry-based studies with detailed exposure data collection are those by Cramer et al. (2016) and Schildkraut et al. (2016), both of which reported a 30–40% increase in the odds of ovarian cancer among women who ever used powder in the perineal area, relative to those who never used powder. In both studies, statistically significant positive trends were observed in the magnitude of the associations according to more frequent use or longer duration of use. The trends observed by Schildkraut et al. (2016) (a study conducted among self-identified Black women in the USA) were more consistently monotonically increasing than those of Cramer et al. (2016), in which the different exposure groups had similar risks. However, Schildkraut et al. also observed strong evidence of differential exposure misclassification; the prevalence of exposure was much higher (52%) in case participants interviewed after widely publicized court cases in 2014 than in those interviewed before that time (37%), whereas reported exposure over time was more consistent among control participants (37% before 2014, 34% after). The positive association between talc and ovarian cancer was attenuated when only the participants interviewed before 2014 were included (OR, 1.19; 95% CI, 0.87–1.63). [The Working Group noted that the previously mentioned trend analysis (Schildkraut et al., 2016) included all participants, regardless of interview date.] O'Brien et al. (2023) also found in their comparison of responses regarding powder use in the baseline survey of the Sister Study cohort in 2003–2009 and follow-up questionnaire in 2017–2019 (after the publicized court cases) that the group of women who had developed ovarian cancer was the only group to report an increase in their genital use of talc.

Considering the case–control literature more broadly, in four separate meta-analyses of the case–control studies, reported meta-OR estimates ranged from 1.26 to 1.35 for ever use of talc (Langseth et al., 2008, meta-OR, 1.35; 95% CI,

1.26–1.46; Berge et al., 2018, meta-RR, 1.26; 95% CI, 1.17–1.35; Penninkilampi and Eslick (2018), meta-OR, 1.35; 95% CI, 1.27–1.43; Kadry Taher et al. (2019), meta-OR, 1.32; 95% CI, 1.24–1.40). Berge et al. (2018) and Penninkilampi and Eslick (2018) reported positive exposure–response associations (also including cohort studies) for both duration of use (meta-RR, 1.16; 95% CI, 1.07–1.26, for every 10 years of use, as reported in Berge et al. (2018), and meta-OR, 1.25; 95% CI, 1.10–1.43, for > 10 years of use versus none, as reported in Penninkilampi and Eslick, 2018) and frequency of use (meta-RR, 1.05; 95% CI, 1.04–1.07, for one additional use per week, as reported in Berge et al. (2018), and meta-OR, 1.42; 95% CI, 1.25–1.61, for > 3600 applications versus none, as reported in Penninkilampi and Eslick, 2018).

A similar estimate was reported for a large, pooled analysis of case–control studies on epithelial ovarian cancer (OR for ever use, 1.24; 95% CI, 1.15–1.33) (Terry et al., 2013). Here, there was an overall positive dose–response trend for increasing number of lifetime applications (ORs for the 1st, 2nd, 3rd, and 4th quartiles of exposure, relative to never users, were 1.14, 1.23, 1.22, and 1.32, respectively; *P* for trend, 0.17).

There have been four cohort studies (all from the USA) in which the relation between perineal use of talc and ovarian cancer has been evaluated, including NHS-I and NHS-II, WHI-OS, and the Sister Study. Generally, compared with case–control studies, cohort studies avoid differential exposure misclassification since the exposure status is obtained before the onset of ovarian cancer, although nondifferential exposure misclassification can occur. Typically, exposure status that is established at one point in time cannot account for subsequent changes in exposure status. Therefore, exposure categories such as "ever-exposed" may be underrepresented and "never exposed" may be overrepresented among study participants. Compared with case–control studies, cohort studies are less likely to have survival bias, because they are more likely to include the sickest patients with the most aggressive disease. Owing to dependence on self-reporting of the exposure, it was very difficult to distinguish between use of talc and use of other kind of body powder in this setting. Although little evidence exists regarding levels of asbestos contamination of cosmetic talc over time, it might be assumed that asbestos contamination was more often present in the earlier years investigated in the available epidemiological studies on body powder (see Section 1.4.1(e)). If that is the case, then any confounding effect of asbestos exposure on ovarian cancer and on other cancers caused by asbestos may be of greater magnitude in those studies in which recruitment occurred in an earlier period, such as NHS-I. This may also have implications for latency effects, since solid tumours may take many years to develop after first exposure. The studies on body powder were unable to account for possible confounding from asbestos contamination of the talc, and few evaluated latency.

Owing to the rarity of ovarian cancer, individual cohort studies have been underpowered for detection of a small association between ovarian cancer and perineal use of talc, as assessed by the use of body powder. Because of small sample sizes in each cohort study, a pooled analysis of the four US cohort studies, NHS-I, NHS-II, WHI-OS, and the Sister Study, best represented the assessment of the relation between talc and ovarian cancer (O'Brien et al., 2020). Participants in the pooled analysis were enrolled between 1976 and 2009. Of the 2168 self-reported epithelial ovarian cancers, 1884 were medically confirmed. The prevalence of genital use of powder was 38% among all women in the cohorts. The HR for ever versus never use of genital powder was 1.08 (95% CI, 0.99–1.17). Among women with a patent reproductive tract, the HR was 1.13 (95% CI, 1.01–1.26). The assessment of exposure differed by cohort and did not allow for a pooled assessment of lifetime or

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cumulative exposure to body powder. However, "long-term use" (HR, 1.01; 95% CI, 0.82–1.25) and "used powder ≥ 1/week" (HR, 1.09; 95% CI, 0.97–1.23) were assessed. It is worth noting that the two studies with the earlier periods of recruitment (NHS-I and WHI-OS), which also covered the period when asbestos contamination in the powder was likely to be higher, had the higher risk estimates.

Overall, the Working Group considered that the case–control studies were likely to be biased upwards because of differential exposure misclassification and the cohort studies may be biased towards the null because of nondifferential misclassification of exposure, with the true magnitude of the association found somewhere between the two sets of estimates. This was demonstrated empirically in the recent quantitative bias analyses by O'Brien et al. (2024) (considering the Sister Study cohort only) and the quantitative bias analysis (considering a larger set of studies) carried out by the Working Group itself (Annex 2, Quantitative bias analysis for exposure misclassification for the effects of ever versus never use of talc on ovarian cancer, available from: https://publications.iarc.who.int/646). As outlined in Sections 2.7.2 and 2.7.3, there are other sources of bias and confounding, such as through asbestos contamination, which are more difficult to assess regarding the impact they might have had on the findings of these studies. It was not possible to examine the changes over time in risk with period of talc use in the available studies, because the studies did not routinely collect or report data on timing of use, and there is uncertainty about the degree of asbestos contamination of talc body powder over time.

Two analyses of bias from exposure misclassification for the association between body powders and ovarian cancer were available to the Working Group. In a detailed bias analysis conducted by the Working Group itself, it was shown that the associations of ever (versus never) exposure would be attenuated in the case–control studies if the expected differential misclassification were present, and strengthened in the cohort studies if the expected nondifferential misclassification were present (see Annex 2, Quantitative bias analysis for exposure misclassification for the effects of ever versus never use of talc on ovarian cancer, available from: https://publications.iarc.who.int/646). In a separate quantitative bias analysis, O'Brien et al. (2024) examined the potential impact of misclassification of talc-based body powder use in the Sister Study cohort. They demonstrated that, although differential misclassification would positively bias HR estimates, a positive association between perineal use of talc and ovarian cancer was still observed in scenarios corrected for low-to-moderate bias.

In addition to the studies on perineal use of talc and ovarian cancer, three of the occupational retrospective cohort studies and two case–control studies have investigated ovarian cancer risks from occupational exposure. The number of studies was small, since most occupational cohorts in relevant industries comprise men only or have few women. The study of women working in the printing industry (Bulbulyan et al., 1999) found an excess risk of ovarian cancer for specific employment processes in which talc was a probable exposure, but no analyses based on talc exposure were reported. A study of women working in a pulp and paper mill in Norway found an excess risk of ovarian cancer incidence, but no analyses based on talc exposure were performed (Langseth and Andersen, 1999). A follow-up nested case–control study of epithelial ovarian cancer in this cohort found no association with talc exposure in their work or with talc use for personal hygiene (Langseth and Kjaerheim, 2004). An IARC-coordinated, multi-country study of 27 different exposures (including talc) among female pulp and paper mill workers found excess ovarian cancer incidence and mortality for women ever worked in

departments that involved high exposure to talc, with weak associations for those who ever worked in departments with any exposure to talc, where chance could not be excluded (Boffetta and Colin, 2001, a report that became publicly available in 2023). The two occupational case–control studies found either no association or chance could not be ruled out (Hartge and Stewart, 1994; Leung et al., 2023). The Working Group concluded that the findings from the occupational studies did not provide convincing evidence for an association between talc exposure and ovarian cancer. Furthermore, there was no information that allowed the Working Group to evaluate asbestos contamination of the talc used in these studies.

The Working Group considered the large number of informative studies published both before and after *IARC Monographs* Volume 93 (IARC, 2010), including findings from three additional cohort studies. The Working Group noted that, among the studies of personal use of body powders, consistent positive associations showing modest excess risks for ever use were found. In addition, adjustment for known confounders was usually undertaken in these studies. There was also evidence for an exposure–response relation in several informative studies and meta-analyses (Terry et al., 2013; Cramer et al., 2016; Berge et al., 2018; Penninkilampi and Eslick, 2018; O'Brien et al., 2024).

Therefore, on the basis of consistency in the positive associations across cohort and case–control studies and evidence of an exposure–response relation, the Working Group concluded that a positive association between talc and ovarian cancer was credible. The bias analysis conducted by the Working Group showed a range of estimates, many, but not all, consistent with a positive association for ever versus never use of talc-based body powder. The Working Group also considered the evidence for probable asbestos contamination of body powders containing talc, which could act as a confounder for ovarian cancer, since this is one of the cancers known to be caused by asbestos. Therefore, bias and confounding by asbestos exposure could not be ruled out with reasonable confidence.

2.7.5 Uterine cancer

The association between talc use and uterine cancer has been examined in one case–control study and four cohort studies, including a pooled cohort analysis. Many of the studies specifically examined endometrial cancers, which make up the majority (approximately 90%) of all uterine cancers.

In a registry-based case–control study in Australia, Neill et al. (2012) did not observe an association between ever perineal use of talc and epithelial endometrial cancer (OR, 0.88; 95% CI, 0.68–1.14). In the NHS-I, Karageorgi et al. (2010) reported a positive association for ever versus never use (RR, 1.13; 95% CI, 0.96–1.33) and for regular perineal use of talc (at least once per week) (RR, 1.17; 95% CI, 0.99–1.40). In the WHI-OS (Crawford et al., 2012), the HR for ever versus never use was 1.06 (95% CI, 0.87–1.28) and in the Sister Study (O'Brien et al., 2019) it was 1.2 (95% CI, 0.94–1.6). After pooling updated data from these three cohorts with data from the NHS-II, O'Brien et al. (2021a) observed no association between uterine cancer and ever versus never genital use of powder (HR, 1.01; 95% CI, 0.94–1.09), or for regular (at least once per week) genital use of powder (HR, 1.05; 95% CI, 0.95–1.16). For non-endometrioid uterine cancer, the HR for long-term use (> 20 years) versus never use was 1.46 (95% CI, 1.00–2.11). Updated results from the Sister Study (O'Brien et al., 2024) that included a more comprehensive exposure assessment also showed no evidence of an association for ever versus never use (HR, 1.01; 95% CI, 0.82–1.25).

Overall, the Working Group found in the few published studies little to no evidence supporting an association between history of genital use of talc and uterine cancers. An exception was the

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finding of an association between long-term genital use of talc and increased risk of the non-endometrioid uterine cancer subtypes, which to a large part include serous uterine cancers. Serous ovarian and serous uterine carcinomas share molecular and morphological features, and it has been suggested that they may share similar cells of origin (Kandoth et al., 2013). This finding is aligned with the observed associations with ovarian cancer, although there was no association between talc or other powder use and the more common and biologically distinct endometrioid uterine cancer subtype. Although the Working Group found this to be a notable and biologically plausible finding supporting an association for the serous subtype of uterine cancer, the Working Group also considered there to be a major gap in the understanding of subtype-specific risk factors for uterine cancer.

In addition to the studies of perineal use of talc and uterine cancer, three of the occupational retrospective cohort studies have investigated uterine cancer risks. These studies had small numbers giving imprecise estimates and/or had methodological limitations regarding exposure assessment.

In its consideration of the above findings, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and uterine cancer.

2.7.6 Lung cancer

Lung cancer is one of the more common cancers to have been reported in occupational studies of workers in talc mining and milling and downstream industries involving talc exposure in some departments. Lung cancer is also one of the main cancers of a priori interest when investigating talc, since inhalation is the main route of exposure in the workplace. Most studies considered by the Working Group were in talc mining and milling, which is the industry thought to have the highest level and prevalence of talc exposure, and in some of these mines the ore was asbestos-free (see Table 1.1). In the five studies in the talc mining industry in which duration or exposure–response relations were investigated, no evidence of any association was found (Honda et al., 2002; Wild et al., 2002; Wergeland et al., 2017; Fordyce et al., 2019; Ciocan et al., 2022a). The Working Group considered these findings of lesser informativeness, because of probable HWSB. In addition, the Working Group conducted a meta-analysis including studies in talc mines and mills that had been considered not to contain asbestos in previously published meta-analyses (Chang et al., 2017; Mundt et al., 2022), including Ciocan et al. (2022a), Fordyce et al. (2019), Wild et al. (2002) (comprising two cohorts), Wergeland et al. (2017), and Fu and Zhang (1992). The meta-SMR when all the six studies were included was 1.28 (95% CI, 1.02–1.60) (Fig. 2.1). An excess risk of lung cancer mortality (meta-SMR, 1.52; 95% CI, 1.09–2.12) was found among the three studies for which there was evidence of asbestos-contaminated ore in the judgement of the Working Group (Table 1.1), but not among the three studies for which the ore was judged to be asbestos-free (meta-SMR, 1.06; 95% CI, 0.87–1.28) (Ciocan et al., 2022a; Wild et al., 2002).

The next most common industry reported was the rubber industry, but four of these studies reported no analyses based on talc exposure (Monson and Fine, 1978; Zhang et al., 1989; Negri et al., 1989; and Li and Yu, 2002). The one study that did report results for talc exposure found a higher risk for longer-term workers, but no account was taken of smoking or co-exposures in the rubber industry (Straif et al., 2000). Of the two studies in the pulp and paper industry, both found a higher risk of lung cancer for shorter-term workers (Langseth and Andersen, 1999; Boffetta and Colin, 2001). One study each in the printing (Bulbulyan et al., 1999), ceramic plumbing fixture (Thomas and Stewart, 1987), fibreglass (Chiazze et al., 1993),

and porcelain (Nie et al., 1992) industries had methodological limitations, such as that in the majority of studies there was no adjustment for smoking, no estimates of talc exposure, and, in one study (Thomas and Stewart, 1987), silica exposure was common. The one case–control study (Ramanakumar et al., 2008) found no association between occupational talc exposure and lung cancer.

In its consideration of the above findings for lung cancer, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and lung cancer.

2.7.7 Digestive system cancers

Many of the studies investigating cancers of the digestive system (oral cavity/pharynx, oesophagus, stomach, colon, rectum, liver, gall bladder, or pancreas) in occupational studies where talc was a possible exposure found too few cases of each type of cancer, with the possible exception of stomach and colon cancer, to make meaningful conclusions. In many cases where numbers permitted, the results were null. In addition, these studies used no exposure metrics based on talc exposure but relied on results for the whole cohort and/or results by department, which reduced the informativeness of these studies. These limitations applied to both the talc mining and milling industry and the downstream industries where talc exposure occurred in some departments of the workplaces, but where other potentially carcinogenic occupational exposures were known to occur. In the one study that found an excess of oral/pharyngeal cancer in talc miners and millers and of oesophagus cancer in miners, but not in millers, no duration–response trend was found for either cancer type (Ciocan et al., 2022a). Another study found some evidence for a talc exposure–response relation for stomach cancer in the rubber industry in Germany (Straif et al., 2000). The community-based case–control study also found no associations of occupational talc exposure with any cancer of the digestive system, but numbers were small (Siemiatycki, 1991). In the study looking at consumption of talc as part of Chinese medical treatment, an excess of stomach cancer was found (Chang et al., 2019). In this study, the talc was assumed to be of pharmaceutical purity and free of asbestos contamination; however, asbestos contamination of this talc could not be excluded before 2005. In addition, the study captured a short exposure period, had short follow-up, and there was some concern about confounding by indication.

In addition to the above studies, the Working Group conducted a meta-analysis of stomach cancer among talc miners and millers, which found an overall meta-SMR of 1.23 (95% CI, 0.95–1.59) (Fig. 2.2) including all the six cohorts selected for the lung meta-analysis – Fordyce et al. (2019), Ciocan et al. (2022a), Wild et al. (2002) (two cohorts), Wergeland et al. (2017), and Fu and Zhang (1992). An excess risk of stomach cancer mortality was found among studies for which there was evidence of asbestos-contaminated ore (Table 1.1) (meta-SMR, 1.42; 95% CI, 0.92–2.17), but not among studies for which the ore was asbestos-free (meta-SMR, 1.14; 95% CI, 0.83–1.56), based on Ciocan et al. (2022a) and the two cohorts included in Wild et al. (2002).

In its consideration of the above findings, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and any type of digestive system cancer.

2.7.8 Urinary tract cancers

Most of the studies investigating cancer of the urinary tract (bladder, kidney) in occupational studies where talc was a possible exposure found too few cases of each type of cancer to draw meaningful conclusions. In most cases where numbers permitted, the results were null for both bladder and kidney cancer. In the very

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few instances where an excess risk was found, results were highly imprecise. In addition, no analyses were based on talc exposure, apart from the case–control study from Montreal, Canada, for which results were null for both kidney and bladder cancer (Siemiatycki, 1991). In consideration of the above findings, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and urinary tract cancer.

2.7.9 Other solid cancers

An analysis within the Sister Study cohort considered the association between genital use of talc at two time points and both pre-enrolment and incident cervical cancer, but there were relatively few cases of cervical cancer (pre-baseline cases, 523; incident cases, 31), and results were inconclusive (O'Brien et al., 2021b).

Several of the lung cancer studies also investigated mesothelioma but, in almost all cases, numbers were zero or very low, and the occupational studies may have been on talc contaminated with asbestos; thus, the Working Group considered that this precluded drawing any reliable conclusion about occupational talc exposure being associated with mesothelioma. In the three available studies of talc miners in mines with asbestos-free ore, no cases of mesothelioma were observed; however, numbers of expected cases were low in all three cohorts (Wild et al., 2002; Ciocan et al., 2022a).

Other types of cancer reported in occupational studies are prostate, brain, breast, thyroid, and testicular. For all these cancer sites, the numbers were usually small, and the findings were either null or, where modest increases were seen for the whole cohort, chance could not be excluded. In the one study (Boffetta and Colin, 2001) in which talc exposure was estimated, the results for all five cancer sites were almost all null for workers ever-exposed or ever highly exposed. For the one community-based cohort study on breast cancer and personal use of talc exposure and the follow-up analysis to adjust for misclassification bias, no associations were found (O'Brien et al., 2024). In consideration of the above findings, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and mesothelioma, brain, prostate, cervical, breast, thyroid, or testicular cancer.

2.7.10 Lymphatic and haematopoietic cancers

Most of the studies investigating cancers of lymphatic and haematopoietic tissue (lymphoma, leukaemia) in occupational studies where talc was a possible exposure found too few cases for each type of cancer to draw meaningful conclusions. In most cases where numbers permitted, the results were either null for all types of lymphohaematopoietic cancer or, in the very few instances where an excess risk was found, results were highly imprecise. In addition, no cohort analyses were based on talc exposure. The case–control study from Montreal, Canada, had a modest excess of NHL, but recall bias could not be ruled out (Siemiatycki, 1991). In consideration of the above findings, the Working Group concluded that there was little evidence regarding a causal association between exposure to talc and any cancers of lymphatic or haematopoietic tissue.

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1.

3.1.1 Inhalation exposure

In a well-conducted study of chronic toxicity and carcinogenicity (NTP, 1993) that complied with Good Laboratory Practice (GLP), groups of 47, 48, and 49 male and 49, 48, and 50 female

Table 3.1 Studies of carcinogenicity in mice exposed to talc

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mice, B6C3F$_1$ (M) 7 wk 104 wk NTP (1993)	Inhalation (whole-body exposure) Talc powder (MP 10-52-grade microtalc); major impurities were 0.7% aluminium and 1% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2 Air 0, 6, 18 mg/m^3 (equivalent to 0, 2, 6 mg/kg bw per day) 6 h per day, 5 d/wk, for 104 wk 47, 48, 49 30, 28, 32	No significant increase in tumour incidence in treated animals		*Principal strengths*: Well-conducted GLP study, covered most of the lifespan, both sexes used, two-dose study, complete histopathology, the adequate duration of exposure and observation.
Full carcinogenicity Mice, B6C3F$_1$ (F) 7 wk 104 wk NTP (1993)	Inhalation (whole-body exposure) Talc powder (MP 10-52-grade microtalc); the major impurities were 0.7% aluminium and 1% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2 Air 0, 6, 18 mg/m^3 (equivalent to 0, 1.3, 1.9 mg/kg bw per day) 6 h per day, 5 d/wk for 104 wk 49, 48, 50 30, 23, 25	No significant increase in tumour incidence in treated animals		*Principal strengths*: Well-conducted GLP study, covered most of the lifespan, both sexes used, two-dose study, complete histopathology, the adequate duration of exposure and observation.
Full carcinogenicity Mouse, Swiss albino mice (sex, NR) 6 wk 32 mo Ozesmi et al. (1985)	Intraperitoneal injection Talc (commercial); purity, NR Physiological saline 0, 20 mg, Single dose of 20 mg 55, 40 46, 24	*Peritoneal cavity* Mesothelioma 3/46, 3/24	NS	*Principal strengths*: Long-term study. *Principal limitations*: Talc was not characterized, and purity was not reported, sex not reported.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, Swiss albino (M, F combined) NR 210 d Sahu et al. (1978)	Intratracheal instillation Talc, purity, NR (impurities, 64% silica and 32% magnesium oxide) NaCl (0.15 M molar solution) 0, 5 mg/mL Single dose of 5 mg/mL 40, 80 18, 58	No significant increase in tumour incidence in treated animals		*Principal limitations:* Sex and age not reported, talc purity and asbestos content not reported, short duration of exposure for several time points, the small number of animals that underwent histopathological evaluation compared with the initial number of control and exposed animals, medium-term study.

d, day(s); F, female; GLP, Good Laboratory Practice; h, hour(s); M, male; mo, month(s); MP, micronized powder; NaCl, sodium chloride, NR, not reported; NS, not significant; wk, week(s).

$B6C3F_1$ mice (age, 7 weeks) were exposed by inhalation (whole-body exposure) to micronized powder (MP) 10-52-grade microtalc [designated as high-purity talc] at target concentrations of 0 (control), 6, or 18 mg/m^3 (concentrations were based on the findings of a 4-week study) for 6 hours per day, 5 days per week, for up to 104 weeks, providing an exposure dose equivalent of 0, 2, or 6 mg/kg body weight (bw) per day for males and 0, 1.3, or 3.9 mg/kg bw per day for females. The average mass median aerodynamic diameters (MMADs) were 3.3 µm and 3.6 µm, and the geometric standard deviations (GSDs) were 1.9 µm and 2.0 µm in the mouse chambers at 6 mg/m^3 and 18 mg/m^3, respectively. The talc was well characterized (the major impurities found were 0.7% aluminium and 1.0% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2). Both lots of talc were extensively characterized and identified as talc using infrared spectroscopy, elemental analysis, thermogravimetric analyses, spark source mass spectrometry, automated scanning electron probe analyses, X-ray diffraction, polarized light microscopy, and TEM. Both lots were found to be asbestos-free by polarized light microscopy and TEM. [The Working Group noted that this method was state-of-the-art for determining asbestos at the time of the study and is sufficiently sensitive to detect asbestos contamination (see Section 1.3)]. Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. At study termination, survival in males was 30/47, 28/48, and 32/49 for the groups at 0, 6, and 18 mg/m^3, respectively; and survival in females was 30/49, 23/48, and 25/50 for the groups at 0, 6, and 18 mg/m^3, respectively. All mice underwent complete necropsy with histopathological evaluation.

No significant increases in the incidence of neoplasms were observed in either sex.

Regarding non-neoplastic lesions, inhalation exposure of mice to talc was associated with chronic active inflammation and the accumulation of macrophages in the lung in males and females.

[The Working Group noted that this was a well-conducted GLP study that covered most of the lifespan, used both sexes and multiple doses, incorporated a complete histopathological examination, and had an adequate duration of exposure and observation.]

3.1.2 Intraperitoneal administration

In a study designed to investigate the carcinogenicity of intraperitoneally injected asbestos (Jagatic et al., 1967), six control groups of 4–12 male White mice [strain and age not reported] were injected intraperitoneally with a 0.5 mL suspension (50%) of talc in saline (sodium chloride, NaCl). The mice were euthanized 26, 57, 112, 147, 170, or 343 days after injection. The talc was described as 6505-147-0000 talc, USP V 7023P-9108, lot B 1842. No further analysis was made. A histopathological examination was performed. No talc-associated development of neoplasia lesions was observed. All mice developed granulomas (see Section 4.2.6). [The Working Group noted that talc was used as a control. The study was poorly reported. Purity, the administered dose of talc, age at start, and strain were not specified. Only one sex was used, and there was no untreated control group. Therefore, the Working Group considered that this study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

In a study by Pott et al. (1976a), female NMRI mice were treated with asbestos-free talc by intraperitoneal injection [the talc was not characterized, and the age, number of animals, and dose were not reported.] No tumours, preneoplastic lesions, or clinical signs were reported in the talc-treated mice except for a mesothelioma in one mouse. [The Working Group noted the very limited reporting, in particular, the lack of information on age, number of animals per group,

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dose, and talc characterization. Therefore, the Working Group considered that this study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

Ozesmi et al. (1985) treated 40 Swiss albino mice [sex not reported] (age, 6 weeks) with a single intraperitoneal injection of 20 mg of ground commercial talc [purity not reported] in 1 mL of physiological saline (NaCl). A group of 55 mice received 1 mL of NaCl and were used as controls. Within 6 months, 16 mice had died. Peritoneal mesotheliomas were observed in 3 of the 24 survivors allowed to live out a normal lifespan (up to 32 months). In the saline-treated controls, 3/46 mice also developed mesothelioma. [The Working Group noted that talc was used as the dust control and saline as the vehicle control, and that mesotheliomas occurred in the saline-treated controls. The Working Group also noted the very limited reporting in this study, in particular, the lack of information on the sex of the mice and the purity and characterization of talc.]

3.1.3 Subcutaneous administration

Neukomm and de Trey (1961) treated a group of 50 female R3 mice (age, 3–6 months) with a single subcutaneous injection of 0.2 mL of a mixture of 8 g of talc [purity not reported] and 20 g of peanut oil (delivered dose, about 80 mg). The mice were observed for life (median survival, 596 days). Another group of 60 female mice served as untreated controls (median survival, 564 days). In this study, talc was used as a control, and untreated mice (referred to as the absolute controls) were used to determine the spontaneous tumour incidence. All mice underwent complete necropsy. For all mice, the lung, heart, liver, kidney, and spleen were sampled for histopathological examination.

No talc-associated development of neoplasia or preneoplastic lesions was observed.

[The Working Group noted the very limited reporting in this study, in particular, the lack of information on the dose used and the purity and characterization of talc. Therefore, the Working Group considered that this study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

Pott et al. (1976a) treated female NMRI mice with asbestos-free talc by subcutaneous injection [age and number of animals, and dose were not reported]. No talc-associated development of neoplasia or preneoplastic lesions was observed. [The Working Group noted the very limited reporting in this study, in particular, the lack of information on the age and number of animals per group, dose, and talc characterization. The Working Group considered that this study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

3.1.4 Intrapleural injection and intratracheal instillation

Davis (1972) treated groups of 25 Balb/C mice [sex and age not reported] with mineral dusts by intrapleural injection of 10 mg of dust suspended in 0.5 mL of distilled water. The talc was a sheet-like silicate with approximate composition $Mg_6(Si_8O_{20})(OH)_4$. The dust sample used in these experiments consisted mostly of irregularly shaped plates of 1–10 µm in length. Mixed with the talc plates were small quantities of asbestos fibres of 0.05–0.5 µm in diameter and up to 2 µm in length. The mice were euthanized between 2 weeks and 18 months after injection [no further details were provided], and histopathological examination was performed.

No talc-associated development of neoplasia or preneoplastic lesions was observed.

[The Working Group noted that the talc was contaminated with asbestos. The Working Group also noted the very limited reporting in

this study, in particular, the lack of information on the sex and age of the mice at the start of the study. Therefore, the Working Group considered that this study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

Sahu et al. (1978) treated a group of 80 male and female Swiss albino mice [sex distribution and age were not reported] with a single intratracheal instillation of talc [asbestos content not reported] at 5 mg/mL dissolved in 0.15 M NaCl. Particle sizes were mainly in the range 0.45–5.12 µm, and the chemical composition was 64% silica and 32% magnesium oxide. A control group of 40 male and female mice [sex distribution not reported] was treated with saline (NaCl). Two mice from each group were euthanized at 24 and 48 hours, and at 7, 15, 30, 60, 90, 120, 150, 180, and 210 days after instillation, and histopathological evaluation of the lungs was conducted (overall, only 22 animals per experimental group were evaluated).

No talc-associated development of neoplasia or preneoplastic lesions was observed.

[The Working Group noted this was a medium-term study. The Working Group also noted the limited reporting, in particular, the lack of information on the age and sex distribution of the mice at the start of the experiment, the lack of information on asbestos content, the short duration of exposure for some of the time points, and the small number of mice undergoing histopathological evaluation compared with the initial number of control and exposed animals.]

3.2 Rat

See Table 3.2.

3.2.1 Oral administration (feed)

In a lifetime study of carcinogenesis, (Gibel et al., 1976), groups of 50 Wistar rats (25 males and 25 females) (age, 10 weeks) were exposed for life to talcum powder [characteristics not reported] at a dose of 20 mg per day by oral administration (in feed), to achieve a final dose of 50 mg/kg bw per day. A control group of 50 rats (25 males and 25 females) received a standard diet only. The mice tolerated the talc well, and the average survival time was 649 days for treated mice and 702 days for controls. After living out their lifespan, the rats were dissected, and organs were histologically analysed [not further specified].

No significant difference in tumour incidence was observed between treated animals and controls. [The Working Group noted that this was a lifetime study that was limited by the use of one dose only, the combination of males and females, the poorly described dosing regimen, the limited details provided on histopathological examination; and the lack of reporting of talc characteristics.]

In a lifetime study (Wagner et al., 1977), groups of 32 Wistar rats (16 males and 16 females) (age, 21–26 weeks) were treated by oral administration (in feed) with talc (at a dose of 100 mg per day (a mixture of 244 g of food + 16 g of talc + 5 mL deionized water) on 101 days in a 5-month period. The talc (Italian grade 00000, in a ready-milled form) had a mean particle size of 25 µm and an upper particle size of 70 µm (no asbestos minerals were detected) [Italian talc 00000 grade contains approximately 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5–1.0% quartz by weight and is considered to be high-purity industrial talc]. A positive control group of 32 rats (16 males and 16 females) was treated with super-fine asbestos (SFA), and a negative control group of 16 rats (8 males and 8 females) received standard diet. Mean survival was 614 days for mice in the talc-treated group, 619 days for the SFA-treated group (positive control), and 641 days for the negative control group. The alimentary canal, spleen, liver, kidneys, heart, lungs, and macroscopic lesions were examined at necropsy, and limited histopathology was performed.

No difference in tumour incidence was observed between talc-treated mice and the

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Table 3.2 Studies of carcinogenicity in rats exposed to talc

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Wistar rat (M, F) 10 wk Lifetime Gibel et al. (1976)	Oral administration (feed) Talc powder; purity, NR Pelleted standard food 20 mg/d for life to achieve doses of 0, 50 mg/kg bw per day 50, 50 49, 45	*Liver* Hepatic carcinoma [hepatocellular carcinoma] 2/49, 3/45 Hepatic carcinoma [hepatocellular carcinoma] 2/49, 3/45	 NS NS	*Principal strengths:* Lifetime study. *Principal limitations:* Only one dose, data combined for males and females, talc was not characterized, lack of detailed histopathology, males and females combined, poorly described in particular the dosing regimen.
Full carcinogenicity Rats, Wistar rat (M, F) 21–26 wk Lifetime Wagner et al. (1977)	Oral administration (feed) Talc powder (Italian talc); purity, 92% (impurities, 3% chlorite, 1% carbonate minerals, and 0.5–1% quartz) Coarsely powdered Spillers small-animals diet and Horlicks malted milk 0, 100 mg 1×/d for 101 d over 5 mo 16, 32 16, 32	*Stomach* Leiomyosarcoma Tumour incidence: 0/16, 1/32	 NS	*Principal strengths:* Lifetime *Principal limitations:* Only one dose group, limited histopathology, short duration of exposure, small number of animals per group; advanced age of animals at start, the combination of males and females, talc characteristics unspecified.
Full carcinogenicity Rats, Wistar rat (M, F) 7–8 wk 25 mo Wagner et al. (1977)	Inhalation (whole-body exposure) Talc powder (Italian talc); purity, 92% (impurities, 3% chlorite, 1% carbonate minerals, and 0.5–1% quartz) Air 0, 10.8 mg/m^3 7.5 h/d, 5 d/wk for 12 mo 48, 24 NR, 12	*Lung* Adenoma 0/48, 1/24	 NS	*Principal strengths:* Adequate number of control animals. *Principal limitations:* Only one dose group, lung histopathology only, small number of treated animals; small number of rats per treated group, males and females combined, talc characteristics unspecified.

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rats, Wistar rat (M, F) 6–8 wk 18 mo Wagner et al. (1977)	Inhalation (whole-body exposure) Talc powder; purity, 92% (impurities, 3% chlorite, 1% carbonate minerals, and 0.5–1% quartz) Air 0, 10.8 mg/m^3 7.5 h/d, 5 d/wk, for 6 mo 48, 24 NR, 12	Lung: No significant increase in the incidence of tumours in treated animals	NS	*Principal strengths:* Adequate number of control animals. *Principal limitations:* Differences in sex not reported, only one dose group, lung histopathology only, short duration of exposure for this arm of the study (6 mo), small number of rats per treated group,, males and females combined, talc characteristics unspecified.
Full carcinogenicity Rat, F344/N rat (M) 6–7 wk 113 wk NTP (1993)	Inhalation (whole-body exposure) Talc powder; the major impurities were 0.7% aluminium and 1% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2 Air 0, 6, 18 mg/m^3 (equivalent dose, 0, 2.8, 8.4 mg/kg bw per day) 6 h/d, 5 d/wk, for 113 wk 49, 50, 50 9, 14, 16	*Adrenal medulla* Benign pheochromocytoma 25/49 (51%), 30/48 (63%), 36/47 (77%)*	$P = 0.007$, logistic regression trend test; $P = 0.007$, Cochran–Armitage trend test *$P = 0.009$, logistic regression test; $P = 0.008$, Fisher exact test	*Principal strengths:* GLP study, covered most of the lifespan, studies in both males and females, two doses used, adequate duration of exposure and observation.
		Benign pheochromocytoma, bilateral 12/49 (24%), 21/48 (44%)*, 16/47 (34%)	[$P = 0.0366$, Fisher exact test]	
		Malignant pheochromocytoma 3/49 (6%), 3/48 (6%), 7/47 (15%)	NS	
		Complex pheochromocytoma 0/49 (0%), 2/48 (4%), 1/47 (2%)	NS	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N rat (M) 6–7 wk 113 wk NTP (1993) (cont.)		Benign, malignant or complex pheochromocytoma (combined) 26/49 (53%), 32/48 (67%), 37/47 (79%)*	*P* = 0.007, logistic regression trend test; *P* = 0.007, Cochran–Armitage trend test **P* = 0.006, logistic regression test; *P* = 0.007, Fisher exact test	
		Lung Bronchioloalveolar adenoma 0/49, 1/50 (2%), 1/50 (2%)	NS	
		Bronchioloalveolar carcinoma 0/49, 0/50, 1/50 (2%)	NS	
		Bronchioloalveolar adenoma or carcinoma (combined) 0/49, 1/50 (2%), 2/50 (4%)	NS	
Full carcinogenicity Rat, F344/N rat (F) 6–7 wk 122 wk NTP (1993)	Inhalation (whole-body exposure) Talc powder; the major impurities were 0.7% aluminium and 1% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2 Air 0, 6, 18 mg/m^3 (equivalent dose, 0, 3.2, 9.6 mg/kg bw per day) 6 h/d, 5 d/wk, for 122 wk 48, 47, 49 11, 13, 9	*Adrenal medulla* Benign pheochromocytoma 13/48 (27%), 14/47 (30%), 18/49 (37%)	NS	*Principal strengths:* Well-conducted GLP study, covered most of the lifespan, males and females used, two doses used, complete histopathology, adequate duration of exposure and observation.

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N rat (F) 6–7 wk 122 wk NTP (1993) (cont.)		Malignant pheochromocytoma 0/48, 1/47 (2%), 10/49 (20%)*	$P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test *$P = 0.001$, logistic regression test; $P = 0.001$, Fisher exact test	
		Benign pheochromocytoma, bilateral 0/48, 4/47 (9%), 7/49 (14%)*	[$P = 0.009$, Cochran–Armitage trend test] [$P = 0.012$, Fisher exact test]	
		Malignant pheochromocytoma, bilateral 0/48, 0/47, 3/49 (6%)	[$P = 0.037$, Cochran–Armitage trend test]	
		Benign or malignant pheochromocytoma (combined) 13/48 (27%), 14/47 (30%), 23/49 (47%)*	$P = 0.014$, logistic regression trend test; $P = 0.021$, Cochran–Armitage trend test *$P = 0.024$, logistic regression test; $P = 0.034$, Fisher exact test	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N rat (F) 6–7 wk 122 wk NTP (1993) (cont.)		*Lung* Bronchioloalveolar adenoma 1/50 (2%), 0/48, 9/50 (18%)*	$P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test *$P = 0.010$, logistic regression test; $P = 0.008$, Fisher exact test	
		Bronchioloalveolar carcinoma Tumour incidence: 0/50, 0/48, 5/50 (10%)*	$P = 0.003$, logistic regression trend test; $P = 0.004$, Cochran–Armitage trend test *$P = 0.028$, logistic regression test; $P = 0.028$, Fisher exact test	
		Bronchioloalveolar adenoma or carcinoma (combined) 1/50 (2%), 0/48, 13/50 (26%)*	$P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test *$P < 0.001$, logistic regression test; $P < 0.001$, Fisher exact test	
		Squamous cell carcinoma 0/50 (0%), 0/48 (0%), 1/50 (2%)	NS	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rats, Wistar rat (F) 8–12 wk Lifetime Pott et al. (1974)	Intraperitoneal injection Talc; purity, NR Saline solution 0, 25 mg 1×/wk, for 4 wk 80, 40 80, 40	*Mesothelium* Sarcomatous mesothelioma 0/80, 1/40	NS	*Principal strengths:* Adequate number of control animals. *Principal limitations:* Only one dose group, limited information on body weight and survival, the duration of exposure and observation and on terminal euthanasia, low sensitivity of the assay to detect the carcinogenesis of exposure to talc, not clear when the last rat was euthanized, no information was provided on the purity of the test material.
Full carcinogenicity Rat, Wistar (M, F) 8–14 wk Lifetime Wagner et al. (1977)	Intrapleural injection Talc (Italian talc 00000 grade); purity, 92% (impurities, 3% chlorite, 1% carbonate minerals, and 0.5–1% quartz) Saline 0, 20 mg Single dose, 20 mg 48, 48 48, 48	*Lung* Adenoma 0/48, 1/48	NS	*Principal strengths:* Covered most of the lifespan, studies in both males and females, adequate number of animals used, randomly allocated in groups, new dosing route for talc. *Principal limitations:* Data combined for sexes; poor description of experimental design, results, statistics; no discussion; single dosing; no explanation regarding the dosage chosen. The size of the "small" lung adenoma was not reported.
Full carcinogenicity Rat, Osborne-Mendel (F) 12–20 wk 2 yr Stanton et al. (1981)	Intrapleural Talc 1; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 26 NR, NR	*Pleura* Pleural sarcoma 29/1518, 1/26	NS	*Principal strengths:* Study of fibre dimensions, adequate control groups, all lesions studied histologically, adequate duration, quality of statistics, the reporting of fibre dimensions. *Principal limitations:* No details on preneoplastic changes, different description of the types of controls in different sections, talc purity unspecified, one sex only.
	Intrapleural Talc 2; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 30 NR, NR	*Pleura* Pleural sarcoma 29/1518, 1/30	NS	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Osborne-Mendel (F) 12–20 wk 2 yr Stanton et al. (1981) (cont.)	Intrapleural Talc 3; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 29 NR, NR	*Pleura* Pleural sarcoma 29/1518, 1/29	NS	
	Intrapleural Talc 4; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 29 NR, NR	*Pleura* Pleural sarcoma 29/1518, 1/29	NS	
	Intrapleural Talc 5; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 30 NR, NR	*Pleura* Pleural sarcoma 29/1518, 0/30	NS	
	Intrapleural Talc 6; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 30 NR, NR	*Pleura* Pleural sarcoma 29/1518, 0/30	NS	
	Intrapleural Talc 7; purity, NR Hardened gelatin 0, 40 mg Single dose of 40 mg 1518, 29 NR, NR	*Pleura* Pleural sarcoma 29/1518, 0/29	NS	

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Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (F) 10–15 wk 12 mo Hamilton et al. (1984)	Ovary, intrabursal injection Talc; purity, NR Phosphate-buffered saline (100 µL) 0 (age-matched controls), 0 (sham-operated controls), 0 (sham-treated controls), 100 mg/mL Single dose of 100 mg/mL 3, 3, 3, 10 3, 3, 3, 10	*Ovary* No significant increase in tumour incidence in treated animals		*Principal strengths:* Good and realistic discussion of results, good histological and ultrastructural study. *Principal limitations:* Histology only performed in animals euthanized at 12 mo, small number of animals per group, short duration of exposure.
Co-carcinogenicity Rat, Wistar (M, F) 10 wk Lifetime Wagner et al. (1980)	Intrapleural Crocidolite (asbestos) + talc; purity, NR Saline 40 mg (talc alone), 40 mg (crocidolite + talc) 20 mg (crocidolite) + 40 mg × 2 equal doses at 8-wk interval (talc) 24, 24 24, 23	*Pleura* Mesothelioma 9/24, 7/23	NS	*Principal limitations:* Males and females combined, poorly reported study, lack of adequate controls.

bw, body weight; d, day(s); F, female; GLP, Good Laboratory Practice; h, hour(s); M, male; mo, month(s); NR, not reported; NS, not significant; wk, week(s); yr, year(s).

controls. [The Working Group noted that this was a lifetime study, but also noted the short duration of exposure, the small number of mice, the advanced age of mice at the start of the experiment, the combination of males and females, the use of one dose only, and the limited histopathology performed.]

3.2.2 Inhalation exposure

In a study by Wagner et al. (1977), groups of 24 male and 24 female Wistar rats (age, 6–8 weeks) were exposed by inhalation to talc at a mean dust concentration of 10.8 mg/m^3 for 7.5 hours per day on 5 days per week for 6 or 12 months (cumulative dust concentration, 8200 and 16 400 mg/m^3 × hours, respectively). The talc (Italian grade 00000, ready milled) had a mean particle size of 25 µm and an upper particle size of 70 µm (no asbestos minerals were detected) [Italian talc 00000 grade contains approximately 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5–1.0% quartz by weight and is considered to be high-purity industrial talc]. Additional groups of 24 rats (12 males and 12 females) were exposed to SFA chrysotile dust (positive control) or were not exposed to either talc or SFA chrysotile and were kept in ordinary cages in racks (negative control) for 6 or 12 months. Ten days after the end of each exposure period, 6 rats per group were euthanized. In the groups of rats treated with talc, 12/24 rats died during the 6-month experiment and 12/24 rats died during the 12-month experiment; 2 rats per group were excluded from the study; and the remaining 4 rats per group were euthanized 1 year after the end of the exposure period. Histopathological evaluations were only carried out on the lungs.

No significant increase in the incidence of lung lesions was observed in rats exposed to talc compared with unexposed rats in the control groups: in the 6-month experiment, the incidence of lung adenoma, adenomatosis, and adenocarcinoma was 0/48 in the 12-month experiment, the incidence of lung adenoma was 1/24, and no cases of lung adenomatosis or adenocarcinoma were observed. There were 7 lung tumours, including 1 adenocarcinoma, in the group of rats exposed to SFA chrysotile for 12 months. No lung lesions were observed in rats on the control group (Wagner et al., 1977). [The Working Group noted the adequate number of animals in the control group, but also noted the short duration of the exposure for one arm of the study (6 months), the small number of animals in the treated groups, the use of a single concentration, histological examination of the lung only, the combination of males and females, and the lack of reporting of talc characteristics.]

In a well-conducted study of chronic toxicity and carcinogenicity that complied with GLP (NTP, 1993), groups of 49 or 50 male and 50 female Fischer 344/N rats (age, 6–7 weeks) were exposed by inhalation (whole-body exposure) to MP 10-52-grade microtalc [designated as high-purity talc] at target concentrations of 0, 6, or 18 mg/m^3 (concentrations were based on the findings of a 4-week study) for 6 hours per day, 5 days per week, for up to 113 weeks for males and 122 weeks for females. These concentrations provided an exposure dose equivalent to 0, 2.8, or 8.4 mg/kg bw per day for males and 0, 3.2, or 9.6 mg/kg bw per day for females. Exposure to talc was scheduled for 6 hours per day plus T90 (theoretical value for the time to achieve 90% of the target concentration after the beginning of aerosol generation; 10 minutes), 5 days per week, for 113 weeks for males and 122 weeks for females (based on a survival rate of 20% in any exposure group). The talc was well characterized (the major impurities found were 0.7% aluminium and 1.0% iron for lot 1, and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2); the overall mean concentration in the inhalation chambers was 6.1 and 18.6 mg/m^3, respectively. The average MMAD and GSD were calculated to be 2.7 ± 1.9 µm and 3.2 ± 1.9 µm for the chambers at 6 and 18 mg/m^3, respectively. Both lots of

talc were extensively characterized and identified as talc using infrared spectroscopy, elemental analysis, thermogravimetric analyses, spark source mass spectrometry, automated scanning electron probe analyses, X-ray diffraction, polarized light microscopy, and TEM. Both lots were found to be asbestos-free by polarized light microscopy and TEM. [The Working Group noted that this method was state-of-the-art for determining asbestos at the time of the study and that it was sufficiently sensitive for the detection of asbestos contamination (see Section 1.3).] [The Working Group noted that particles with these dimensions appeared to be respirable for rats. For more information about MMAD, see Section 1.] The authors described some difficulties with the aerosol concentration monitoring system for the rat chambers at 18 mg/m^3, with variation of approximately 30–40 mg/m^3 at the beginning of study week 11 for a period of 7 weeks and also around week 70 for 12 weeks, during which time the chamber concentrations were lower than the target concentrations; these problems had no apparent effect on lung talc burdens. At study termination, survival in the treated groups (males, 9/49, 14/50, and 16/50, and females, 11/50, 13/50, and 9/50, for the groups at 0, 6, and 18 mg/m^3, respectively) was similar to that in the control groups. The mean body weights of the males and females at the higher concentration were slightly less than those of the controls after week 65. At euthanasia, a slight nonsignificant decrease in body weight of 4% in males and of 14% in females was observed in the group at the higher dose compared with that in the control group. All rats underwent complete necropsy with histopathological evaluation. In the group at 18 mg/m^3 compared with the control group, absolute and relative lung weights were significantly higher in males at interim evaluations at 6, 11, and 18 months, and at the end of the study, and in females at 11, 18, and 24 months, and at the end of the study (NTP, 1993).

In males, there was a significant positive trend in the incidence of benign pheochromocytoma of the adrenal medulla (P = 0.007, logistic regression trend test; P = 0.007, Cochran–Armitage trend test) with the incidence – 25/49 (51%), 30/48 (63%), and 36/47 (77%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased (P = 0.009, logistic regression test; P = 0.008, Fisher exact test) in the group at the higher dose. The incidence of bilateral benign pheochromocytoma was 12/49 (24%), 21/48 (44%), and 16/47 (34%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively, and was significantly increased [P = 0.0366, Fisher exact test] in the group at the lower dose. The incidence of malignant pheochromocytoma of the adrenal medulla was 3/49 (6%), 3/48 (6%), and 7/47 (15%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively. The incidence of complex pheochromocytoma of the adrenal medulla was 0/49 (0%), 2/48 (4%), and 1/47 (2%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively. [The authors described the complex pheochromocytomas as a mixture of neoplastic pheochromocytes and neuroblasts, ganglion cells, and/or Schwann cells, but did not report whether these complex tumours were benign or malignant.] The incidence of bilateral malignant pheochromocytoma was 1/49 (2%), 0/48, and 1/47 (2%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively. There was a significant positive trend in the incidence of benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla (P = 0.007, logistic regression trend test; P = 0.007, Cochran–Armitage trend test), with the incidence – 26/49 (53%), 32/48 (67%), and 37/47 (79%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased (P = 0.006, logistic regression test; P = 0.007, Fisher exact test) in the group at the higher dose. The incidence of lung bronchioloalveolar adenoma was 0/49 (0%), 1/50 (2%), and 1/50 (2%), in the groups at 0 (control), 6, and 18 mg/m^3 group, respectively. The incidence of

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lung bronchioloalveolar carcinoma was 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively. The incidence of bronchioloalveolar carcinoma or adenoma (combined) was 0/49 (0%), 1/50 (2%), and 2/50 (4%), in the groups at 0 (control), 6, and 18 mg/m^3, respectively.

In females, the incidence of benign pheochromocytoma of the adrenal medulla was 13/48 (27%), 14/47 (30%), and 18/49 (37%) in the groups at 0 (control) 6, and 18 mg/m^3, respectively. There was a significant positive trend in the incidence of malignant pheochromocytoma of the adrenal medulla ($P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test), and the incidence – 0/48 (0%), 1/47 (2%), and 10/49 (20%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – was significantly increased ($P = 0.001$, logistic regression test; $P < 0.001$, Fisher exact test) at the higher dose. There was a significant positive trend [$P = 0.009$, Cochran–Armitage trend test] in the incidence of bilateral benign pheochromocytoma, with the incidence – 0/48, 4/47 (9%), and 7/49 (14%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased in the group at the higher dose [$P = 0.012$, Fisher exact test]. There was a significant positive trend [$P = 0.037$, Cochran–Armitage trend test] in the incidence of bilateral malignant pheochromocytoma, with the incidence being 0/48, 0/47, and 3/49 (6%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively. There was a significant positive trend in the incidence of benign or malignant pheochromocytoma (combined) of the adrenal medulla ($P = 0.014$, logistic regression trend test; $P = 0.021$, Cochran–Armitage trend test), with the incidence – 13/48 (27%), 14/47 (30%), and 23/49 (47%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased ($P = 0.024$, logistic regression test; $P = 0.034$, Fisher exact test) in the group at the higher dose. No complex pheochromocytomas were observed in females.

There was a significant positive trend in the incidence of bronchioloalveolar adenoma ($P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test), with the incidence – 1/50 (2%), 0/48 (0%), and 9/50 (18%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased ($P = 0.010$, logistic regression test; $P = 0.008$, Fisher exact test) in the group at the higher dose. There was a significant positive trend in the incidence of bronchioloalveolar carcinoma ($P = 0.003$, logistic regression trend test; $P = 0.004$ Cochran–Armitage trend test), with the incidence – 0/50 (0%), 0/48 (0%), and 5/50 (10%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased ($P = 0.028$, logistic regression test; $P = 0.028$, Fisher exact test) in the group at the higher dose. There was a significant positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined) ($P < 0.001$, logistic regression trend test; $P < 0.001$, Cochran–Armitage trend test), with the incidence – 1/50 (2%), 0/48 (0%), and 13/50 (26%) in the groups at 0 (control), 6, and 18 mg/m^3, respectively – being significantly increased ($P < 0.001$, logistic regression test; $P < 0.001$, Fisher exact test) in the group at the higher dose. A single (1/50) lung squamous cell carcinoma was observed in females in the group at the higher dose. [The Working Group noted a significant positive trend in the incidence of pheochromocytoma in both males and females (benign tumours and the combination of benign, complex or malignant tumours in males; and malignant tumours and the combination of benign or malignant tumours in females). Pheochromocytoma (especially malignant pheochromocytoma) of the adrenal medulla is quite a rare lesion. In the historical control database for studies started between 1984 and 1993 (NTP, 1997), the incidence of pheochromocytoma was, in general, lower than that in controls in the present study (conducted between 1984 and 1986), and therefore was probably not appropriate for comparison. The overall incidence of benign

pheochromocytoma in historical controls was 24.5% (24/98) in males and 7.3% (7/97) in females. The overall incidence of malignant pheochromocytoma was 2% (2/98) in males and 0% (0/96) in females (NTP, 1997).]

Regarding preneoplastic lesions of the lung, deposition of talc in the lungs caused an inflammatory and proliferative response, with alveolar epithelial hyperplasia, squamous metaplasia, intra-alveolar accumulation of macrophages, chronic granulomatous inflammation, interstitial fibrosis, and squamous cysts of the lung (considered by the authors as a form of squamous metaplasia) in males and females. Regarding non-neoplastic lesions of the lung, statistically significant increases in incidence in both treatment groups and sexes were observed compared with the control group. In females, the incidence of lung granulomatous, histiocytic peribronchial hyperplasia, lung alveolar epithelium hyperplasia, and focal fibrosis of the interstitium was significantly increased in both treated groups; the incidence of cyst (squamous type) hyperplasia and of squamous alveolar metaplasia was significantly increased in the group at the higher dose.

[The Working Group noted that this was a well-conducted GLP study that covered most of the lifespan, used an adequate number of animals per group, both sexes, two doses, and an adequate duration of exposure and observation.]

3.2.3 Intraperitoneal administration

In a study by Bluemel et al. (1962), 30 albino rats [age and sex not reported] were treated, after laparotomy (intraperitoneal application), with 400 mg of talc powder [not further characterized]. Ten rats were used as negative controls and underwent the surgical procedure only. Granuloma formations (see Section 4.2.6) were observed after 6 months in treated rats [no indication was given as to the percentage of animals and the exact location of the granulomas]. Talcum granuloma contains numerous foreign body giant cells. No granulomas were observed in the controls. No increase in the incidence of tumours was observed in treated rats. [The Working Group noted the lack of information on talc characteristics, age and sex of the animals, and in life end-points such as body weight, the short study duration, and the small number of rats used. Therefore, the Working Group considered this study to be uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

A group of 40 female Wistar rats (age, 8–12 weeks) was exposed through intraperitoneal injection to 25 mg of talc (in the form of magnesium silicate) in 2 mL of saline, once per week, for 4 weeks (Pott et al., 1974, 1976a, b). The sample was not contaminated with fibres such as asbestos [characteristics not further specified]. A control group of 80 female rats was injected with 2 mL of saline alone. The rats were observed until spontaneous death or euthanized when moribund. The average survival time was 602 days for exposed rats and 592 days for rats in the control group. The histological examination was limited to tissues suspected of being tumours in the chest or abdomen.

A single tumour (2.5%) occurred among the 40 treated rats that were necropsied, and no tumours occurred in the 80 controls. The tumour was described by the author as "histologically nearly the sarcomatous mesotheliomata" and was observed at day 587 (Pott et al., 1974, 1976a, b).

[The Working Group noted the adequate number of controls. Only one dose was tested, and no information was provided on talc purity, or on body weight and survival, duration of exposure and observation, and terminal euthanasia. The Working Group also noted the low sensitivity of this assay for the detection of carcinogenesis after exposure to talc, because partial histopathology was performed only on macroscopic lesions observed at necropsy. It was

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not clear when the last rat was euthanized. The only time-related information provided was the duration that elapsed before development of the first tumour.]

3.2.4 Intrapleural and intrathoracic administration

In a study by Wagner et al. (1977), 48 Wistar rats (24 females and 24 males) (age, 8–14 weeks) were inoculated intrapleurally (in the right pleural cavity) with a single dose of 20 mg of talc diluted in a saline solution to a concentration of 50 mg/mL. The talc (Italian grade 00000) had an upper particle size of 70 µm and a mean particle size of 25 µm and did not contain asbestos [Italian talc 00000 grade contains approximately 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5–1.0% quartz by weight and is considered to be high-purity industrial talc]. For comparison, 24 female and 24 male rats were injected intrapleurally with a single dose of 20 mg of SFA chrysotile (asbestos). The control group consisted of 24 female and 24 male rats that were injected intrapleurally with saline. The rats were kept until natural death or euthanized if they appeared to be distressed. The last rat died approximately 2 years and 8 months after inoculation. Mean survival times were 598 days for rats in the chrysotile group, 655 days for the talc group, and 691 days for the control group. The approximately 1-month difference in survival in rats in the talc group compared with the control group was found to be statistically nonsignificant and was attributed to chance.

Of the rats injected with chrysotile, 18/48 (37.5%) developed mesothelioma, whereas none of the rats injected with talc or saline developed mesothelioma. Intrapleural inoculation with talc resulted in injection-site granulomas, and one rat injected with talc developed a small pulmonary adenoma and died 25 months after injection. No other relevant pathology of the lung was identified in these animals.

[The Working Group noted that this was a lifetime study, used both sexes, had an adequate number of animals per group, randomly allocated in groups, and used a new dosing route for talc. However, only a single dose was used, the data for males and females were combined, and there was a lack of information on the statistical tests performed. In addition, the reporting was very limited; in particular, there was a lack of data on the proportion of animals affected by injection-site granulomas, no explanation was given regarding granuloma development time, and no histological description of the granulomas (presence of talc, types of cells, etc.) was provided. The size of the "small" lung adenoma was not reported.]

In a study comprising 72 experiments by Stanton et al. (1981), durable minerals, in the form of particles of respirable size, were applied intrapleurally to observe the development of pleural sarcoma in rats and its relation to the dimensional distribution of the particles. Among these 72 experiments, there were seven (experiment numbers 53, 60–62, and 70–72) involving seven types of talc particle, named talc 1 to talc 7. [Purity information for these talcs was not provided. However, it was noted that these talcs were refined for the synthesis of commercial products and were from a variety of sources.]

A single dose of 40 mg of particles [purity not reported] uniformly dispersed in hardened gelatin was applied by open thoracotomy directly to the left pleural surface in outbred female Osborne-Mendel rats (age, 12–20 weeks). In each of the seven experiments, a group of 26–30 rats was treated (talc 1, 26 rats; talc 2, talc 5, and talc 6, 30 rats; talc 3, talc 4, and talc 7, 29 rats) and followed for 2 years, after which the survivors were euthanized. According to the authors, the positive response was the observation of pleural sarcoma, which resembles human mesenchymal mesothelioma, after the first year. [The Working Group noted that in the "Materials and methods" section of the article, it was indicated that three

types of control were included: untreated rats, rats with thoracotomy only, and rats with thoracotomy and pleural implants of nonfibrous material. In another section of the article ("Results"), the three groups of controls were described as untreated rats, rats with thoracotomy and non-carcinogenic pleural implants, and rats with thoracotomy and non-carcinogenic pulmonary implants, of the same sex and age.] The incidence of pleural sarcoma in the control rats was 0.6% (3/488) in untreated rats, 2.1% (9/432) in controls with non-carcinogenic pulmonary implants, and 2.8% (17/598) in controls with non-carcinogenic pleural implants. For comparison with the treated groups, a combined control group was created by summing the incidence of the three control groups (total, 1.9%; 29/1518).

The probability of the incidence of pleural sarcoma [according to the authors "resembling human mesothelioma"] in the control and treated groups was calculated using the life-table method and was 7.7 ± 4.2% in the combined controls. In none of the talc-treated groups was incidence significantly higher than in the combined controls: talc 1 (experiment 53), tumour incidence, 1/26, tumour probability, 7 ± 6.9%; talc 2 (experiment 61), tumour incidence, 1/30, tumour probability, 4 ± 3.8%; talc 3 (experiment 60), tumour incidence, 1/29, tumour probability, 4 ± 4.3%; talc 4 (experiment 62), tumour incidence, 1/29, tumour probability, 5 ± 4.9%. In the groups treated with talc 5, talc 6, or talc 7 (experiments 70, 71, and 72, respectively), the tumour incidence was 0/30, 0/30, and 0/29, respectively.

The authors mentioned that some spontaneous tumours developed that could confuse the study results: fibrosarcomas of the mammary gland (which were surgically removed) and subcutaneous fibrosarcomas induced by suture material, which were avoided by using appropriate suture material. Despite these precautions, a few tumours in both control and treated groups remained questionable and were counted as pleural sarcomas.

[The Working Group noted the adequate duration of the study, the multiple (and adequate) control groups, the thorough histopathological evaluation, the reporting of fibre dimensions, and the well-conducted statistical analysis. The Working Group also noted that the definition of the types of control differed in two different sections of the article (see above). Talc purity was not reported, and only one sex was used. There were no details reported on the preneoplastic changes that the authors found in the 72 experiments; the authors did not specify which preneoplastic changes appeared and in which experiments.]

3.2.5 Intravaginal or perineal application

In this experiment, 28 female Sprague-Dawley rats [age not reported], were divided into four groups of 7 rats each to test the local application of talc in the vagina and perineum (Keskin et al., 2009). There were two control groups: group 1 was untreated, and group 2 was treated intravaginally with 0.5 mL of saline. Additionally, there were two treated groups that received intravaginal or perineal applications of talc (groups 3 and 4, respectively). Talc [purity not reported] was administered in aerosol form at a dosage of 100 mg in 0.5 mL of saline on a daily basis for 3 months. Baseline cervicovaginal smears were obtained and revealed vaginitis in 2 rats (one from a treated group and the other from a control group). At the end of the experiment [assumed to be 3 months], the rats were euthanized, and samples of the vulva, vagina, uterus, fallopian tubes, and ovaries were collected for histopathology. [The Working Group noted that the perineum was not sampled.] At this point, there was no significant difference in body weight between the control groups (251 ± 23 g) and the treated groups (229 ± 17 g). Rats in the talc-treated groups (groups 3 and 4) exhibited foreign body reactions [without further specification], findings of infection [specific findings not reported],

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and an increased number of inflammatory cells, although there were no neoplasms or peritoneal changes.

No neoplasms were observed in control or treated rats.

[The Working Group noted that this study was poorly conducted and reported. In addition, the Working Group noted the small number of animals per group, that talc purity was not reported, and the short duration of the study. Regarding the results, there were contradictions between the different sections of the article, and it contained numerous mistakes. The Working Group considered that the study was uninformative for the evaluation of the carcinogenicity of talc in experimental animals, and it was not tabulated.]

3.2.6 Ovary implantation (by intrabursal injection)

Talc was bilaterally injected into the ovarian bursae, which were extracted through surgery from 50 female Sprague-Dawley rats (age, 10–15 weeks). These rats were kept in close proximity to male rats. The injection consisted of 100 µL of a talc suspension (Italian grade 00000) at a concentration of 100 mg/mL in phosphate-buffered saline. The talc suspension was composed of a heterogeneously sized population of platy crystals with a size range of 0.3–14 µm and contained no asbestos [Italian talc 00000 grade contains approximately 92% talc, 3% chlorite, 1% carbonate minerals, and 0.5–1.0% quartz by weight and is considered to be high-purity industrial talc] (Hamilton et al., 1984). Fifteen age-matched controls, 15 sham-operated controls, and 15 sham-treated (vehicle only) controls were included. At intervals of 1, 3, 6, 12, and 18 months after treatment, 10 treated animals, 3 age-matched controls, 3 sham-operated controls, and 3 sham-treated controls were euthanized. Histology of the ovaries and associated (adherent) tissues was performed only in treated and control rats euthanized at 12 months.

No neoplasms were observed in the ovaries of treated or control animals. In four of the injected ovaries, a notable occurrence of small focal areas displaying papillary changes, without evidence of cytoplasmic or nuclear atypia, was observed. Mitotic figures were not identified. In the control cases, these papillary changes were absent.

Foreign body granulomas (see Section 4.2.6), devoid of any surrounding inflammation and typically located in the cortical areas, were observed in five of the ovaries that had been injected with talc. Similar lesions were also identified in the supracapsular fat and in the connective tissue matrix of the capsule [specific numbers not provided]. The presence of talc within the granulomas was confirmed through both histological examination and electron microscopy microanalyses.

3.2.7 Co-carcinogenicity studies

A total of 256 barrier-protected Caesarean-derived Wistar rats [age not reported] were used in seven batches to study whether secondary intrapleural injections of bacillus Calmette–Guérin (BCG) vaccine, crystalline silica, and talc influence the appearance of crocidolite (asbestos)-induced mesotheliomas. Crocidolite was suspended in physiological saline (50 mg/mL), and a dose of 20 mg was injected into the right pleural cavity. Several months after the injection of crocidolite asbestos, a supplemental treatment course was initiated for some rats, and others were left untreated as controls within the batches (Wagner et al., 1980).

In batch 7, 24 female and 24 male rats (age, 10 weeks) underwent crocidolite treatment and, 13 months later, received intrapleural talc (Italian grade 00000) as an additional treatment. The talc, amounting to 40 mg, was suspended in saline and injected in two equal doses with

an 8-week interval. In this batch, 12 female and 12 male rats were additionally treated with talc, and another 12 female and 12 male rats served as untreated controls. [The Working Group noted that there was a lack of adequate controls (crocidolite followed by saline only).] Rats were allowed to live until death unless they displayed signs of distress. In batch 7, one control rat died 2 days after asbestos injection, and another rat died after talc injection and was considered as lost.

In batch 7 (crocidolite followed by talc), the incidence of mesothelioma in the rats in the talc-treated group was 7/23 (30%), and mean survival was 604 days. In comparison, the incidence of mesothelioma was 9/24 (37.5%) in the rats treated with crocidolite only, and mean survival was 592 days. The first mesothelioma in the talc-treated group appeared after 455 days, whereas in the control group, the first mesothelioma occurred after 506 days.

[The Working Group noted that in this study males and females were combined, the study was poorly reported, and there was a lack of adequate controls.]

3.3 Hamster

See Table 3.3.

3.3.1 Inhalation exposure

Three groups of 50 male and 50 female Syrian golden hamsters (age, 4 weeks), were exposed to an aerosol of talc baby powder prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite, and rutile) for 3, 30, or 150 minutes per day, 5 days per week, for 30 days (Wehner et al., 1977a, 1979). The average aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and an MMAD of 4.9 µm. [The Working Group noted that this appeared to be a respirable dimension for hamsters.] Two other groups of 50 male and 50 female Syrian golden hamsters (age, 7 weeks) were exposed to talc aerosol for 30 or 150 minutes per day, 5 days per week, for 300 days, with an average aerosol concentration of 27.4 mg/m^3, a measurable respiratory fraction of 8.1 mg/m^3, and an MMAD of 6.0 µm. The two control groups included 25 males and 25 females that were placed in the exposure chamber with filtered room air for 30 or 300 days to simulate the same stress as the exposed groups. The hamsters were observed for their natural lifespan. The experiment was terminated when 90% of the hamsters had died in the group with the most survivors. The number of deaths was recorded throughout the course of the experiment. In all groups, males survived longer than did females. There was no significant difference in survival between the exposed groups and their respective controls. Most of the hamsters in the groups designed to be exposed to talc for 300 days died before completion of the whole exposure. [The specific reason for these deaths was not reported.] The survivors of these groups and the corresponding control group were euthanized at the age of 20 months when all females and more than 80% of males were dead. Histopathological examination was conducted on the lungs with trachea and larynx, heart, liver, one kidney, stomach, one ovary and the uterus, or one testis, and all gross lesions.

No primary tumours were observed in the lungs of any hamster. The incidence, type, and severity of the lesions in the larynx and trachea, lungs, heart, and liver showed no significant difference between exposed and control groups. Overall, there was no significant increase in the incidence of any tumour type after exposure to talc. [The Working Group noted that both sexes were used, the duration of the observation was adequate, there was an adequate number of animals per exposed group, and multiple exposure groups were tested. The Working Group also noted that the daily exposure duration was short and the number of control animals per sex was

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Table 3.3 Studies of carcinogenicity in hamsters exposed to talc

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Hamster, Syrian golden (M) 4 wk Lifetime Wehner et al. (1977a)	Inhalation Talc powder; purity, 95% (w/w) Room air 0 (filtered air), 3, 30, 150 min/d, 5 d/wk, for 30 d (average aerosol concentration, 37.1 mg/m^3) 25, 50, 50, 50 NR, NR, NR, NR	*Systemic (multiple organs)* No significant increase in tumour incidence in treated animals		*Principal strengths:* Both sexes used, adequate number of animals per exposed group, multiple dose studies, adequate duration, stratified randomization of animals. *Principal limitations:* Excessive mortality early in the study, statistical tests not specified, short daily exposure duration, small number of control animals per sex group, high mortality rate, and detailed methods for statistical analysis not reported.
Full carcinogenicity Hamster, Syrian golden (F) 4 wk Lifetime Wehner et al. (1977a)	Inhalation Talc powder; purity, 95% (w/w) Room air 0 (filtered air), 3, 30, 150 min/d, 5 d/wk, for 30 d (average aerosol concentration, 37.1 mg/m^3) 25, 50, 50, 50 NR, NR, NR, NR	*Systemic (multiple organs)* No significant increase in tumour incidence in treated animals		*Principal strengths:* Both sexes used, adequate number of animals per exposed group, multiple dose studies, adequate duration, stratified randomization of animals. *Principal limitations:* Excessive mortality early in the study, statistical tests not specified, short daily exposure duration, small number of control animals per sex group, high mortality rate, and detailed methods for statistical analysis not reported.
Full carcinogenicity Hamster, Syrian golden (M) 7 wk Lifetime Wehner et al. (1977a)	Inhalation Talc powder; purity, 95% (w/w) Room air 0 (filtered air), 30, 150 min/d, 5 d/wk, for 300 d (average aerosol concentration, 27.4 mg/m^3) 25, 50, 50 NR, NR, NR	*Systemic (multiple organs)* No significant increase in tumour incidence in treated animals		*Principal strengths:* Both sexes used, adequate number of animals per exposed group, multiple dose studies, adequate duration, stratified randomization of animals. *Principal limitations:* Excessive mortality early in the study, statistical tests not specified, short daily exposure duration, small number of control animals per sex group, high mortality rate, and detailed methods for statistical analysis not reported.
Full carcinogenicity Hamster, Syrian golden (F) 7 wk Lifetime Wehner et al. (1977a)	Inhalation Talc powder; purity, 95% (w/w) Room air 0 (filtered air), 30, 150 min/d, 5 d/wk, for 300 d (average aerosol concentration, 27.4 mg/m^3) 25, 50, 50 NR, NR, NR	*Systemic (multiple organs)* No significant increase in tumour incidence in treated animals		*Principal strengths:* Both sexes used, adequate number of animals per exposed group, multiple dose studies, adequate duration, stratified randomization of animals. *Principal limitations:* Excessive mortality early in the study, statistical tests not specified, short daily exposure duration, small number of control animals per sex group, high mortality rate, and detailed methods for statistical analysis not reported.

Table 3.3 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Co-carcinogenicity Hamster, Syrian golden (M, F) 9 wk Lifetime Stenbäck and Rowlands (1978)	Intratracheal instillation Talc, USP grade Saline Control (untreated), control (saline-treated), talc, talc plus B[a]P (3 mg/dose) 1×/wk, for 18 wk 48, 48, 48 46, 48, 45	*Systemic (multiple organs)* No significant increase in the incidence of any tumour type by talc exposure		*Principal strengths:* Studies in both males and females, adequate number of animals, adequate duration of observation. *Principal limitations:* Only one dose, lack of group treated with B[a]P only, data combined for both sexes, short survival.

B[a]P, benzo[*a*]pyrene; d, day(s); F, female; h, hour(s); M, male; min, minute(s); NR, not reported; USP, United States Pharmacopeia; wk, week(s); w/w, weight per weight.

small, the mortality rate of the animals was high, and detailed methods for the statistical analysis were not reported.]

3.3.2 Intratracheal administration

Four groups of 48 Syrian golden hamsters (24 males and 24 females) (age, 9 weeks) received 18 weekly treatments by intratracheal administration of: (i) 3 mg of talc (USP grade; 61–63% silica oxide, 32–34% magnesium oxide, 0.85–1.06% other dusts; 93.3% of fibres were < 25 µm in diameter) in 0.2 mL of saline; (ii) 3 mg of talc with 3 mg of benzo[*a*]pyrene (B[*a*]P) in 0.2 mL of saline; (iii) 0.2 mL of saline; or (iv) were untreated (Stenbäck and Rowlands, 1978). The hamsters were observed for their lifespan. The average median lifespan was 46 weeks, 52 weeks, and 55 weeks, for the groups of males and females (combined) treated with talc, talc plus B[*a*]P, and saline, respectively. The survival rate was lower in females than in males in all groups except the saline-treated group. Histopathological examination was conducted on the lungs, trachea, larynx, liver, kidneys, spleen, and other organs showing gross lesions.

There was no significant difference in the incidence of any tumour type in talc-treated hamsters and controls. Additionally, in the talc-treated group, no neoplasms were found in the respiratory system.

In the concomitant co-carcinogenicity experiment, respiratory tract malignancies were observed in 33/45 hamsters treated with talc plus B[*a*]P. Tumours were found throughout the respiratory tract but mainly in the lung. [The Working Group noted that both sexes were used, the duration of observation was adequate, and there was an adequate number of animals per group. The Working Group also noted that results were given for males and females combined, only one dose was tested, there was no adequate control group for the co-carcinogenicity experiment (a B[*a*]P-treated group), and survival was short.]

3.4 Evidence synthesis for cancer in experimental animals

The carcinogenicity of talc has been assessed in one well-conducted GLP study in male and female B6C3F$_1$ mice treated by inhalation (whole-body) (NTP, 1993), and in one well-conducted GLP study in male and female F344/N rats treated by inhalation (whole-body) (NTP, 1993). The carcinogenicity of talc was also evaluated in studies that did not comply with GLP. Specifically, talc was tested by oral administration (in feed) in male and female Wistar rats in two studies (Gibel et al., 1976; Wagner et al., 1977); by inhalation (whole-body) in one study in male and female Wistar rats (Wagner et al., 1977), and one study in male and female Syrian golden hamsters (Wehner et al., 1977a, 1979); by intraperitoneal administration in one study in female NMRI mice (Pott et al., 1976a), one study in Swiss albino mice [sex not reported] (Ozesmi et al., 1985), one study in male White mice (Jagatic et al., 1967), one study in Swiss albino rats [sex not reported] (Bluemel et al., 1962), and one study in female Wistar rats (Pott et al., 1974); by subcutaneous injection in one study in female R3 mice (Neukomm and de Trey, 1961) and one study in female NMRI mice (Pott et al., 1976a); by intrapleural administration in one study in Balb/C mice [sex not reported] (Davis, 1972), one study in male and female Wistar rats (Wagner et al., 1977), and one study in female Osborne-Mendel rats (Stanton et al., 1981); by intratracheal instillation in one study in male and female Swiss albino mice (Sahu et al., 1978) and one study in male and female Syrian golden hamsters (Stenbäck and Rowlands, 1978); by intrapleural or perineal application in one study in female Sprague-Dawley rats (Keskin et al., 2009); and by

ovary implantation (intrabursal injection) in one study in female Sprague-Dawley rats (Hamilton et al., 1984). In addition, there was one co-carcinogenicity study in male and female Wistar rats treated by intrapleural injection (Wagner et al., 1980).

In the inhalation study that complied with GLP in male and female F344/N rats (NTP, 1993), for males, there was a significant positive trend in the incidence of benign pheochromocytoma of the adrenal medulla, and in the incidence of benign bilateral pheochromocytoma of the adrenal medulla, and benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla, with the incidence being significantly increased in the group at the higher dose.

For females, there was a significant positive trend in the incidence of malignant pheochromocytoma of the adrenal medulla, and in the incidence of benign or malignant pheochromocytoma of the adrenal medulla, with the incidence being significantly increased at the highest dose. There was a significant positive trend in the incidence of bilateral malignant pheochromocytoma and bilateral benign pheochromocytoma of the adrenal medulla, with the incidence of benign bilateral pheochromocytoma being significantly increased at the higher dose. There was a significant positive trend in the incidence of bronchioloalveolar adenoma, in the incidence of bronchioloalveolar carcinoma, and in the incidence of bronchioloalveolar adenoma or carcinoma (combined), with the incidence being significantly increased at the higher dose. A single case of lung squamous cell carcinoma was observed in females at the higher dose.

[This study used MP 10-52-grade, well-characterized microtalc (no asbestos fibres were detected), and the major impurities found were 0.7% aluminium and 1.0% iron for lot 1 and 0.1% calcium, 0.5% aluminium, and 1% iron for lot 2. The Working Group noted that this study showed a significant increase in malignant tumours in females (i.e. bronchioloalveolar carcinoma and malignant pheochromocytoma of the adrenal medulla). The Working Group also noted a significant increase in the combination of benign or malignant tumours in the same organ (adrenal medulla) in females (benign or malignant pheochromocytoma) and in males (benign, complex, or malignant pheochromocytoma). In addition, the Working Group noted that this study included two unusual results: (i) the significant increase in the incidence of bilateral pheochromocytoma (benign and malignant) in females; and (ii) the development of adrenal tumours after exposure to talc by inhalation.]

In the inhalation study that complied with GLP in male and female B6C3F$_1$ mice (NTP, 1993), no significant increases in the incidence of neoplasms were observed in either sex. In addition, no significant increases in the incidence of neoplasms were observed in the studies that did not comply with GLP. Specifically, no significant increases in the incidence of neoplasms were observed by oral administration (in feed) in male and female Wistar rats in two studies (Gibel et al., 1976; Wagner et al., 1977); by inhalation (whole-body) in male and female Wistar rats in one study (Wagner et al., 1977), and in male and female Syrian golden hamsters in one study (Wehner et al., 1977a; 1979); by intraperitoneal administration in Swiss albino mice [sex not reported] in one study (Ozesmi et al., 1985) and in female Wistar rats in one study (Pott et al., 1974); by intrapleural administration in male and female Wistar rats in one study (Wagner et al., 1977) and in female Osborne-Mendel rats in one study (Stanton et al., 1981); by intratracheal instillation in male and female Swiss albino mice in one study (Sahu et al., 1978) and in male and female Syrian golden hamsters in one study (Stenbäck and Rowlands, 1978); by ovary implantation (intrabursal injection) in female Sprague-Dawley rats in one study (Hamilton et al., 1984); and by intrapleural injection (co-carcinogenicity) in male and female Wistar rats in one study (Wagner et al., 1980).

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Studies on subcutaneous injection in female R3 mice (Neukomm and de Trey, 1961) and female NMRI mice (Pott et al., 1976a); on intraperitoneal administration in male White mice (Jagatic et al., 1967) and in albino rats [sex not reported] (Bluemel et al., 1962); on intrapleural administration in Balb/C mice [sex not reported] (Davis, 1972); and on intrapleural or perineal application in female Sprague-Dawley rats (Keskin et al., 2009) were considered to be uninformative for the evaluation of the carcinogenicity of talc in experimental animals.

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

Information on the absorption, distribution, and excretion of talc was sparse, and most relevant studies were conducted in the early 1960s to 1990s. These studies showed limitations in the sensitivity of the detection methods used and in the measurement of particle size. There was no evidence that talc is metabolized either in humans or in experimental systems. The Working Group noted that the identified studies in humans that provided evidence of the absorption and distribution of talc, reported below, were not designed to evaluate absorption, distribution, and excretion, but were observational studies, often with the aim of measuring disease-related outcomes such as pneumoconiosis and fibrosis.

4.1.1 Exposed humans

(a) Absorption, distribution, and excretion

(i) Inhalation

In six workers from the talc industry, the observation of talc particles and talc bodies in bronchoalveolar lavage fluid, sometimes many years after the end of exposure, suggested that talc can be inhaled and accumulate in the lung (de Vuyst et al., 1987). Transmission electron microscopy coupled to energy-dispersive X-ray spectrometry (TEM-EDX) and selected area electron diffraction were used to identify talc in these samples. In another study, the bronchoalveolar lavage fluid of 51 occupationally exposed participants, including six talc millers, was examined for nonfibrous particle content using a transmission electron microscope fitted with a scanning attachment (STEM) (Dumortier et al., 1989). Among the talc millers, the lavage fluid of two workers contained almost exclusively talc, while for the other millers the fluid contained about 60% talc and 40% chlorite. In other workers, talc generally accounted for < 3% of the particles in lavage fluid. It was noted for one of the millers that, although exposure had ceased 21 years before the examination, talc particles were still present in the lavage fluid. In a small group of steelworkers, STEM showed that the bronchoalveolar lavage fluid contained nonfibrous particles, including talc. The particle number per millilitre of bronchoalveolar lavage fluid, especially for iron hydroxides and silicates, was higher in blast-furnace workers than in office workers (Corhay et al., 1995).

Talc particles have been found at autopsy in the lungs of patients with "talc pneumoconiosis" (Schepers and Durkan, 1955a; Seeler, 1959; Kleinfeld et al., 1963; Abraham and Brambilla, 1980; Berner et al., 1981; Vallyathan and Craighead, 1981, cited in IARC, 2010). In the form of platy or elongated particles, talc has been found at autopsy in the lungs of urban residents, farmers, and asbestos miners (Seeler, 1959; Langer et al., 1971; Pooley, 1976; Gylseth et al., 1984, cited in IARC, 2010).

In addition, talc has been reported to be concentrated in lung scar tissue, as detected by SEM with EDX (Yao et al., 1984). In a group of 14 male smokers who had lung cancer, but no history of occupational exposure to dust, concentrations of mineral fibres and nonfibrous

particles (determined by TEM-EDX) were higher than in the control group of men without cancer (Churg and Wiggs, 1985). Kaolinite, talc, mica, feldspar, and crystalline silica comprised the majority of fibrous and nonfibrous particles in both groups; asbestos was present in some cases. In a subsequent study, Churg and Wiggs (1987) examined the distribution of mineral fibres in the lungs of 10 male smokers who did not have lung cancer or a history of occupational exposure to dust. Kaolinite, silica, and mica accounted for 64% of the fibres; feldspar and talc accounted for 9% and 7%, respectively. There was a significant correlation between smoking history and particle concentration (number of particles per gram of tissue) in the upper lung lobes (Churg and Wiggs, 1987).

The presence of talc was observed in the lung area affected by interstitial pulmonary fibrosis in a patient who had a history of almost daily recreational inhalation of methamphetamine (Baylor et al., 2013). In another clinical case, talcosis was attributed to the patient's habit since childhood of powdering the whole body with talcum powder after bathing. Extracellular sheets and fibres were found in extensive amounts, and SEM combined with back-scattered electron imaging and EDX analysis of the crystals in the lung biopsy specimen showed the presence of particles of magnesium, silicon, and (sporadically) chlorine. The structure of these particles, together with the presence of magnesium and silicon, was consistent with talc (van Huisstede et al., 2010). In a woman aged 50 years with talcosis, bronchoalveolar lavage fluids were found to contain abundant macrophages with white crystals, consistent with inhalational pulmonary talcosis; talcosis was associated with excessive application of talcum face powder during the previous 2 years (Cho et al., 2021). In another case, pulmonary talcosis was associated with daily inhalation of talc, since the morphology of the crystals found in granulomas was similar to that of talc, and the patient reported abundant use (Verlynde et al., 2018).

The presence of talc fibres was also observed in the intestinal wall of a patient aged 46 years who had severe intestinal pain and was diagnosed with intestinal talcosis (Anani et al. 1987). The possible source of exposure was talc contained in oral medications for the treatment of tuberculosis, which the patient had taken nearly 20 years previously over a period of 22 hours (total talc intake, 183 g).

(ii) Intraperitoneal and intravenous injection

Talc is often added as a filler in some materials used to prepare illicit drugs; this can lead to systemic distribution of talc particles throughout the body, including the lungs (reviewed in IARC, 2010). Crystalline plates of talc were observed in the lungs of a patient who had an addiction to heroin and died of respiratory failure (Crouch and Churg, 1983). [The Working Group noted that the massive granulomas observed in the lungs of this patient may have been a consequence of intravenous injection of talc.]

Induction of lung disease was also considered in a patient with multiple scattered pulmonary lesions and a history of intravenous drug use (Krimsky and Dhand, 2008). In a patient presenting with talc retinopathy associated with an approximately 10-year period of intravenous drug use, fine, irregularly shaped retractile deposits were observed in the retinal microvasculature (Martidis et al., 1997). In a study of 12 patients, small yellow-white particles, probably of talc, in the retina were linked to intravenous injection of crushed methylphenidate hydrochloride (Ritalin) (Schatz and Drake, 1979). Pulmonary talcosis, characterized by the presence of perivascular foreign body granuloma formation in the lungs, was reported in 17 out of 80 patients who had been previously using heroin and dissolving oral methadone tablets for intravenous injection (formulated with 5% talc) (Paré et al., 1979); in people with an addiction to

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cocaine (Lazzaro et al., 2021); and in other drug users (Low and Nicol, 2006). Most patients had talc particles in their organs (Paré et al., 1979). [The Working Group noted that, in many of the case reports, the identified particles were not always proven to be talc.]

Lazzaro et al. (2021) evaluated fibres considered to be consistent with talc according to electron microscopy followed by EDX analysis. The fibres were initially described as amphibole asbestos on the basis of morphology (Lazzaro et al., 2021). [The Working Group noted that, on the basis of the limited information provided by the authors, it was unclear whether the EDX spectral analysis was consistent with the presence of fibrous talc.]

Griffith et al. (2012) reported the presence of talc crystals (detected by polarized light microscopy, PLM), some described as plate-like material and others as more needle-like, in the lymph nodes, liver, bone marrow, and heart of nine patients clinically diagnosed with pulmonary hypertension. Six of the patients had reported a history of (intravenous) drug addiction (Griffith et al., 2012). The persistence of talc particles in patients with a drug addiction has been documented in autopsy and biopsy specimens of the lung, spleen, liver, bone marrow, and lymph nodes (Mariani-Costantini et al., 1982), and kidneys (AtLee, 1972). Abraham and Brambilla (1980) observed the formation in the lungs of larger size talc particles after intravenous injection than after inhalation (Abraham and Brambilla, 1980).

(iii) Other routes of exposure

Distribution through the female perineum and reproductive tract

In five case reports of women with ovarian carcinoma who reported perineal use of talc, the presence of talc was detected at multiple pelvic sites distant from the perineum (McDonald et al., 2019a). Talc was detected (by both PLM and SEM, plus EDX analysis) in each of the patients, typically at two or more of the following locations: pelvic region lymph nodes, uterine cervix, uterine corpus, fallopian tubes, and ovaries. Numerous birefringent particles (size range, 1–5 µm) were reported within the macrophages of a left external iliac lymph node. The migration of particles to lymph nodes and to other pelvic sites suggested the importance of lymphatic pathways in the distribution of talc. [The Working Group noted that talc may access the lymphatic system directly at the perineum (the typical initial exposure location) or at any point in its ascent through the genital tract towards the fallopian tubes and ovaries.]

Noteworthy, the talc identified by McDonald et al. was mostly polygonal and nonfibrous; nevertheless, 18 fibre-like talc particles were found with an aspect ratio of 5:1 or more. These were found in areas where talc accumulated the most e.g. macrophages, lymph nodes. [The Working Group noted that the presence of more heterogeneously sized particles was most likely to be because of the natural distribution of these particles.] Only four fibres with a long aspect ratio (≥ 10:1) were found, and these were not asbestos.

McDonald et al. (2019b) measured talc particles in the pelvic lymph nodes of 22 patients with ovarian cancer. The mean concentration of talc particles in the pelvic lymph nodes of women with perineal use of talc was higher than that in women without perineal use of talc. However, of the 10 women who reported perineal use of talc, nine also indicated regular use of talc on other parts of the body. [The Working Group noted that, on the basis of the provided information, it could not be determined whether the talc was specifically derived from perineal application.]

The presence of plate-like particles of talc was also observed in the pelvic lymph nodes of a woman with ovarian cancer who reported daily use of talc for 30 years as a body powder on the perineum (Cramer et al., 2007). Talc was also detected in ovarian tissue from 24 women who had undergone incidental oophorectomy, which

was suggestive of transvaginal transport of the talc applied to the perineum. However, the talc particle counts showed no quantitative relation with estimated level of talc use (Heller et al., 1996b).

Surgically resected pelvic tissue (from hysterectomies) from talc-exposed patients with ovarian carcinoma contained small, isodiametric particles similar to those that were predominant in talc-containing baby powder, showing that particles could migrate from the perineum and lodge in distal structures of the female reproductive tract (Johnson et al., 2020). Most of the talc particles found in resected tissue from patients with ovarian carcinoma had both a small area and a small aspect ratio; elongated fibres of talc with a large aspect ratio were rarely found in these resected specimens. In a study of ovarian tissue samples from 100 women with "grossly normal" ovaries who were undergoing surgery for pelvic disease, "crystalline foreign particles" were reported in histological evaluations of the samples from 9% of women. Of these sample, four were analysed (by SEM and microscopic X-ray analysis) and shown to contain particles that were composed largely of magnesium and silicon, and were thus consistent with talc (Mostafa et al., 1985).

Some of the studies have addressed the transport of talc particles through the female reproductive tract. Green et al. (1997) observed that tubal sterilization was associated with a 39% reduction in risk of ovarian cancer in 104 study participants and that the use of talc in the perineal region slightly but significantly increased cancer risk among women with patent (normal) fallopian tubes, although no *P*-value was reported (Green et al., 1997). [The Working Group noted that these findings supported the theory that contaminants from the vagina (such as talc) and from the uterus (such as endometrium) could gain access to the peritoneal cavity through patent fallopian tubes and might enhance the malignant transformation of ovarian surface epithelium. The Working Group also noted that these data were further supported by the results of larger pooled studies (see Section 2; O'Brien et al., 2020)]

[The Working Group noted that studies from Egli and Newton (1961), De Boer (1972), and Venter and Iturralde (1979) suggested that other substances could migrate from the vagina through the uterus and the fallopian tubes to the peritoneal cavity and ovaries, supporting the existence of this route of distribution.]

In earlier studies, talc particles were identified in approximately 10 out of 13 ovarian tumours analysed and were also found to be embedded within the tumour tissue of the cervix (Henderson et al., 1971). In addition, talc was detected in 11 out of 13 samples of ovarian tissue collected from women who were exposed to household asbestos and had previously undergone ovarian surgery, and from 17 women (controls) who were undergoing oophorectomy for benign ovarian neoplasms (Heller et al., 1996a). [The Working Group noted that the two studies above, although reporting relevant evidence of talc accumulation in target organs, did not adequately describe exposure to the agent.]

The same research groups provided further evidence of the presence of talc in the ovaries of women who had purportedly had perineal exposure to talc (Henderson et al., 1979; Heller et al., 1996b).

Distribution after intrapleural exposure and deposition into the lungs

In six surgical specimens collected from patients who had previously undergone talc pleurodesis (2–15 hours earlier) followed by extrapleural pneumonectomy, talc particles were observed underneath the pleura and, in some cases, also in the lung parenchyma (Ghio et al., 2012).

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Talc particles were also detected in hernia sacs, suggesting possible routes of access of particulate material to the subserosa of hernia sacs including the blood stream, lymphatic system, and the peritoneal cavity, in which the cellular response is weak (Pratt et al., 1985). The authors postulated that talc flakes, in the form of tiles, observed in five consecutive inguinal herniorrhaphy procedures might have migrated through the gastric or intestinal epithelium, submucosa, wall, and serosa, with no requirement for perforation.

Accidental talc aspiration

Fifty-nine cases of aspiration pneumonia were investigated for the presence of exogenous material into the lungs. Highly polarizable material consistent with talc and microcrystalline cellulose were found in 7 of the 59 tissue samples (12%) (Mukhopadhyay and Katzenstein, 2007). The presence of talc, microcrystalline cellulose, and crospovidone was linked to presumably accidental aspiration of medications containing these components. [The Working Group noted that aspiration of talc has been rarely reported, mainly accidentally in children; aspiration of components from oral medications has not been specifically reported. In addition, the Working Group noted that there was uncertainty as to whether the material observed in the lungs was talc.]

Talc crystals were present in stomach tumour tissues. Particulate material was detected in stomach tumours removed from Japanese male patients, and talc crystals (in addition to asbestos) were shown to be present in all the seven samples of tumour tissue (Henderson et al., 1975). [The Working Group noted that the source of exposure was uncertain, and some of the tumour tissues also contained asbestos.]

(b) Metabolism

No evidence was available on whether talc is metabolized in exposed humans.

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

(i) Inhalation

Inhaled talc is retained in the lungs of rodents exposed chronically. Hanson et al. (1985) and Pickrell et al. (1989) studied lung burden in groups of five male and five female F344/N rats and $B6C3F_1$ mice after inhalation exposure to talc for 6 hours per day, 5 days per week, for 4 weeks. The mean exposure concentrations used were 2.3, 4.3, or 17 mg/m^3 for rats and 2.2, 5.7, or 20.6 mg/m^3 for mice. The resulting lung talc burdens were 0.08, 0.19, and 0.87 mg/g of lung for rats and 0.1, 0.33, and 1.2 mg/g of lung for mice. [The Working Group noted that these data clearly indicated that the amount of talc retained per unit of lung tissue was proportional to the dose.] In rats exposed for 7.5 hours per day, 5 days per week, to aerosols of Italian talc (see description in Section 3) (mean concentration of respirable dust, 10.8 mg/m^3), the average amounts of talc retained in the lungs were 2.5, 4.7, and 12.2 mg per animal after exposures of 3, 6, and 12 hours, respectively (Wagner et al., 1977). However, in hamsters treated with a single dose of 2.7 mg of talc by inhalation (2-hour, nose-only), approximately 6–8% of the talc was observed to be retained in the alveoli for up to 7–10 days (biological half-life in the lungs), with complete clearance at around 4 months after administration (Wehner and Wilkerson, 1981). In the above study, no migration of talc was observed to other organs such as the liver, kidneys, or ovaries. Also, deposition of talc particles was observed in the lungs of Syrian golden hamsters exposed to talc aerosol for 3, 30, or 150 minutes per day, 5 days per week, for 30 days, or once for 30 or 150 minutes per day (Wehner et al., 1977a, b).

The results of a lifetime study in F344 rats exposed to talc aerosol at 0, 6, or 18 mg/m^3 (NTP, 1993) suggested effects in other organs in addition to the lung. The aerosol contained talc that was non-asbestiform and of cosmetic

grade; effects were observed in the lung and the adrenal gland (see Section 3.2.2). The accumulation of talc in the lungs of rats exposed at 6 mg/m^3 was similar in males and females and increased progressively from 6 to 24 hours. After a higher dose of 18 mg/m^3, the talc burden in the lungs increased progressively between 6 and 24 hours in female rats, whereas the level of talc in the lungs of male rats remained unchanged up to 18 months. In a 2-year study in B6C3F$_1$ mice exposed to aerosols containing talc at 0, 6, or 18 mg/m^3, non-neoplastic effects were observed in the lungs. Exposure to talc at 6 or 18 mg/m^3 in both sexes progressively increased the burden in the lungs from 6 to 24 months, except for males at 18 months. [The Working Group noted that the burden in the lungs of mice exposed to talc at 18 mg/m^3 was disproportionately greater than that of mice exposed at 6 mg/m^3, thus suggesting that clearance of talc from the lungs was impaired to a greater extent in mice at 18 mg/m^3 than in mice at 6 mg/m^3.]

(ii) Intraperitoneal and intravenous injection

Limited distribution of talc in alveolar capillaries of the lungs, liver, and abdominal lymph nodes was seen after repeated intravenous injection in guinea-pigs (75 mg per animal). Some talc particles in these organs, but no severe effects, were observed at up to 150 days after injection (Dogra et al., 1977). [The Working Group noted that the particles of talc, obtained from India, were well characterized; size distribution and chemical analysis were reported.]

Persistence of talc in peritoneal tissues was originally described by Miller and Sayers (1936) in studies in which talc, among other dust particles, was administered intraperitoneally to guinea-pigs. The authors described an "inert reaction", meaning that the amount of injected dust remained approximately the same in the peritoneal cavity throughout the duration of the studies, but nodules were observed, and fine particles of dust were distributed by phagocytes over quite extensive areas in the peritoneum (Miller and Sayers, 1936).

(iii) Oral administration

Orally ingested talc was excreted shortly after dosing. The absorption and disposition of ^{3}H-labelled talc, administered as a single oral dose at 50 mg/kg to rats, at 40 mg/kg to mice, and at 25 mg/kg to guinea-pigs, was investigated by Phillips et al. (1978). In all three species, > 95% of the dose was excreted in the faeces 3–4 days after dosing. Less than 2% of the radioactivity was recovered in the urine. [The Working Group noted that the presence of the radioactivity probably reflected contamination of urine samples with faeces.] No radioactivity was found in the liver or kidneys of these animals.

Talc was administered by gastric intubation to six Syrian golden hamsters (aged 10 weeks) kept in metabolism cages (Wehner et al., 1977b). The hamsters were killed 24 hours after gavage, and the skinned carcass, gastrointestinal tract, lungs, liver, kidneys, and samples of urine and faeces were analysed. An average of approximately 3 mg of talc was found in the tissues and in the excreta. Of this, 74.5% was found in the faeces, 23.5% in the gut, and 1.9% in the carcass. The concentrations of talc in the lungs, kidneys and liver did not differ significantly from those in the control tissues, suggesting that intestinal absorption of talc was negligible, and it could have contributed only minimally to the body burden of talc found in hamsters in a previous study (Wehner et al., 1977a). Therefore, no or negligible intestinal absorption or translocation of ingested talc to the liver and kidneys was detected, and the majority of the talc was excreted shortly after dosing. [The Working Group noted that the use of ^{3}H-labelled talc is an unusual approach, referenced only in a brief letter by Gangolli et al. (1973). The Working Group also noted some overinterpretation of the findings.]

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(iv) Other routes of administration

Intravaginal or intrauterine exposure

After intravaginal exposure in rabbits, no translocation to the ovaries was observed. Translocation in rabbits after administration of a single or multiple intravaginal doses (50 mg/kg) was investigated by Phillips et al. (1978); no talc was found in rabbit ovaries.

Similarly, no translocation from the vagina to the uterus was observed in monkeys. A pilot study of intravaginal exposure in two monkeys treated with 125 mg of neutron-activated talc (suspended in 0.3 mL of deionized water containing 1% carboxymethyl cellulose) did not show any measurable quantity (i.e. > 0.5 pg) of talc translocated from the deposition site in the vagina to the uterine cavity and beyond. Likewise, no translocation was observed for a 1% bone black suspension (Wehner et al., 1985). A second study from the same group confirmed that no measurable quantities of talc, deposited by multiple applications in the vaginal fornix of the cynomolgus monkey, translocated to the uterus or beyond (Wehner et al., 1986).

In contrast, talc particles were identified in the ovaries of all the rats that received a single dose of 250 µL of a talc suspension of 100 mg/mL (in saline phosphate-buffered solution) by intrauterine administration and in two rats that received talc by intravaginal administration and were killed after 4 days, although it was not seen in rats killed at 24 and 48 hours (Henderson et al., 1986).

Whole-body exposure

Potential transport of talc particles to the ovaries was explored as one element of the NTP toxicity study of lifetime whole-body exposure in rats (Boorman and Seely, 1995) (see also Section 3). In this study, rats were exposed to a talc aerosol at concentrations sufficient to cover their fur and cage bars, providing opportunity for perineal as well as oral and respiratory exposure. Examination of the ovaries and ovarian bursa showed no evidence of material consistent with talc, although talc was identified in the lungs.

Intrapleural exposure

Intrapleural exposure of talc, in general, did not result in relevant systemic distribution in rodents. After the administration of sterile talc at 0.2 mg/mL, by pleurodesis, in the right hemithorax of rats, examination of the brain, liver, and kidney did not reveal any systemic distribution, and granulomas caused by talc were observed in the opposite hemithorax (Zorlu et al., 2021). In another study, no systemic dispersion of talc particles was reported 24 or 72 hours after the administration of talc at 40 mg/mL by intrapleural exposure (Fraticelli et al., 2002). Despite high doses of talc (extrapolated from a dose of 10 g for an adult man weighing 70 kg), few talc particles were found in the liver of two rats and in the spleen of one rat, and only one particle of talc was observed at the brain surface of a rat studied by SEM. No particles were found in other organs, the contralateral lung, or blood (Wagner et al., 1977).

In contrast, rapid absorption through the pleural surface, not dose-related, and systemic distribution were reported in rats. Systemic distribution of 10 or 20 mg/mL of talc crystals (a dose usually employed for pleurodesis) was observed 24 or 48 hours after instillation into the pleural space of rats (Werebe et al., 1999). Talc crystals distributed to every organ – lungs, chest wall, liver, kidneys, spleen, heart, and brain – independently of the talc dose used or the time of death.

In rabbits, asbestos-free talc, administered intrapleurally, distributed systemically through the blood stream (Stamatelopoulos et al., 2009). Intrapleural administration of talc at 200 mg/kg led to a high degree of early talc deposition followed by epithelial injury in the tissues examined: lungs, mediastinum, and parietal pleura. Talc of large size was absorbed

rapidly through the pleura, reaching the blood stream via the lymphatic system, and was deposited in the various intrathoracic organs shortly after intrapleural administration.

In one study (Ferrer et al., 2002), two groups of 10 rabbits received asbestos-free talc particles of 8.4 µm or 12 µm in size at a dose of 200 mg/kg bw. Five animals from each group were killed 24 hours and 7 days after talc instillation. An increase in extrapulmonary distribution of the smaller particles was observed at 7 days after instillation; these particles were identified in the pericardium of 3 out of 5 rabbits. The smaller particles were also identified in the liver of 3 out of 5 rabbits 7 days after instillation; other animals did not show particles in the liver. Smaller particles were also found in the kidney in a single rabbit (1 out of 5), 24 hours after instillation. For the larger particles, talc was observed in the pericardium at each time point in 1 out of 5 rabbits. Both particle types were found in the spleen 24 hours after instillation in 1 out of 5 rabbits. [The Working Group noted that the results indicated that talc reached the lung parenchyma by breaching the mesothelial and elastic layers, and that migration was greater for the smaller particles.]

In another study, Montes et al. (2003) induced pleurodesis in rabbits (20 per group) with talc at doses of 50 and 200 mg/kg bw. Doses were chosen to simulate the treatment of a patient with a body weight of 60 kg with 3 g or 12 g of talc. Talc was found in the lungs of 2 rabbits at the lower dose and 14 rabbits at the higher dose. In the group at the higher dose, 6 rabbits had talc in the pericardium and 5 had talc in the liver. Talc was not detected in these organs in rabbits at the lower dose. Systemic distribution was dose-dependent.

(v) In vitro data

The uptake of talc particles by rabbit lung fibroblasts was investigated in cell culture, where it was shown that the particles could penetrate the cell membrane (Henderson et al., 1975).

(b) Metabolism

No evidence was available that talc is metabolized experimental systems (see also Section 4.1.1).

In summary, although no relevant data on the metabolism of talc could be identified, the available data in humans and the experimental data suggested that inhaled talc is retained in the lungs, whereas talc that is injected intravenously is distributed systemically. Conversely, in rodents, inhaled talc was not observed in other organs apart from the lungs; orally ingested talc was excreted shortly after dosing; and no or negligible intestinal absorption or translocation of talc to the liver and the kidneys was observed. The persistence of inhaled talc in the human lung for years after exposure cessation was documented in a few case reports, whereas in rodents exposed to talc for up to 4 weeks, alveolar clearance was reported to be essentially complete between 4 and 12 months.

In humans, talc was identified at multiple pelvic sites distant from the perineum, was lodged in distal structures in the female reproductive tract and was associated with reported perineal use of talc. However, in most studies in animals, no translocation from the perineal region to the ovaries was reported.

4.2 Evidence relevant to key characteristics of carcinogens

This section reviews the mechanistic data for the 10 key characteristics of carcinogens (Smith et al., 2016) encompassed by talc. Evidence was available on whether talc exhibits the key characteristics "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "alters DNA repair or causes genomic instability", "induces epigenetic alterations", "induces oxidative stress", "induces chronic inflammation", "is immunosuppressive", "modulates receptor-mediated effects", and "alters cell proliferation, cell death, or nutrient supply". No data were available

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for the evaluation of the key characteristic "causes immortalization".

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

In the only relevant study identified, Lundberg et al. (1997) reported on interactions between mineral talc and proteins. The authors aimed to investigate to what extent glove powders of different origins and brands (one mineral talc and five cornstarch powders) were able to bind and release latex allergens. For this purpose, the various powders were incubated with natural rubber latex sap. According to the information provided by the manufacturer, the mineral talc (Talc FM20, Herkules Kemiska AB, Germany) contained 46% silicon dioxide (SiO_2), 0.4% aluminium(III) oxide (Al_2O_3), 1.1% iron(III) oxide alias ferric oxide (Fe_2O_3), 3% iron(II) oxide alias ferrous oxide (FeO), 2.2% calcium oxide (CaO), and 32% magnesium oxide (MgO). Of the powders tested, talc showed the highest tendency to bind isotope-labelled proteins such as β-lactoglobulin and rabbit immunoglobulin, thus reducing free allergen from latex gloves. In addition, it showed a strong capacity to firmly bind latex allergens, as observed in vitro in serum samples from patients with an allergy to latex gloves. It was shown that the surface of mineral talc can attract proteins, including haptens.

[The Working Group considered that this study was of limited relevance because of the absence of specific information on the protein-binding mechanism that would have allowed a conclusion to be drawn regarding the electrophilic properties of talc.]

4.2.2 Is genotoxic

(a) Humans

(i) Exposed humans

No data on the genotoxic effects of talc in exposed humans were available to the Working Group.

(ii) Human cells in vitro

In an in vitro assay for chromosomal aberrations in anaphase cells, human embryonic lung (WI-38) cells were exposed to talc at concentrations of 2, 20, and 200 µg/mL (Table 4.1). Talc did not induce chromosomal aberrations (US FDA, 1974). [The Working Group considered this study to be of limited relevance because of the lack of characterization of the agent and the lack of scoring of anaphase cells.]

Talc from two different geographical regions (India or North America) were tested in human lung epithelial cells (A549 cell line) (Akhtar et al., 2014). Indigenous nanotalc (IN) particles were collected from Rajasthan, India. Commercial nanotalc (CN) particles of North American origin were purchased from the MK Impex company in Mississauga, Canada. When measured with TEM microscopy, the test samples IN and CN were shown to contain nanotalc of crystalline nature, with an average particle size of 94 or 91 nm, respectively. IN and CN talc induced DNA fragmentation, as a marker of cell death or apoptosis; however, there was no assay for end-points specifically associated with genotoxicity. [The Working Group noted that the relevance of the end-point for genotoxicity was low.] The authors also reported that both talc samples induced cytotoxicity and alteration in cell cycle phases and induced oxidative stress, as indicated by the generation of ROS, lipid peroxidation, and depletion of antioxidant levels (see also Section 4.2.5).

Table 4.1 End-points relevant to genotoxicity in human cells in vitro exposed to talc

End-point	Tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Chromosome aberrations (in anaphase)	Human embryonic lung cultures (WI-38)	–	NT	NA	Tested at 2, 20, 200 µg/mL. No indication of exposure time. Sensitive method for the detection of chemical clastogens, but not for other types of aberration.	US FDA (1974)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NT, not tested.
[a] –, negative.

(b) Experimental systems

Non-human mammals in vivo

Mutagenicity was investigated in three different test models: a host-mediated assay, in vitro and in vivo; cytogenetics assays, in vitro and in vivo; and an assay for dominant lethal mutation in vivo. The test compound was described as FDA 71-43, talc, lot number 11-16-17 (#141), as supplied by the Food and Drug Administration (Table 4.2) (US FDA, 1974). [The Working Group noted that no other information on the identity of the agent was available.]

In this study, talc did not induce chromosomal aberrations in vivo. Groups of male albino rats were exposed by gavage to talc at 30, 300, 3000, or 5000 mg/kg per bw as a single dose or as repeated doses once daily, for 5 days (US FDA, 1974). Saline was used as the negative control, and triethyl melamine (0.3 mg/kg per bw, intraperitoneal administration) as the positive control. Fifty metaphase spreads were scored per animal. [The Working Group noted that the study was limited by the quality of the study protocol, in which fewer than the 200 metaphases per animal, recommended for the study design, were scored.]

Talc did not induce dominant lethal mutations in male rats exposed as described above. The authors measured fertility index, total implants (numbers of live fetuses plus early and late fetal deaths), total deaths (early and late fetal deaths), dead implants per total implants, and preimplantation loss (calculated as the difference between the total counts for corpora lutea and for total implants). Two experiments were performed. In the first experiment, exposure to talc as a single dose or once daily for 5 days at 30, 300, or 3000 mg/kg bw by gavage caused significant dose-related decreases in average corpora lutea and preimplantation losses at weeks 4 and 5. The average number of resorptions increased significantly at week 3, and the subacute exposures caused significant differences in the proportions of females with one or more and two or more dead implants at week 6.

In the second experiment, exposure to talc as a single dose or once daily for 5 days at 5000 mg/kg per bw by gavage did not cause any significant differences in all the above measured parameters between talc-treated rats and rats in the negative control group (US FDA, 1974). [The Working Group noted that a small number of animals was used for the study. The Working Group also noted that, although the authors concluded that there were no dose–response or time-trend patterns and that talc did not induce dominant lethal mutations, the positive findings could not be ruled out.]

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Table 4.2 End-points relevant to genotoxicity in non-human mammals in vivo exposed to talc

End-point	Species, strain, (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Gene mutation (host-mediated assay with *S. cerevisiae* in mice) (For comparison, a microdrop of 0.01–0.25 mL of talc was evaluated in an Ames test using *Salmonella typhimurium* TA1530 and G46 and *Saccharomyces cerevisiae* D)	Mice, ICR (M)	*S. typhimurium* TA1530 and G46 and *S. cerevisiae* D3 were the indicator organisms	–	30, 300, 3000 (LD_5), 5000 mg/kg bw talc	Gavage, single dose, killed 3 h after dosing	No significant increase in mutant or recombinant frequencies in the host-mediated assay. Saline was the negative control and dimethyl nitrosamine (100 mg/kg bw) and ethyl methane sulfonate (intramuscular administration, 350 mg/kg bw) were the positive controls. (Talc was not mutagenic in the Ames test.)	US FDA (1974)
			–	30, 300, 3000 (LD_5), 5000 mg/kg bw talc	Gavage, once daily for 5 d, killed 0.5 h after last dose		
Gene mutation (dominant lethal assay)	Rat, Sprague-Dawley (M)		–	30, 300, 3000 (LD_5), 5000 mg/kg bw	Gavage, single dose, killed 3 h after dosing	Some positive parameters but did not show dose–response or time-trend patterns and results were considered negative. Saline was used as the negative control and triethyl melamine (intraperitoneal, 0.1 µg/mL) was used as the positive control.	US FDA (1974)
			–	30, 300, 3000 (LD_5), 5000 mg/kg bw	Gavage, once daily for 5 d, killed 0.5 h after last dose		
Chromosomal aberrations	Rat, albino (M)	Bone marrow	–	30, 300, 3000 (LD_5), 5000 mg/kg bw	Gavage, single dose, killed at 6, 24, or 48 h after dosing	Saline was used as the negative control and triethylmelamine (intraperitoneal, 0.3 mg/kg bw) was used as the positive control.	US FDA (1974)
			–	30, 300, 3000 (LD_5), 5000 mg/kg bw	Gavage, once daily for 5 d, killed 6 h after last dose		

bw, body weight; d, day(s); h, hour(s); HID, highest ineffective dose; LD_5, lethal dose for 5% of the animals; LED, lowest effective dose; M, male.

[a] –, negative.

Talc was reported to give negative results in the host-mediated assay (US FDA, 1974). In this assay, *Salmonella typhimurium* strains TA1530 and G46 and *Saccharomyces cerevisiae* D3 were the indicator organisms, and groups of male ICR mice were exposed as described above. Saline was the negative control, and dimethyl nitrosamine (100 mg/kg per bw) and ethyl methane sulfonate (350 mg/kg per bw) (intramuscular) were the positive controls. [The Working Group noted that the methodology for the assay described in the report lacked detailed information. The studies were also deemed of limited relevance because of the lack of characterization of the agent.]

In an older study from Van Wissen and Prop (1972), no clear effects on DNA levels were observed in the nuclei of peritoneal cells sampled from mice exposed to talc (Van Wissen and Prop, 1972). Two mice were injected intraperitoneally with 2 mL of a talcum powder suspension (0.9% saline solution) and were killed after 48 hours. Peritoneal cavity cells were analysed by Feulgen staining and classified in DNA percentage classes. The formation of sustained adhesions in the peritoneal cavity were observed, and this limited the analysis at 48 hours. [Although the staining method used in the study was considered to be specific and sensitive for evaluating DNA damage, and DNA quantification in cell nuclei by image cytometry could allow the evaluation of ploidy, the Working Group noted that the work was poorly reported and lacked a thorough description of the talc sample. Therefore, the negative result was not deemed relevant for the present evaluation.]

Synopsis

[The Working Group noted that few studies were available, and mainly negative findings were reported. Notably, most of the genotoxicity studies were conducted before the implementation of GLP, and had limited design protocols; thus, they did not appropriately address the evidence of genotoxicity-associated end-points.]

4.2.3 Alters DNA repair or causes genomic instability

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

A sample of talc-based powder (USP, catalogue No. 8476, control NAP, Mallinckrodt) was tested for the capacity to support transfection in a simple system based on picornavirus RNAs and mammalian cells in vitro, alongside 13 forms of asbestos, non-asbestos minerals, and chemicals (Dubes and Mack, 1988). These samples were tested in four different cell lines: human carcinoma cells (KB), epithelioid cells from normal chimpanzee liver (CLI), epithelioid cells from normal rhesus monkey kidney (Eta), and mouse embryo fibroblasts from normal Swiss mouse embryo (NIH3T3). An inoculum of viral RNA was used to induce transfection, with or without the presence of talc (2.5 mg/mL); the results suggested that talc facilitates transformation and thus may have some impact on carcinogenesis. [The Working Group considered that the relevance of this test system for informing DNA repair or genomic instability was low, since the methods served to translocate nucleic acids across cell membranes rather than to affect DNA per se. In addition, the test item was poorly described, and only a single concentration was tested.]

More recently, Endo-Capron et al. (1993) measured unscheduled DNA synthesis (UDS) and sister-chromatid exchange (SCE) in rat pleural mesothelial cells (PMCs). In this study, three test samples of European talc provided by Eurotalc (Brussels, Belgium) were studied: (i) French talc (No. 7841); (ii) Italian talc (No. 5726); and (iii) Spanish talc (No. 5725). The samples contained 90–95% talc together with chlorite and dolomite. Particles were dispersed in culture medium

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at a concentration of 560 µg/mL by sonication for 5 minutes (20 kHz, 3 W). TEM was used to analyse particles at a concentration of 100 µg/mL and showed that none of the three samples of talc contained asbestos fibres. The number of long particles (> 4 µm) was much higher in asbestos samples than in the talc samples. TEM studies indicated that talc was mainly located in the perinuclear region of the PMCs. However, none of the talc samples induced UDS (10, 20, and 50 µg/cm^2, 24 hours), SCE, or aneuploidy (2.5, 10, and 15 µg/cm^2, 48 hours). The positive controls for UDS, crocidolite and chrysotile, showed enhancement of UDS; the positive controls for SCE, mitomycin C and potassium chromate, induced statistically significant increases in the frequency of SCE (Table 4.3). [The Working Group noted that the scientific community considers UDS and SCE end-points measured in vitro to be of less relevance for "alters DNA repair" than are other end-points related to genotoxicity or DNA repair.]

Synopsis

[Overall, the Working Group noted that few studies were available.]

4.2.4 Induces epigenetic alterations

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

Yumrutas et al. (2015) treated 28 female rats with talcum powder at a dose of 100 mg/kg via the intraluminal route at the uterine horn during the proliferative phase of the menstrual cycle, for 1 month; the ovarian tissues were excised at the end of the experiment. The authors measured expression levels of four microRNAs (miRNAs) (miR-15b, miR-21, miR-34a, and miR-98) and the expression of selected antioxidant, apoptotic and antiapoptotic genes in the ovarian tissues. In the exposed group, upregulation of two antioxidant genes, glutathione reductase (GSR) and superoxide dismutase 1 (SOD1), was reported (see Section 4.2.5). Although miRNA expression levels were higher in the treated group than in the non-treated group, the difference was not statistically significant. [The Working Group noted that no information on the purity or composition of talc was reported. The Working Group also noted that while some genes were upregulated, results were not significantly different to those for the control group.]

(ii) Non-human mammalian systems in vitro

Using a model for studying the macrophage/phagocyte response, Emi et al. (2021) exposed a phagocytic murine cell line (J774) to asbestos-free talc (manufacturer-certified USP grade; particle diameter, < 10 µm) at a concentration of 10 µg/well in 100 mm Petri dishes (concentrations of approximately micrograms per millilitre), with or without pretreatment with 17β-estradiol (E2) (2 µg/mL). The macrophages in the groups treated with talc plus estradiol demonstrated dysregulation of proteins related to epigenetic maintenance. Subsequently, genome-wide DNA methylation profiling of these cells showed 1243 differentially methylated positions ($P < 0.05$, not adjusted for multiple testing) and overall global demethylation of the genome. Overall demethylation was observed only in the group treated with talc plus estradiol, compared with the group treated with the vehicle, but not in the groups treated with estradiol or talc alone. Immune and inflammatory genes were epigenetically dysregulated. In addition, combined exposure to talc plus estradiol induced substantially more transcriptomic signatures than did exposure to talc alone, thus suggesting a general response of the macrophages to talc and potential synergism. [The Working Group noted that the main effect of talc alone was not described in detail in this study, and multiple hypothesis testing was not

Table 4.3 End-points relevant to genotoxicity in non-human mammalian cells in vitro exposed to talc

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
UDS	Rat, PMCs (primary cells)	–	NT	10, 20, 50 µg/cm^2 (1 µg/cm^2, equivalent to 5 µg/mL)	Crocidolite and chrysotile were used as the positive controls, and both showed enhancement of UDS. It appeared that the number of cells was reduced compared with that of untreated cells, but no sign of cytolysis was detected by TEM.	Endo-Capron et al. (1993)
SCE	Rat PMCs (primary cells)	–	NT	2, 5, 10, 15 µg/cm^2 (1 µg/cm^2 was equivalent to 5 µg/mL) 48-h exposure	The positive controls, mitomycin C and potassium chromate, induced statistically significant increases in SCE, but crocidolite did not. It appeared that the number of cells was reduced, compared with that of untreated cells, but no sign of cytolysis was detected by TEM.	Endo-Capron et al. (1993)

h, hour(s); HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; PMC, pleural mesothelial cell; SCE, sister-chromatid exchange; TEM, transmission electron microscopy; UDS, unscheduled DNA synthesis.

[a] –, negative.

considered in the interpretation of the results. The Working Group also noted that the alteration in global DNA methylation observed in the cells was a nonspecific effect and was measured within a very short period (24 hours).]

Synopsis

[The Working Group noted that only in a single study in vivo was it reported that the administration of talc to female rats upregulated the expression of some miRNAs in ovarian tissues, although the results did not reach statistical significance. In another study in an in vitro model of the macrophage/phagocyte response, talc, when co-administered with estradiol, was reported to induce changes in the DNA methylation changes in immune and epigenetic maintenance related genes. However, statistical analysis and poor study design limited the relevance of the findings. Overall, the evidence was scarce that talc induces epigenetic alterations.]

4.2.5 Induces oxidative stress

(a) Humans

(i) Exposed humans

See Table 4.4.

The pro-oxidant properties of talc were investigated in one study in exposed humans. This study involved 48 subjects with pneumoconiosis and 90 healthy controls from a cohort of stone-craft workers in Hualien, Taiwan, China. The author identified 8-oxo-2′-deoxyguanosine (8-oxodG) in the urine of workers exposed to asbestos-contaminated minerals (nephrite, antigorite, talc) (Yang, 2019). [The Working Group considered that this study was not informative because the asbestos content of the individual materials was not reported, and the level of serum soluble mesothelin-related peptide was identified as a parameter that was positively associated with the severity of pneumoconiosis. In addition, no specific information on the impact of talc on oxidative stress induction was provided; thus, this report should be regarded being focused on the health impacts of asbestos contamination, rather than those of talc itself. The Working Group noted that urinary 8-oxodG/creatinine-adjusted levels were higher in the workers than in the controls, (mean ± SD, 185 ± 393.2 ng/mg versus 133.1 ± 65.2 ng/mg), although the difference was not statistically significant. However, the author used logistic regression to calculate the area under the receiver operating characteristic curve and, according to the criteria used, urinary 8-oxodG was still a predictor for pneumoconiosis. The Working Group also noted the lack of information regarding the exposure assessment.]

(ii) Human cells in vitro

See Table 4.5.

The role of talc in the neoplastic transformation of human ovarian cells and the potential protective effects of plant bioflavonoids were investigated by Buz'Zard and Lau (2007). Talc was shown to induce a dose-dependent increase in ROS in immortalized normal ovarian epithelial cells (OSE2a), and normal granulosa ovarian stromal non-tumorigenic cells (GC1a), as well as in primary polymorphonuclear neutrophils in heparinized venous blood collected from healthy volunteers.

Talc treatment of human cancer cell lines, including lung adenocarcinoma A549 and acute monocytic leukaemia THP-1 cells, was reported to induce ROS production and lipid peroxidation, and to alter the levels of the antioxidant glutathione (GSH) (Akhtar et al., 2010, 2014; Ahmad, 2011). [However, the Working Group considered these studies to be of limited informativeness because they used cancer cell lines. Also, limited information was reported regarding the study design and methodology applied.]

(b) Experimental systems

See Table 4.6.

Table 4.4 End-points relevant to oxidative stress in humans exposed to talc

End-point	Assay	Biosample type	Location, setting, study design	Exposure level, No. of exposed and controls	Response[a] (significance)	Covariates controlled	Comments	Reference
8-oxodG/ creatinine-adjusted	ELISA	Urine	Hualien, China Cohort of stone-craft workers Observational study	Workers exposed to asbestos-contaminated minerals (48 participants with pneumoconiosis, 90 healthy controls)	↑ ($P = 0.37$)	Smoking	The study did not specifically focus on the health impacts of talc, but rather on the possible effects of asbestos contamination. Logistic regression model.	Yang (2019)

ELISA, enzyme-linked immunosorbent assay; 8-oxodG, 8-oxo-2′-deoxyguanosine.
[a] ↑, increase.

Table 4.5 End-points relevant to oxidative stress in human cells in vitro exposed to talc

End-point	Assay	Cell type	Results[a]	Concentration (LEC or HIC)	Treatment, duration	Comments	Reference
ROS	DCFH-DA	Immortalized normal ovarian epithelial (OSE2a) and ovarian granulosa (GC1a) cell lines	↑	0.5 µg/mL	0–500 µg/mL for 24–120 h	Talc from Sigma, St Louis, Missouri, USA.	Buz'Zard and Lau (2007)
		Primary polymorphonuclear neutrophils	↑				
ROS, GSH, MDA, LDH	DCFH-DA, TBARS, fluorometry	Lung adenocarcinoma (A549)	↑	50 µg/mL	50–200 µg/mL for 48 h	Microtalc/nanotalc, particle size = 65 µm to 120 nm. Talc nano powder, particle size = 70–120 nm. From MK Impex Canada, Mississauga, Canada, but origin was USA. Microtalc (indigenous), particle size = 50–65 µm. Used as control. From Udaipur, Rajasthan, India.	Akhtar et al. (2010)
LPO, LDH ROS, GSH; TNFα	DCFH-DA, TBARS, fluorometry; RT-PCR, WB	Lung adenocarcinoma (A549), acute monocytic leukaemia (THP-1)	↑	50 µg/mL	50–200 µg/mL for 48 h	Limited information on study design and methods. The study cited results published in Akhtar et al. (2010).	Ahmad (2011)
ROS, LPO, GSH	DCFH-DA, TBARS, fluorometry	Lung adenocarcinoma (A549)	↑	200 µg/mL	200 µg/mL for 48 h	Nanotalc, average particle size ~90 nm.	Akhtar et al. (2014)
Activity of SOD, CAT	Spectrophotometry-based methods		↓				
Pro-oxidants iNOS, NO_2^-/NO_3^-, and MPO	RT-PCR and NO_2^-/NO_3^- assays		↑				

CAT, catalase; DCFH-DA, 2′,7′-dichlorodihydrofluorescein diacetate; GSH, glutathione; h, hour(s); HIC, highest ineffective concentration; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; LEC, lowest effective concentration; LPO, lipid peroxidation; MDA, malondialdehyde; MPO, myeloperoxidase; NO_2^-, nitrite; NO_3^-, nitrate; ROS, reactive oxygen species; RT-PCR, reverse transcription-polymerase chain reaction; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substances; TNFα, tumour necrosis factor alpha; USA, United States of America; WB, western blotting.

[a] ↓, decrease; ↑, increase.

Table 4.6 End-points relevant to oxidative stress in non-human mammalian systems exposed to talc

End-point	Assay	Species, strain (sex)	Tissue cell line	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Superoxide	Indirect effect	Dog, beagle (M, F)	Artery	Prophylactic effect of hr-SOD on basilar artery narrowing	0.1 g in 7.5 mL saline solution	0.1 g/7.5 mL saline, single injection; talc/hr-SOD infusion Talc injection to basilar artery; administration of hr-SOD	No information on talc properties; indirectly shows that talc induces oxidative stress that may impact vasocontraction.	Mori et al. (1995)
SOD2, GPx-1	WB	Rat, Sprague-Dawley (M, F)	Lung	↑ SOD2 Effects for GPx-1 limited to males at the lowest dose (5 mg/m^3)	SOD2: Males, 5 mg/m^3 Females, 100 mg/m^3	0, 5, 50, and 100 mg/m^3; inhalation for 6 h daily, 5 d/wk for 4 wk	Ultra-fine white talcum powder from Rex Material, Republic of Korea; no asbestos reported in the test item.	Shim et al. (2015)
GSR, SOD1	RT-PCR	Rat, Wistar albino (F)	Ovary	↑	100 mg/kg	100 mg/kg; talc powder inserted in uterine horn to mimic non-surgical sterilization, and observations made 1 month after exposure	No information on talc properties. A study reporting effects of talc in ovarian tissue.	Yumrutas et al. (2015)
LPO	Indirect measurement	Mouse, C57BL/6 × DBA/2) F_1 (F)	Splenocytes	↑ Stress	200 µg/mL	Cells pretreated with 10 µg/mL *Escherichia coli* 055:B5 LPS, then exposed to talc at 0–2000 µg/mL for 72 h; in vitro experiment	Talc of USP grade (magnesium silicate), particle size = 3–5 µm). From JT Baker Chemical Co., New Jersey, USA. LPO was not directly measured in the study. Data were not clearly reported.	Hoffeld (1983)
LPO	TBARS	Rat, Sprague-Dawley (M)	Alveolar macrophages	↑	2 mg/mL	2 mg/mL; in vitro experiment	Talc from commercial source, Montana talc, Montana, USA.	Ghio et al. (1992)
ROS, expression of cancer-related genes	Flow cytometry (ROX Green)	Mouse	Ovarian surface epithelial cells, macrophages (J774 and IC-21)	↑	1 µg/well	Up to 20 µg/well; in vitro experiment	Talc particle diameter < 10 µm. From JT Baker, USA. Asbestos-free.	Mandarino et al. (2020)

bw, body weight; CAT, catalase; DMPO, 5,5-dimethyl-1-pyrroline *N*-oxide; d, day(s); F, female(s); GPx, glutathione peroxidase; GSH, glutathione; GSR, glutathione reductase; GST, glutathione *S*-transferase; h, hour(s); HID, highest ineffective dose; hr, human recombinant; LED, lowest effective dose; LPO, lipid peroxidation; LPS, lipopolysaccharide; M, male(s); MDA, malondialdehyde; NR, not reported; RT-PCR, reverse transcription-polymerase chain reaction; ROS, reactive oxygen species; ROX, 6-carboxy-X-rhodamine; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substances; USA, United States of America; USP, United States Pharmacopeia; WB, western blotting; wk, week(s).
↑, increase.

(i) Non-human mammals in vivo

In dogs, a single injection of talc induced inflammation in the basilar artery that was reversed by administration of human recombinant SOD (hr-SOD), suggesting a role for superoxide (Mori et al., 1995). [The Working Group noted that no information was reported on talc purity and source.]

Talc inhalation affected the expression of antioxidant enzymes (SOD2, GPx-1) in rats (Shim et al., 2015) and the induction of antioxidant genes (GSR, SOD1) expression in rat ovarian tissue (Yumrutas et al., 2015). [The Working Group noted that Yumrutas et al. did not report information on talc purity and identity (see also Section 4.2.4).]

[The Working Group also noted that in the study by Mori et al. (1995), it was not clear why extracellular hr-SOD (administered to the dogs) would have reduced the effects of superoxide generated intracellularly (e.g. in macrophages). The control injection was saline. Inactivated hr-SOD might have been a better control since the observed effect of SOD could have been nonspecific rather than caused by its activity.]

(ii) Non-human mammalian systems in vitro

Talc induced lipid peroxidation in cultured splenocytes from (C57BL/6 × DBA/2)F_1 female mice (Hoffeld, 1983). Lipid peroxidation was assessed indirectly by measuring the inhibition of the effects of talc (0–2000 µg/mL) in lipopolysaccharide-stimulated cells (10 µg/mL) with antioxidants (α-tocopherol or 2-mercaptoethanol. [The Working Group noted that the study had limitations regarding the data reporting and because of the use of an indirect measurement of oxidative stress.]

In rat alveolar macrophages, an increase in levels of thiobarbituric acid-reactive substances (TBARS) was observed after exposure to commercial talc pretreated with iron, reflecting increased generation of oxidants and lipid peroxidation (Ghio et al., 1992). [The Working Group noted that this study did not include control cells, and data were not properly reported.]

A co-culture of murine ovarian surface epithelial cells and macrophages was treated with talc at a concentration of up to 20 µg/sample, and ROS production was assessed after 4 hours of exposure (Mandarino et al., 2020). In this artificial system used to investigate a potential mechanism for an increased risk of ovarian cancer associated with perineal use of talc, elevated ROS production was found in macrophages in the presence of estradiol. [The Working Group considered that this study was of limited informativeness, because the effects of talc were investigated together with co-exposure to estradiol.]

Synopsis

[The Working Group noted that the reviewed studies indicated a role for talc in the induction of oxidative stress, although with some limitations. The only identified study in human populations was not designed to investigate the oxidative effects of talc in humans; thus, its findings needed cautious interpretation. Experiments in human cells were mostly limited to cancer cell lines whose nature (e.g. genome instability, physiologically/morphologically heterogeneous cultures) may lead to misleading results. In one study in vivo (Mori et al., 1995), the control was not optimally selected, and the observed effects (i.e. decreases in superoxide production) were not sufficiently explained. Overall, there was a limited number of relevant studies and some of the reported end-points of oxidative stress are known to be of low specificity.]

4.2.6 Induces chronic inflammation

(a) Humans

(i) Exposed humans

Medical use of talc (talc pleurodesis)

Because of its irritant properties, talc is able to trigger a strong acute inflammatory response. Therefore, talc has been widely used as a chemical irritant in pleurodesis, a therapeutic surgical procedure to obliterate the pleural space to prevent or treat recurrent pleural effusion or pneumothorax. Talc applied in the pleural cavity causes an inflammatory response that leads to collagen and fibrin deposition and subsequent adhesion of the mesothelial cells of the visceral and parietal pleural membranes (Terra et al., 2020; Zablockis et al., 2021).

Several studies on talc pleurodesis investigated the course of inflammatory reactions locally in the pleural cavity or systemically. In general, an increase in inflammatory markers (e.g. C-reactive protein, CRP, tumour necrosis factor alpha, TNFα, interleukin-8, IL-8) was observed immediately after talc exposure for up to 72 hours (van den Heuvel et al., 1998; D'Agostino et al., 2003; Kotyza et al., 2004, 2006; Maskell et al., 2004; Ukale et al., 2004; Froudarakis et al., 2006; Psathakis et al., 2006; Bilgin et al., 2007; Montes-Worboys et al., 2010; Arellano-Orden et al., 2013; Habal et al., 2013; Habal et al., 2015; Hojski et al., 2015; Chang et al., 2020b; Zablockis et al., 2021; Watanabe et al., 2023). In most of the evaluated studies, pleurodesis was performed in patients with malignant pleural effusions (van den Heuvel et al., 1998; Maskell et al., 2004; Ukale et al., 2004; Psathakis et al., 2006; Montes-Worboys et al., 2010; Habal et al., 2013, 2015; Hojski et al., 2015; Chang et al., 2020b; Zablockis et al., 2021; Bilgin et al., 2007).

Arellano-Orden et al. (2013) observed that talc containing a high concentration of small particles (about 50% of total particles with diameter < 10 μm) induced greater production of acute inflammatory cytokines than did talc containing large particles (< 20% of total particles with diameter < 10 μm).

[The Working Group noted that it was difficult to estimate the potential for chronic inflammation on the basis of studies on levels of inflammatory markers at up to 72 hours after talc exposure. In addition, patients with chronic diseases might have been experiencing forms of chronic inflammation and/or immunosuppression before the talc treatment, and these would have confounded attempts to determine whether later effects were specifically associated with talc exposure.]

No patients developed acute respiratory distress syndrome in a multicentre prospective cohort study of 558 patients with malignant pleural effusion who underwent thoracoscopy and talc poudrage (pleurodesis) (Janssen et al., 2007). However, in some case-report studies it was shown that patients who developed acute pulmonary distress after the talc pleurodesis procedure had bilateral interstitial infiltrates and pleural effusion (Bouchama et al., 1984), acute lung injury (Gonzalez et al., 2010), intense mesothelioid reaction (Faynberg et al., 2017), eosinophilic cholecystitis (Caesar et al., 2016), or pneumonitis (Kim et al., 2006) after the procedure.

Vandemoortele et al. (2014) reported the formation of pleural talcomas (pleural masses) in three patients treated with pleurodesis (of these, two had been previously exposed to asbestos). The talcomas exhibited active inflammatory processes and hypermetabolic status, even 20 years after the initial talc insufflation, resulting in positive fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scan. [The Working Group considered that increased metabolic uptake was an indicator of potential malignancy, infection, or active inflammation.] Kurian (2017) described similar findings in a case report of pleural talcoma after pleurodesis;

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however, the patient had a positive history for stage III lung cancer.

Mild restrictive impairment of lung function and pleural thickening was observed after treatment of idiopathic spontaneous pneumothorax with talc poudrage in 80 patients. However, asbestos contamination of the talc could not be ruled out (Lange et al., 1988).

[The Working Group noted that although the procedure of pleurodesis is intended to cause intense inflammation and fibrosis subsequently leading to adhesions between the two pleural membranes, the procedure is most commonly used in patients with recurrent malignant pleural effusions involving metastatic breast or ovarian cancer or advanced lung cancer. The body of literature available, excluding some exceptions such as Lange et al. (1988), comprises studies conducted in patients with advanced cancer. Much like asbestos contamination, advanced malignancies may independently induce chronic inflammatory states in the lungs, thus representing a confounding factor for establishing the association between chronic inflammation and specific exposure to talc.]

Cosmetic application of talc

Some of the case–control studies that were used to assessed risk of ovarian cancer in women using talc powder (see Section 2.5.2) provided data on the association between use of cosmetic talc and alterations in markers of acute inflammation (for example, using a subset of the data collected) (Ness et al., 2000; Cramer et al., 2005; Merritt et al., 2008; Wu et al., 2009; Williams et al., 2014; Schildkraut et al., 2016; Gabriel et al., 2019). [The Working Group considered that the above studies were not informative because contamination of the talc by asbestos could not be excluded and because the nature of the talc exposure was not well characterized since it was based on self-reported data. Furthermore, the study designs were not aimed at testing mechanisms, and thus only limited qualitative information was provided regarding the evaluation of chronic inflammation.]

Pneumoconiosis

Workers involved in industrial and mining occupations may be exposed to particles of varying types and sizes and can develop pneumoconiosis characterized by dyspnoea on exertion, coughing, inflammation, and fibrosis. In case reports and cohort studies in workers exposed to talc, interstitial lung fibrosis, and potentially restrictive pulmonary disease and pulmonary arterial hypertension were reported in later phases (Wild et al., 2002; Neghab et al., 2007; Griffith et al., 2012; Karkhanis and Joshi, 2012; Jasuja et al., 2017; Wergeland et al., 2017; Ciocan et al., 2022a). [Overall, the Working Group considered that these studies were not informative for the evaluation of chronic inflammatory end-points resulting from talc exposure, because contamination by asbestos and silica could not reasonably be excluded. This has a bearing on the potential association between pneumoconiosis and exposure to talc, since pneumoconiosis may also arise from exposure to other particles, including silica and asbestos. In addition, the study design was considered not appropriate for the evaluation of mechanistic end-points.]

Talcosis

Talcosis is a rare form of pneumoconiosis caused by exposure to talc dust and is listed under the International Classification of Diseases 10th revision (ICD-10) J62.0.

Several case reports were identified in which talcosis was reported after continuous exposure by inhalation to commercially available cosmetic talc. The intensity and duration of exposure varied from months to several years and included daily application to the face (Cho et al., 2021) or to another part of the body (Jasuja et al., 2017); 4 months of daily sniffing of perfumed talc (Shakoor et al., 2011); decades of whole-body application twice daily (van Huisstede

et al., 2010); or abundant daily inhalation of talc powder over several years (Verlynde et al., 2018). Although the individuals described in these case reports experienced a wide variety of nonspecific clinical symptoms, computed tomography (CT) scan of the chest demonstrated bilateral nodular opacities throughout the lungs (van Huisstede et al., 2010; Shakoor et al., 2011; Jasuja et al., 2017; Cho et al., 2021).

Transbronchial biopsies showed evidence of granulomatous inflammation, characterized by foreign body multinucleated giant cell reaction and abundant crystals of negatively birefringent, polarizable material. Cho et al. (2021) also noted the presence of titanium particles in bronchiolar biopsy samples, which the authors justified as an expected co-exposure, since titanium dioxide (TiO_2) is frequently used in commercial talc products to provide the characteristic white colour.

In one case, foreign bodies detected initially as birefringent, polarizable crystals were identified by SEM and EDX analysis as talc (van Huisstede et al., 2010). Wells et al. (1979) reported a case of a woman aged 41 years who developed pulmonary talcosis because of talc inhalation after excessive use of cosmetic talc (daily application for many years) for personal hygiene. Histology of the lungs reported a typical granulomatous reaction around the refracting crystals of talc. In an older case report, Creery et al. (1957) described a talc granuloma of the umbilicus in an infant who had had "a standard proprietary talcum baby-powder" applied to the umbilicus. [No information was reported on the nature of the agent.]

[The Working Group noted that most of the case reports lacked proper quantitative assessment of the exposure and information on talc source and purity. The talc was generally presumed to be of cosmetic grade for inhalation exposures.]

Talcosis was described in other case reports of occupational exposures (Nath et al., 2014; Kobayashi et al., 2019). One report concerned the posthumous diagnosis of talcosis in a worker with normal lung parenchyma altered by the presence of large and small stellate foci of fibrosis around the bronchovascular bundles, with collection of spindle-shaped to polygonal histiocytes and giant cells within the interstitium (Nath et al., 2014). The worker was reported to have spent 5 years working for 10–12 hours daily in a dusty setting with no ventilation.

Kobayashi et al. (2019) reported talcosis in a former heavy smoker (20 cigarettes per day for 10 years, starting at age 20 years), who worked for > 20 years for a confectionery company producing candies containing talc. The worker was diagnosed with primary papillary adenocarcinoma of the upper right lung. Histology revealed fibrous scars in the central part of the tumour, numerous Langerhans and/or foreign body giant cells, and histiocytic cells that had phagocytosed numerous small transparent crystals, which were identified as talc by powder X-ray diffraction analysis. The analysis confirmed the diagnosis of lung talcosis. [The Working Group noted that no information was available on previous occupational exposures.]

[The studies described above provided evidence that pulmonary talcosis is a disorder caused by talc, with chronic inflammation as an underlying condition. However, the Working Group identified several limitations relative to the exposure assessment, study design, and quality of data reporting (including description of the mechanistic end-points of chronic inflammation), the limited description of the workplace (Gysbrechts et al., 1998; Nath et al., 2014) and of the data (van Huisstede et al., 2010; Jasuja et al., 2017; Verlynde et al., 2018), and potential contamination by asbestos or other minerals.]

Sarcoidosis

Several case reports and case series described sarcoidosis after talc exposure. A chronic pulmonary granulomatous reaction observed in two women aged 58 and 55 years who were

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exposed to talc, one in the rubber industry and the other after cosmetic use, was considered to be identical to sarcoidosis. Serum angiotensin-converting enzyme levels were raised in both patients (Tukiainen et al., 1984). Gysbrechts et al. (1998) identified abnormal inflammatory cell distribution with an increased proportion of lymphocytes, elevated CD4/CD8 cell ratio in the bronchoalveolar lavage fluid, and heavy granulomatous reaction in a women aged 62 years who had worked for approximately 46 years in a factory making rubber hoses, who had no dust controls or protection and a high level of exposure. A lung biopsy showed the deposition of talc particles. These particles were examined by SEM and EDX and were characterized as being contaminated with other minerals.

In another study, two individuals who used cosmetic talc on irritated cutaneous areas developed enlarged lymph nodes and were diagnosed with sarcoidosis. Histological examination with PLM showed the presence of crystalline birefringent particles within vessels in contact with the granulomatous areas. In situ microanalysis allowed the identification of birefringent particles, with a size of roughly 0.25 µm, as mostly silica or silicate, or possibly talc (Vincent et al., 2004). [The analysis suggested possible induction of a disseminated granulomatous reaction after application of cosmetic products. However, the Working Group considered that this study was not informative because of contamination of the cosmetic product with silica and other minerals.]

A woman aged 38 years was initially diagnosed with sarcoidosis, but a bronchoscopic biopsy obtained subsequently revealed the presence of numerous foreign body giant cells and birefringent particles forming non-caseating granulomas, supporting a diagnosis of talc-related lung disease. The authors concluded that it was difficult to differentiate between chronic sarcoidosis and talc-related lung disease, even after complete clinical and histological evaluation (Iqbal et al., 2008). In patient presenting with bilateral pulmonary nodules, mediastinal and hilar lymphadenopathy, and an abdominal mass, the initial diagnosis was sarcoidosis, but this was subsequently changed to talcosis, on the basis of pathological demonstration of non-necrotizing granulomas, polarizable crystals, and findings after SEM-EDX analysis (Van Treeck et al., 2019).

[The Working Group noted that potential contamination with asbestos or other minerals could not be excluded in these case reports.]

Other exposures

In other case reports, talc exposure was reported after surgery (i.e. exposure to talc from surgical gloves), intravenous drug use, and through aspiration of ingested medical tablets containing talc. Chronic granulomatous inflammation was reported to be associated with talc exposure in several target organs, mostly the lung, but also the eye, thumb, peritoneum, and fallopian tubes (Fienberg, 1937; German, 1943; Roberts, 1947; Saxen and Tuovinen, 1947; Swingle, 1948; McCormick et al., 1949; Baar, 1953; Diffenbaugh, 1953; Michelson et al., 1979; Waller et al., 1980; Crouch and Churg, 1983; Tao et al., 1984; Fukushima et al., 1996; Ahmed and Shrager, 2003; Mukhopadhyay and Katzenstein, 2007; Peek et al., 2009; Montes-Worboys et al., 2010; Tenconi et al., 2010; Castro et al., 2012). In other case reports, inhalation (recreational or occupational) and dermal or mucosal contact with talc provoked an inflammatory response in humans (Porro et al., 1942; Jaques and Benirschke, 1952; Creery et al., 1957; Graham and Gaensler, 1965; Berner et al., 1981; Tao et al., 1984; Baylor et al., 2013; Nguyen et al., 2016; Kobayashi et al., 2019; Babalola et al., 2021).

[The Working Group noted, that as described above, potential contamination with asbestos or other minerals could not be excluded in these case reports.]

(ii) Human cells in vitro

See Table 4.7.

Considering the available evidence for end-points relevant to chronic inflammation in human cells in vitro and in non-human mammalian systems in vivo and in vitro, the Working Group conducted an evaluation to determine which studies used talc that was most probably not contaminated with asbestos, based on information detailed in the study, information on the deposit of origin (Section 1.2), and other relevant information. The aim of this additional analysis was to identify the extent to which the strength of evidence might be influenced by potential contamination with asbestos.

[The Working Group screened the studies for information on the properties of the test items used, which was interpreted according to expert judgement. The Working Group adopted a stepwise approach:

Step 1. If the name, purity, code, and/or source of the talc was reported, a literature search was performed to determine whether data were available on sample purity, presence or absence of asbestos and quartz, and experimental characterization (namely by electron microscopy).

Step 2. If the origin of the talc was not sufficiently clear, other papers from the same authors or related groups were reviewed for further information.

Step 3. An assessment was made as to whether the talc originated from a natural source or from a commercial supplier. Two possible situations might have occurred:

3a. If the talc was from a natural source, information on country of origin and geology and mineralogy of the origin deposit was evaluated; or

3b. If the talc was from a commercial source, research on the supplier was carried out to determine the origin and the information on characterization, including whether a certificate of purity was provided.

Step 4. If the talc was described as cosmetic, a qualitative analysis was carried out, and an indicative assumption was made based on sample history and record.

If the publication described a cosmetic talc that was in use before the year 2000, then the talc was regarded as more likely to be contaminated by asbestos. If the publication described cosmetic talc that was in use after the year 2000, then the talc was regarded to be less likely to be contaminated by asbestos.

A similar approach was applied for studies relevant to the key characteristic "alters cell proliferation, cell death, or nutrient supply", as reported in Section 4.2.9). Information on the source of the talc tested in the various studies in experimental systems is reported in Tables 4.7 and 4.8.]

Few studies (Nasreen et al., 1998; Shukla et al., 2009; Ghio et al., 2012; Bougen-Zhukov et al., 2020; Mierzejewski et al., 2021) have measured secretion of cytokines or chemokines and/or expression after exposure to talc at concentrations of up to 250 µg/mL in primary mesothelial cells and lung tissue, or in immortalized mesothelial cells, by immunoassay (ELISA) or quantification of mRNA, respectively. In some of these studies, upregulation of IL-8, a major recruiter of inflammatory cells, was observed consistently (Matsushima et al., 2023). [The Working Group noted that effects were observed at a dose comparable to that experienced by humans exposed at work for 1 day (8 hours) to talc at 5.6 mg/m^3. This estimation was based on an inhalation volume of 0.36 m^3 per hour and a pleural surface area of 4000 cm^2 (Zocchi, 2002). The Working Group estimated that differences in the dose leading to this effect may depend on talc properties or the use of well-characterized primary cells versus cell lines.] Levels of other cytokines or chemokines,

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Table 4.7 End-points relevant to chronic inflammation in human cells in vitro exposed to talc

End-points	Assay	Cell type	Results[a]	Concentration (LEC or HIC)	Treatment, duration	Comments	References
Secretion of IL-8	ELISA	PMCs, primary	↑	2 μg/cm²	PMCs enriched from pleural effusion of patients with congestive heart failure, exposed to talc at 2–64 μg/cm² for 24 h[b]	Talc, average particle diameter = 2.1 μm. From Humco Laboratory, Texarkana, Texas, USA. Highest effect at 4 μg/cm². No information on the test compound.	Nasreen et al. (1998)
Secretion of MCP-1	ELISA		↑	4 μg/cm²	PMCs exposed to talc at 4 μg/cm² for 0–72 h	Highest effect at 24 h.	
IL-8 and MCP-1 mRNA expression	RT-PCR		↑	4 μg/cm²	PMCs exposed to talc at 4 μg/cm² for 24 h	Qualitative result.	
Neutrophils, chemotaxis	Boyden chamber		↑	4 μg/cm²	Conditioned medium from PMCs exposed to talc at 4 μg/cm² for 24 h	40% dependent on IL-8, on the basis of suppression by neutralizing antibodies.	
Monocytes, chemotaxis	Boyden chamber		↑	4 μg/cm²	Conditioned medium from PMCs exposed to talc at 4 μg/cm² for 24 h	52% dependent on MCP-1, on the basis of suppression by neutralizing antibodies.	
ICAM-1 surface expression	Fluorescence-activated cell sorting		↑	4 μg/cm²	PMCs exposed to talc at 4 μg/cm² for 24 h		
Secretion of IL-1β, IL-6, and IL-8	ELISA	PMCs (primary) from pleural biopsy	No change	20 μg/mL	Conditioned medium from PMCs (from one coronary artery by-pass surgery) exposed to talc at 2 and 20 μg/mL for 6 h and 24 h	Commercial talc, Steritalc: pure pharmaceutical grade. From Novatech SA, France. Very heterogeneous results, probably because the PMCs in the biopsy comprised different cell types (67% CD45– CD14– CD90+ CD71+).	Mierzejewski et al. (2021)
IL-1β, TGFβ, IL-6, IL-8, MCP-1, and IL-17 mRNA expression	RT-qPCR		No change	20 μg/mL	PMCs (from one coronary artery by-pass surgery) exposed to talc at 2 and 20 μg/mL for 6 and 24 h		

Table 4.7 (continued)

End-points	Assay	Cell type	Results[a]	Concentration (LEC or HIC)	Treatment, duration	Comments	References
Secretion of IL-8	ELISA	Immortalized mesothelial cells (Met5A) Immortalized bronchial epithelial cells (BEAS-2B)	↑	Met5A, 100 µg/mL BEAS-2B, 50 µg/mL	Conditioned medium of cells exposed to talc at 50–250 µg/mL for 24 h	Commercial talc, Sclerosol, average particle diameter = 26.6 µm.[c] From Bryan Corporation, USA. Bryan Corporation aerosol talc (NDA 020587, approved by US FDA in 1997). Tested by Tate (1997) and found to be asbestos-free.	Ghio et al. (2012)
IL-6 and IL-8 mRNA expression	RT-qPCR		↑	100 µg/mL	Cells exposed to talc at 100 µg/mL for 4 h		
Secretion of IL-6	ELISA	Lung cancer cells (H1975)	↑	250 µg/mL	Cells exposed to talc at 250 µg/mL for 24 h Dependent on activation of PI3K signalling on the basis of reversion of the effect by PI3K inhibitors and silencing of PI3K	Commercial talc, Steritalc, maximum particle size ~40 µm; pure pharmaceutical grade. From Novatech SA, France.	Bougen-Zhukov et al. (2020)
IL-8 mRNA expression	RT-PCR	Immortalized mesothelial cells (LP9/TERT-1)	↑	75 µm²/cm²	Cells exposed to talc at 15 and 75 µm²/cm² per dish for 8 h	Commercial talc MP 10-52, average particle diameter = 1.1 µm. From Barretts Minerals Inc., Montana, USA. No information on the test compound.	Shukla et al. (2009)
CXCL3, PTGS2, CXCL2, IL-6, CCL20, IL-1β expression	Microarray		↑	75 µm²/cm²	Cells exposed to talc at 15 and 75 µm²/cm² per dish for 8 h	Microarray analysis not validated.	

CCL20, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; ELISA, enzyme-linked immunosorbent assay; h, hour(s); HIC, highest ineffective concentration; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LEC, lowest effective concentration; MCP-1, monocyte chemotactic protein 1; mRNA, messenger RNA; PI3K, phosphoinositide 3-kinase; PMC, pleural mesothelial cell; PTGS2, prostaglandin-endoperoxide synthase 2; RT-PCR, reverse transcription-polymerase chain reaction; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; TGFβ, transforming growth factor beta; USA, United States of America; USP, United States Pharmacopeia.

[a] ↑, increase.

[b] Assay performed in a 24-well plate, surface is about 2 cm² and estimated volume used is 2 mL. Therefore, for comparison with the other studies it can be considered similar to µg/mL.

[c] Gilbert et al. (2018).

Table 4.8 End-points relevant to chronic inflammation in non-human mammalian systems in vivo exposed to talc

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Genital inflammation							
Numbers of animals with vulvovaginitis, endometriosis, pelvic inflammatory disease, salpingitis, and tubal occlusion were increased	Rat, Sprague-Dawley (F)	Genital tissues	↑	100 mg in 0.5 mL saline	Intravaginal and perineal application, daily for 3 mo	No information on the test compound.	Keskin et al. (2009)
Peritoneal inflammation							
Numerous foreign body giant cells, fibre-rich granulation tissue surrounding crystals, granuloma formation, adhesions between intestinal loops, and deposition of collagen	Rat, "albino"	Peritoneum	↑	400 mg	Peritoneal application after laparoscopy End-points observed after 6 mo	No information on the test compound.	Blumel et al. (1962)
Neutrophilic peritoneal lavage	Mouse, C57BL/6 (F)	Peritoneum and peritoneal lavage	↑	30 mg/animal	Intraperitoneal injection; end-points observed after 7 d	Talc, Sigma Chemical Co. Pure pharmaceutical grade.	Frazier-Jessen et al. (1996)
Pleural and systemic inflammation							
Pleural fluid WBC count, LDH, and protein	Rabbit, White New Zealand	Pleura and pleural effusion	↑	400 mg/kg bw	Pleural fluid analysis was performed at 24 h	No information on the test compound.	Liao et al. (2007)
Pleural fluid IL-8, VEGF, and TGFβ	Rabbit, New Zealand	Pleural effusion	↑	400 mg/kg bw	Analysis was at 6, 24, and 48 h	Asbestos-free talc, mixed particle size. From Magnesita, Brumado, Brazil. Pure pharmaceutical grade.	Genofre et al. (2009)
Blood neutrophils, serum LDH, IL-8, TGFβ, and CRP	Rabbit, White New Zealand (M)	Blood	↑	400 mg/kg bw	Blood analysis was at 1–7 d	Talc, particle size = 25.4 µm. From Magnesita, Bahia, Brazil. Contamination with asbestos could not be ruled out.	Marchi et al. (2009)

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Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Pleural fluid cell count, LDH, IL-8, and VEGF	Rabbit, White New Zealand	Pleura and pleural effusion	↑	400 mg/kg bw	Pleural fluid analysis was performed at 1–7 d	Talc, USP Pharmacy, from São Paulo, Brazil. Probably pure pharmaceutical-grade talc, but no experimental evidence provided.	Ribeiro et al. (2009)
Pleural infiltration of macrophages and interstitial lymphocytes	Rabbit, White New Zealand (M)	Pleura	↑	Talc 200 mg/kg	Analysis was at 6, 12, and 18 h	Talc, mixture of large particles, size = 50–100 µm. From Merck KGaA, Germany.	Stamatelopoulos et al. (2009)
Pleural fluid WBC counts, neutrophils, and LDH. Blood WBC count, percentage neutrophils, VEGF, and IL-8	Rabbit, White New Zealand (M)	Pleural effusion and blood	↑	400 mg/kg bw	Intrapleural injection Samples of blood and pleural fluid were collected after 6 h	Talc from USP Pharmacy, São Paulo, Brazil. Probably pure pharmaceutical-grade talc, but no experimental evidence was provided.	Marchi et al. (2004)
Pleural fluid leukocyte counts, neutrophils, LDH, IL-8, and VEGF Blood leukocyte counts, neutrophils, IL-8, and VEGF	Rabbit, White New Zealand (M)	Pleural effusion and blood	↑	100 and 400 mg/kg bw	Intrapleural injection; samples of blood and pleural fluid were collected after 6, 24, and 48 h	Talc, asbestos-free, mean particle diameter = 25.4 µm. From USP Pharmacy, São Paulo, Brazil. Probably pure pharmaceutical-grade talc, but no experimental evidence was provided. Study was designed to compare talc with silver nitrate.	Marchi et al. (2005)
Pleural fluid IL-8, VEGF, and TGFβ	Rabbit, White New Zealand (M)	Pleura and blood	↑	200 mg/kg bw	Intrapleural injection; samples of pleural fluid were collected after 6, 24, and 48 h	Talc, average particle diameter = 25.4 µm (range, 6.4–50.5 µm). From Magnesita, Bahia, Brazil. Contamination with asbestos could not be ruled out.	Marchi et al. (2006)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Pleural inflammation (models of pleurodesis)							
Leukocytic pleural effusion	Rabbit, White New Zealand (M)	Pleural effusion	↑	400 mg/kg bw	Intrapleural administration (using a chest tube) Chest tubes were aspirated at intervals of 2, 4, 24, and 48 h until they were removed after 4 d Rabbits were killed at 28 d	Sterile talc, from Sigma Chemical Company, St Louis, Missouri, USA.	Cheng et al. (2000)
Pleural inflammation and fibrosis	Rabbit, White New Zealand	Pleura	↑	400 mg/kg bw	Intrapleural injection Pleural macroscopic and microscopic changes observed from 1 mo to 1 year after the intrapleural injection	Talc, xilolite, asbestos-free, average particle diameter = 21.5 µm. From Salvadore, Brazil. Talc was contaminated with minute amounts of dolomite, kaolinite, chlorite, and forsterite.	Vargas et al. (2001)
Pleural inflammation	Sheep, mixed breeds	Pleura	↑	5 g	Intrapleural injection Pleurodesis was measured at day 14	Talc powder, asbestos-free, gas sterilized and mixed in 0.9% NaCl. From Sigma, St Louis, Missouri, USA.	Lee et al. (2002)
Pleural fluid leukocyte count; IL-8 secretion	Rabbit, White New Zealand	Pleural effusion	↑	400 mg/kg bw	Intrapleural injection All samples were collected by aspiration via chest tube 24 h after the intrapleural injections	Talc, Sigma, St Louis, Missouri, USA, mixed in 0.9% NaCl. Pure pharmaceutical grade.	Lee et al. (2003b)
Foreign body granulomas, neutrophils, and macrophages	Rabbit, White New Zealand (M)	Pleura	↑	50 and 200 mg/kg bw	Intrapleural injection Analyses were performed at 4 h, 1 d, 1 wk, and 1 mo after instillation	Talc, Distalc, mean particle diameter = 8.36 µm. Barcelona (Spain). The talc was from the Respina mine in León, Spain (produced by Luzenac, Spain, and distributed by Distribuidora de Talco, Distalc; Barcelona, Spain). Talc was asbestos-free.	Montes et al. (2003)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Pleural fluid volume, LDH, protein, and VEGF, and blood LDH and TGFβ	Rabbit, New Zealand	Pleura, pleural effusion, and blood	↑	400 mg/kg bw	Intrapleural injection Analysis were performed after 4, 24, 48, 72 h or 7, 14, or 28 d after the procedure	Talc was described as asbestos-free of "mixed size" from Magnesita, Brazil. Contamination with asbestos could not be ruled out.	Teixeira et al. (2009)
CRP, VEGF, and IL-8	Rabbit, New Zealand	Pleura, blood, and lung lavage	↑	400 mg/kg bw	Intrapleural injection Analyses were performed 6, 24, 48, 72 and 96 h after the procedure; talc produced an acute inflammatory response: blood levels of CRP, VEGF, and IL-8 increased in the first 48 h after the procedure, with a fall at subsequent time intervals	Commercial calibrated talc, probably pure pharmaceutical grade, containing small particles. From Sigma Aldrich, Steinheim, Germany.	Rossi et al. (2010)
Pleural fluid total cell count, LDH, IL-8, and VEGF	Rabbit, White New Zealand	Pleura and pleural fluid	↑	400 mg/kg bw	Intrapleural administration using a chest tube Analysis was performed 7, 14, or 28 d after the procedure	Talc, USP Pharmacy, São Paulo, Brazil. Probably pure pharmaceutical-grade talc, but no experimental evidence was provided.	Teixeira et al. (2011)
Visceral pleural thickening (fibrous tissue)	Mouse, BALB/C nude (M)	Pleura	↑	400 mg/kg bw	Intrapleural administration	Talc, Steritalc: particle size = 24.5 µm; Novatech SA, La Ciotat, France. Pure pharmaceutical grade. Model for lung metastasis and pleural effusion.	Iwasaki et al. (2016)
Pleural effusion volume, LDH, VEGF, and IL-6	Mouse, C57BL/6 (M)	Pleura	↑	400 mg/kg bw at 24 h	Intrapleural injection; observations made after 24 h, 3 d, and 8 d	Talc for pleurodesis. No information on the test compound.	Sabbion et al. (2020)
Granulomatous inflammation	Rat, Wistar albino (M)	Pleura	↑	4 g	Intrapleural injection Macroscopic and microscopic examination after 30 d	Steritalc, Novatech SA, La Ciotat, France. Pure pharmaceutical grade.	Zorlu et al. (2021)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Mononuclear inflammation with fibrin deposition and bleeding in the airway, alveolar capillary congestion	Rabbit, New Zealand	Pleura	↑	400 mg/kg bw	Intrapleural injection Histopathological evaluation performed 28 d after procedure	Talc particle size ~15 µm. No information on the test compound.	Sumer et al. (2022)
Cardiac inflammation							
Atrial tachyarrhythmias	Dog, cross-bred (M)	Heart	↑	5 g	Pericardial injection, observations made after 1 wk	No information on the test compound. Talc was instilled into the pericardium in 15 dogs to simulate postoperative inflammation.	Yoo et al. (2010)
Counts of inflammatory cells and adherence scores	Rat, Wistar (M)	Heart	↑	10 mg	Epicardial application after thoracotomy and pericardiotomy, "sprinkled" Analysis performed 8 wk after procedure	Probably pure pharmaceutical-grade talc, but no information on the source was provided.	de Oliveira et al. (2014)
IL-17A	Rat, Sprague-Dawley	Heart	↑	"Generous dusting"	Epicardial application and observations made on postoperative days 0–7	No information on the test compound.	Fu et al. (2015)
TNFα expression.	Rat, Wistar (M)	Heart	↑	30 mg/kg bw	Pericardial administration Analyses performed after 48 h	Talc from Sigma Aldrich, St Louis, Missouri, USA.	Glück et al. (2016)
Expression of IL-1β, IL-6, TGFβ, and TNFα	Rat, Sprague-Dawley	Heart	↑	"Generous dusting"	Atrial application and observations made on postoperative days 1–14 in atrial specimens	Sterile talcum powder (no other information available).	Huang et al. (2016)
Cardiac inflammation	Mouse, C57/Black 6 (M)	Heart	↑	2.5 and 5.0 mg/g bw	Pericardial injection at low (2.5 mg/g) or high (5 mg/g) dose and observations made at 1, 2, and 4 wk post-injection	Talc, Unitalc, from Nobelpharma, Tokyo, Japan. Pharmaceutical grade, tested for purity by the laboratory of Professor S. Toyokuni, Nagoya University, Japan.	Kojima et al. (2019)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Neutrophil infiltration in the atria; expression of IL-1β and IL-6	Rat, Sprague-Dawley (M)	Heart	↑	"Generous dusting"		No information on the test compound. No clear information on the dose.	Wu et al. (2020)
IL-6 expression	Rat, Sprague-Dawley	Heart	↑	"Dusted"	Atrial application	No information on the test compound. No clear information on the dose.	Liao et al. (2021)
Testicular inflammation							
Inflammatory reaction by orchiopexy	Rat, Sprague-Dawley (M)	Testes	↑	1 g	Instilled in the cavum vaginale Analyses performed 30 d after the procedure	No information on the test compound.	Rodriguez and Kaplan (1988)
Lung inflammation							
Neutrophils and monocytes	Rat, "white"	Lung	↑	"Very heavy exposure"	Inhalation, 3 h/day for 12 d	No information on the test compound. No clear information on the dose.	Policard (1939–1940)
Macrophages in alveolar spaces (containing talc)	Rat, F344/Cr1 (F and M) and Mice, B6C3F$_1$ (F and M)	Lung	↑	17 mg/m^3	Inhalation, 6 h/d for 5 d/wk and 4 wk	Talc obtained from Midwest Research Institute, Kansas City, Missouri, USA, a subcontractor of the National Toxicology Program, National Institute of Environmental Health Sciences. The talc was reported to be free of asbestos as indicated by electron microscopic examination and dispersion staining (Midwest Research Institute, "Reprocurement report, analysis of talc", 23 February 1983). Talc was asbestos-free.	Pickrell et al. (1989)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Granulomas, neutrophils	Rat, F344/N (F and M)	Lung and lung lavage	↑	6, 18 mg/m^3	Inhalation, 5 d/wk for up to 113 wk (M) or 122 wk (F) until mortality reached 80%	Talc from Walsh and Associates, North Kansas City, Missouri, USA. Talc was asbestos-free. Pathology evaluations at 6, 11, 18, and 24 mo showed granulomatous inflammation that increased with the duration of talc exposure. Near the foci of inflammation, there was also epithelial hyperplasia and fibrosis. An accumulation of macrophages with phagocytosed talc was observed in peribronchial lymphoid tissue and lymph nodes. Lavage at 24 mo revealed increased neutrophils in male rats at 6 mg/m^3 and female rats at 6 and 18 mg/m^3.	NTP (1993)
	Mouse, B6C3F$_1$ (F and M)	Lung and lung lavage	↑	6, 18 mg/m^3	Inhalation, 5 d/wk for up to 104 wk	Talc from Walsh and Associates, North Kansas City, Missouri, USA. Pathology evaluations at 6, 12, 18, and 24 mo showed chronic active inflammation with an accumulation of macrophages in the lung. There was also an accumulation of macrophages containing talc present in the bronchial lymph node. With lavage at 18 and 24 mo, the numbers of neutrophils and macrophages were increased after exposure of mice to talc at 18 mg/m^3.	

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Infiltration of foamy macrophages on the alveolar walls and near the terminal and respiratory bronchioles	Rat, Sprague-Dawley (F and M)	Lung	↑	50 and 100 mg/m^3	Inhalation, for 6 h daily, 5 d/wk, for up to 4 wk	Talc (non-asbestiform) was provided as ultra-fine white talcum powder from Rex Material, Republic of Korea; certified as asbestos-free (by Rex Material), pharmaceutical grade. Talc was asbestos-free.	Shim et al. (2015)
Neutrophilic inflammation with giant cells	Rat, "white"	Lung	↑	50 mg (total)	Intratracheal instillation, in two exposures	No information on the test compound.	Luchtrath and Schmidt (1959)
Neutrophils, LDH, and albumin	Hamster, Syrian Golden	Lung lavage	↑	0.75 and 3.75 mg/100 g bw	Intratracheal instillation	Talc was collected in a mill in central Vermont, USA, near a bagging operation. Talc samples showed that quartz was present as a trace mineral (~5%) in only 15% of the bulk samples (Boundy et al., 1979). No asbestos was found in any of the bulk samples. Scanning electron microscopic evaluation of airborne filter samples provided further evidence that asbestos contamination of these samples was minimal (Boundy et al., 1979). Contamination with quartz and asbestos could not be ruled out.	Beck et al. (1987)
Neutrophilic lung injury	Rat, Sprague-Dawley (M)	Lung	↑	6 mg	Intratracheal instillation Analyses performed 96 h after the procedure	Talc from Montana, USA. Contamination with asbestos could not be ruled out.	Ghio et al. (1992)
Macrophages, neutrophils, and multinucleate giant cells	Hamster, Syrian Golden (M)	Lung lavage	↑	3.75 mg/100 g bw	Intratracheal instillation Analysis performed up to 14 d after the procedure	Same sample used by Beck et al. (1987). Contamination with quartz and asbestos could not be ruled out.	Sato et al. (2020)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Dermal and systemic inflammation							
Infiltration of neutrophils, granuloma formation, and increases in IgM and IgG	Mouse, NZB, NZW, and Strong A (M, F))	Skin and blood	↑	300 mg	Subcutaneous, in one single injection, 2 injections at different times, or a double injection	Talc was USP grade.	Carson and Kaltenbach (1973)
Monocytic and neutrophilic infiltration, and granulomatosis	Rat, Fischer (F)	Skin	↑	800 mg	Subcutaneous, in 2 to 4 injections	Talc from Merck, Darmstadt, Germany; pure pharmaceutical grade.	Marusić et al. (1990)
Decrements in blood zinc	Rat, Fischer (F)	Skin and blood	↑	800 mg	Subcutaneous, in 2 to 4 injections	Talc from Merck, Darmstadt, Germany; pure pharmaceutical grade.	Marusić et al. (1991)
Dermal inflammation							
Granulomas and giant cells	Guinea-pig, Camm-Hartley (M)	Skin	↑	3 mL, 2%	Injection into the front and hind fat pads	No information on the test compound.	Goldner and Adams (1977)
Granulomatous reaction with foreign body giant cells	Rat, CH bb Thom-Bib (F)	Skin	↑	400 mg	Subcutaneous, daily for 21 d	No information on the test compound.	Minne et al. (1984)
Acute and chronic granulomatosis	Rat, Wistar (M)	Skin	↑	100 mg	Subcutaneous, at 2 sites	Talc, extra fine powder, from Merk, Darmstadt, Germany; pure pharmaceutical grade.	Peters et al. (1986)
Granuloma	Mouse, BALB/c (M)	Skin	↑	0.4 g	Subcutaneous at 5 sites	No information on the test compound.	Ben Dror et al. (1993)
Systemic inflammation							
Serum α-1-acid glycoprotein	Rat, Wistar (F)	Blood	↑	3.2 g total per animal	Subcutaneous in 4 injections Blood samples taken on days 41 and 80 after the procedure	Contamination with asbestos could not be ruled out.	Puel at al. (2004)
Serum α-1-acid glycoprotein	Rat, Wistar (F)	Blood	↑	3.2 g total per animal	Subcutaneous in 4 injections Blood samples taken on days 41 and 80 after the procedure	Magnesium silicate, ICN Pharmaceuticals, France. Contamination with asbestos could not be ruled out.	Puel et al. (2005)

Table 4.8 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Serum fibrinogen	Rat, Wistar (F)	Blood	↑	3.2 g total per animal	Subcutaneous in 4 injections Blood samples taken on day 100 after the procedure	Magnesium silicate, ICN Pharmaceuticals, France. Contamination with asbestos cannot be ruled out.	Puel et al. (2006)
Serum α-1-acid glycoprotein	Rat, Wistar (F)	Blood	↑	3.2 g total per animal	Subcutaneous in 4 injections	Talc; ICN Biomedicals, Illkirch, France.	Puel et al. (2007)
Vascular inflammation							
Vascular injury with nodular collections of macrophages and lymphocytes	Guinea-pig (M)	Lung	↑	75 mg total per animal	Intravenous, 3 doses of 25 mg each Analysis conducted up to 150 d after the procedure	Talc sample obtained from Jaipur, India, prepared with particle size = 0.25–5.2 μm; contained traces of various minerals and metals.	Dogra et al. (1977)
Accumulation of neutrophils was noted around intravascular talc crystals	Dog, mongrel (sex not reported)	Lung	↑	2.5 mg/kg bw	Intravenous Analysis performed 5–15 min after injection	Contamination with asbestos cannot be ruled out.	Farber et al. (1989)

bw, body weight; CRP, C-reactive protein; d, day(s); F, female; h, hour(s); Ig, immunoglobulin; IL, interleukin; LDH, lactate dehydrogenase; M, male; min, minute(s); mo, month(s); NaCl, sodium chloride; TGFβ, transforming growth factor beta; TNFα, tumour necrosis factor alpha; USP, United States Pharmacopeia; VEGF, vascular endothelial growth factor; USA, United States of America; WBC, white blood cell; wk, week(s).

[a] ↑, increase.

or downstream effects, such as the recruitment of inflammatory cells, were also increased, but were assessed only in a single study in well-characterized mesothelial cells (Nasreen et al., 1998).

(b) Experimental systems

See Table 4.8.

(i) Non-human mammals in vivo

In the studies described below, the potential inflammatory effects of talc were investigated after direct exposure by application to various serous membranes (such as the peritoneum, pleura, pericardium, and cavum vaginale), and by inhalation, dermal application, and application to other tissues.

Genital and peritoneal inflammation

After either intravaginal or intraperitoneal administration of talc (100 mg in 0.5 mL of saline, daily for 3 months) in female Sprague-Dawley rats, there was histopathological evidence of inflammation of the vulva, vagina, uterus, fallopian tubes, and ovaries, on inspection with light microscopy (Keskin et al., 2009). Increased levels of inflammatory cells and a foreign body reaction were described in genital tissues after talc exposure. Histopathological changes included vulvovaginitis, endometriosis, pelvic inflammatory disease, salpingitis, and tubal occlusion and were increased in rats exposed to talc (intravaginal or perineal administration) relative to controls (with no manipulation or an equal volume of intravaginal saline). The incidence of ovarian infections was also increased in rats exposed to talc relative to controls. Introduction of talc into the peritoneal cavity was employed in animal models of post-surgical adhesion after contamination of the abdominal cavity during the procedure (Blumel et al., 1962; Frazier-Jessen et al., 1996). In several studies, talc (both in a dry state and suspended in saline) caused an increase in levels of neutrophils, formation of giant cells, granuloma formation, granulation tissue adjacent to the crystals and connective tissue deposition, and adhesions between intestinal loops.

Pleural and systemic inflammation

Animal models of pleurodesis have been frequently tested with talc (Cheng et al., 2000; Vargas et al., 2001; Lee et al., 2002, 2003a; Montes et al., 2003; Marchi et al., 2004, 2005, 2006, 2009; Liao et al., 2007; Genofre et al., 2009; Ribeiro et al., 2009; Stamatelopoulos et al., 2009; Teixeira et al., 2009, 2011; Rossi et al., 2010; Iwasaki et al., 2016; Sabbion et al., 2020; Zorlu et al., 2021; Sumer et al., 2022). In the listed studies, the authors reported an increase in capillary permeability and lymphocyte passage after exposure of the pleura to talc; evolution of an effusion; development of mononuclear cell inflammatory processes (lymphocytes and macrophages), followed by an incursion of fibroblasts, deposition of collagen, and ultimately progress to symphysis. In most of the studies, individual particles and aggregates of talc were observed in the submesothelial space. [The Working Group noted that the exposed mesothelial cells might contribute to the inflammatory pleural response, with mediator release after talc exposure.] In addition, mediators of the inflammatory response in the pleura, including growth factors and cytokines (e.g. TNFα; vascular endothelial growth factor, VEGF; IL-8; and transforming growth factor, TGFβ), were released. These mediators recruited leukocytes, augmented the vascular capillary response, and activated fibroblasts. Together with local inflammation, pleural exposure to talc could induce a systemic inflammatory response in these animal models. Inflammation, as indicated by both histopathological and pleural fluid changes, was observed at long durations (30 days) of follow-up after exposures to either asbestos-free talc or commercial talc assumed to be closer to pure talc (Zorlu et al., 2021). [The Working Group noted that talc, like all sclerosing agents, can induce pleural inflammation followed by fibrosis. The

activation of the inflammatory pathway leads to the required fibrotic state and pleurodesis.]

Cardiac inflammation

The pericardium is the third serous membrane exposed to talc in animal models of postoperative inflammation, postoperative atrial flutter or fibrillation, and postoperative adhesions. Pericardial injection of talc is employed in animal models of postoperative pericardial adhesions, which are frequently seen after cardiac surgery. In several studies on exposure of the pericardial space or epicardium, talc induced incursion of macrophages and myofibroblasts, as well as inflammatory fluid accumulation (i.e. sterile pericarditis with an effusion) (Yoo et al., 2010; de Oliveira et al., 2014; Fu et al., 2015; Glück et al., 2016; Huang et al., 2016; Kojima et al., 2019; Wu et al., 2020; Liao et al., 2021).

Testicular inflammation

The cavum vaginale was the fourth serous membrane exposed to talc. In a rat model for treatment of testicular torsion (orchiopexy), Rodriguez and Kaplan (1988) instilled the space between the layers of tunica vaginalis with talc.

As observed in the other three spaces lined by serous membranes (i.e. the peritoneal, pleural, and pericardial spaces) described above, exposure to talc led to inflammation, fibrosis, and sclerosis.

Lung inflammation

Animal models of exposure to talc by inhalation (Policard, 1939–1940; Pickrell et al., 1989; NTP, 1993; Ozaki et al., 2002; Shim et al., 2015) and intratracheal instillation (Luchtrath and Schmidt, 1959; Beck et al., 1987; Ghio et al., 1992; Sato et al., 2020) showed inflammatory responses in the respiratory tract. After inhalation, talc induces alveolitis with neutrophils and monocytes (Policard, 1939–1940). There is an increased number of alveolar macrophages that phagocytose the talc; some of these macrophages infiltrate the terminal and respiratory bronchioles as well as the alveolar walls and can be "foamy" in appearance (Pickrell et al., 1989; Shim et al., 2015). A granulomatous inflammation and interstitial fibrosis along with proteinosis, chronic active inflammation, hyperplasia of the alveolar epithelium, and histiocytosis were observed in mice and rats in a GLP inhalation study, in which granulomas were also observed (NTP, 1993; Ozaki et al., 2002). Intratracheal instillation of talc is similarly associated with neutrophilic alveolitis; multinucleated giant cells are frequent (Luchtrath and Schmidt, 1959; Beck et al., 1987; Ghio et al., 1992; Sato et al., 2020). [The Working Group noted that the intratracheal instillation of talc can overwhelm clearance pathways, resulting in particle overload.]

Dermal, systemic, and vascular inflammation

Subcutaneous application of talc has been employed in animal models of osteopenia. After subcutaneous injection of talc, inflammation developed locally, with neutrophil incursion and granuloma (foreign body) formation. There was also an acute-phase response that can include osteoblast insufficiency, bone loss and decreased bone formation, and alteration of blood parameters such as serum α-1-acid glycoprotein (Carson and Kaltenbach, 1973; Goldner and Adams, 1977; Minne et al., 1984; Peters et al., 1986; Marusić et al., 1990, 1991, 1993; Ben Dror et al., 1993; Puel et al., 2004, 2005, 2006, 2007).

Animal models in guinea-pigs and dogs used intravenous administration to talc to mimic inflammatory lung injury after chronic injection of crushed suspended tablets in humans. Vascular injury in the pulmonary tissue showed rapid accumulation of neutrophils and nodular collections of macrophages and lymphocytes around the vessel (Dogra et al., 1977; Farber et al., 1989). [The Working Group noted that contamination of the talc by asbestos or other minerals could not be ruled out in these two studies.]

Inflammation in other tissues

Other tissues have been exposed to talc in animal models of human disease. These include the cochlea, tympanic membrane, and middle ear; abdominal muscle; and the anterior chamber of the eye and infraorbital foramen. Exposure of these tissues was also associated with inflammation characterized by granuloma. In guinea-pigs, histopathological evidence of chronic (3–4 months after surgery) granulomatous inflammation after application of talc to the cochlea, tympanic membrane, and middle ear was demonstrated (Abramson et al., 1975). In Sprague-Dawley rats, acute and chronic inflammation with giant cell formation, granulomas, histiocytes, lymphocytes, collagen, and fibroblasts was demonstrated on histopathological examination between 1 day and 16 weeks after exposure to talc as a contaminant on surgical sutures and in a pellet implanted intramuscularly (abdominal) (Sheikh et al., 1984). In rabbits, injection of talc (1 mg) into the anterior chamber of the eye induced histopathological inflammation with incursion of lymphocytes and plasma cells within 7 days after talc exposure, followed by formation of granulomatous nodules within 4–12 weeks after exposure (Karcioglu et al., 1988). In Wistar (male) rats injected with 90 mg of talc in the infraorbital foramen region (i.e. an animal model of trigeminal neuralgia) showed histopathological inflammation with increased expression of TNFα and IL-1β in the area of the infraorbital nerve between 3 days and 12 weeks after exposure (Wang et al., 2018).

(ii) Non-human mammalian systems in vitro

Alveolar macrophages from male Sprague-Dawley rats showed increased release of the inflammatory mediator leukotriene B4 after exposure to talc (Montana talc, USA) at 2 mg/mL for 16 hours (Ghio et al., 1992).

Increased cellular release of a second inflammatory mediator, IL-8, was observed in rabbit mesothelial cells, after exposure to talc (Sigma, St Louis, Missouri, USA) (0.1–10 mg/cm^2) for 24 hours (Lee et al., 2003b).

Similarly, incubation of rabbit PMCs for 6–48 hours with talc (mean size, 21.2 µm; range, 6.6–52.6 µm; Magnesita, São Paulo, Brazil) at 25 µg/cm^2 (dissolved in RPMI culture medium) induced the release of IL-8, VEGF, and TGFβ1 (Acencio et al., 2007). An increase in the release of interferon gamma (IFNγ), IL-17, IL-8, and IL-6 was also observed in CD1 mouse bone marrow monocytes incubated for 24, 36, or 48 hours with talc (0.1, 1, 10, and 100 µg/mL) (Toledano-Magaña et al., 2021). [The Working Group noted that the release of these mediators in vitro might reflect the potential to coordinate an inflammatory response to talc.]

Synopsis

[The Working Group noted that in exposed humans, talc can elicit a strong acute inflammation that may persist to become chronic inflammation and evolve into chronic fibrosis. The medical intervention of talc pleurodesis demonstrates the possibility that this series of events can occur, although in a very specific scenario. Numerous case reports describing an association between prolonged external exposure to talc and granulomatous inflammation in different organs have provided support for the hypothesis that talc causes chronic inflammation. However, none of the reviewed studies directly evaluated mechanistic end-points of chronic inflammation per se caused by exposure to talc independently of other known risk factors for chronic inflammatory lung disease. In vivo exposure of non-human mammals to talc, at varying sites and through different route of exposure, appeared to be associated with chronic inflammation. The relevance of this inflammation appeared to be contingent on persistence of the talc in the exposed tissue. Almost all these models employed exposure routes that precluded effective clearance of the agent particles (e.g. vaginal, peritoneal, pleural,

pericardial, cavum vaginale, subcutaneous, and intravenous). Subsequently, the talc-associated inflammation persisted and could progress to a chronic inflammation and fibrosis. Notably, considering the number of experimental studies in vivo and in vitro in which end-points relevant to the key characteristic of "induces chronic inflammation" were reported, the Working Group analysed which studies used talc known not to be contaminated by asbestos. This additional screening step was intended to determine the extent to which the strength-of-evidence evaluation might be influenced by potential contamination. The results of this analysis did not change the Working Group's conclusions about the strength of the evidence.]

4.2.7 Is immunosuppressive

(a) Humans

In 11 patients with a diagnosis of cancer, Froudarakis et al. (2007) investigated the effects of asbestos-free talc (Steritalc, Novatech, France), used as sclerosing agent in a thoracoscopic procedure (4 g for malignant pleural effusion, $n = 10$; 2 g for pneumothorax, $n = 1$), on cell counts for peripheral blood lymphocytes (PBL) and eosinophils before (control) and 24 and 48 hours after the procedure. A significant decrease in absolute cell counts of total PBL ($P < 0.007$), and specifically of CD3+ ($P < 0.005$), CD4+ ($P < 0.022$), and CD8+ T lymphocytes ($P < 0.03$), was observed at both time points after the procedure. Eosinophil count also decreased significantly ($P < 0.005$). [The Working Group noted that the study included a limited number of patients with a cancer diagnosis. Additionally, after thoracoscopy, the patients received a 25 mg fentanyl citrate patch for pain management.]

(b) Experimental systems

See Table 4.9.

In two studies, end-points relevant to immunosuppression were investigated in experimental systems exposed to talc. Radić et al. (1988) observed alterations in leukocyte count and histology of lymphoid organs, indicative of an immunosuppressive effect, in Wistar rats exposed to a talc as a single subcutaneous dose (1 g per rat) at four different sites. Three days after talc administration, the authors observed a decrease in the dimensions of the thymic cortex, and an increase in the thymic medulla, indicating a decrease in the generation of naive T cells. Concurrently, a decrease in the white pulp portion of the spleen (which consisted of T and B lymphocytes) and an increase in the red pulp portion (which contained macrophages) were observed. In addition, the authors observed an increase in the germinal centre fraction of the axillary lymph node, where B lymphocytes undergo maturation and differentiation. [The Working Group noted that the latter change was not informative per se regarding immunosuppression, although some B cells might become immunosuppressive upon differentiation.] In this study, rats exposed to talc exhibited reduced ability to reject an allogeneic skin graft, demonstrating increased tolerance. This effect was reproduced using serum or spleen cells from rats with talc granulomatosis. [The Working Group noted that although the source of the talc was described as prepared for hospital purposes, its properties and purity were not clearly reported.]

Alessi et al. (1990) investigated in mice the potential of delayed-type hypersensitivity (DTH) reaction caused by a transplant of granuloma tissue, which was previously induced by intraperitoneal injection of 10 mg of talc of unknown origin. The DTH response (T-cell-driven) comprises both sensitization and elicitation (challenge) phases. During the sensitization phase, pathogen-derived antigenic peptides sensitize T cells; and, upon secondary challenge with the same antigen a strong response by the sensitized T cells is elicited, which is accompanied by tissue swelling and the release of several cytokines (Kobayashi et al., 2001). Footpad

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Table 4.9 End-points relevant to immunosuppression in non-human mammalian systems exposed to talc

End-points	Assay	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
WBC count, cell counts (spleen)	Smearing on glass slide and May–Grünwald-Giemsa staining	Rat, WVM, Wistar, (M, F)	Blood and spleen	↓ WBCs transient at 5 d and 7 d (both $P < 0.01$), normal at 14 d after talc administration. ↑ spleen on days 7–21 (all $P < 0.01$), $n = 6$ ↓ WBCs suppressed at day 7 by splenectomy with no talc exposure. No change in WBCs with splenectomy plus talc exposure	1 g/rat	Subcutaneous (4 sites) injection. Observations at 3, 5, 7, 14, and 21 d after talc injection	Commercial talc powder, as preparation for hospital purposes sterilized by heating at 160 °C for 1 h; from Jugohospitalia, Zagreb, Croatia.	Radić et al. (1988)
Thymus cortex and medulla area fraction; axillary lymph node germinal centre fraction; spleen white pulp, red pulp and macrophage fraction	Histomorphometric analysis (Morphomat 10, Opton)		Thymus, axillary lymph node and spleen	↓ in thymic cortex and ↑ in thymic medulla fraction 3 d after talc injection ($P < 0.001$) ↑ in axillary lymph node germinal centre fraction 15 h and 3 d after talc injection ($P < 0.001$) ↓ in spleen white pulp ($P < 0.01$) at 15 h, day 3 and day 14; ↑ in spleen red pulp ($P < 0.01$) at 15 h and day 3; and ↓ in spleen macrophage fraction area ($P < 0.001$) at day 3				
Allogenic skin graft survival (in the presence or absence of splenectomy)	Tail skin grafting[b]	Rat, inbred Fischer	Skin	↑ in rats without splenectomy at day 7 ($P < 0.01$), $n = 8–10$			Splenectomy was performed 7 d before talc exposure and 14 d before skin grafting.	
Allogenic skin graft survival (in the presence or absence of serum or spleen cells)	Tail skin grafting[b]	Rat, inbred Fischer	Skin	↑ in the presence of serum or spleen cells from rats with talc granulomatosis ($P < 0.01$)			Allografts with serum or spleen cells from rats with talc granulomatosis.	

Table 4.9 (continued)

End-points	Assay	Species, strain (sex)	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
Allogenic skin graft survival (in the presence or absence of lymph node cells and/or spleen cells)	Tail skin grafting[b]	Rat, T-cell deficient (thymectomized, then lethally irradiated and bone marrow-reconstituted)	Skin	↑ in rats with allograft obtained by co-injection of lymph node cells with spleen cells from talc-exposed mice after 7 d, ($P < 0.01$), $n = 9–11$			Allografts were co-injected or not the day of grafting with lymph node cells from syngeneic alloimmune donors in the presence or absence of spleen cells from rats with talc-granulomas.	
Delayed-type hypersensitivity reaction produced by injection of heat-killed Bacillus Calmette–Guérin	Footpad swelling	Mouse, Balb/c (M, F)	Footpad	No change compared with sham-operated (control) group, $n = 8$, after 1 d and 8 d		Transplantation of 150 mg of peritoneal granuloma induced by 10 mg of talc vs sham-operated (control) into the peritoneum of mice	Talc of unknown origin.	Alessi et al. (1990)

d, day(s); F, female; h, hour(s); M, male; vs, versus; WBC, white blood cell.

[a] ↑, increase; ↓, decrease.

[b] Vidović et al. (1982).

swelling was measured in this study. Talc-induced granuloma did not decrease or increase DHT when compared with granuloma derived from heat-killed Bacillus Calmette–Guérin. [The Working Group noted that tissue swelling was not as precise a marker as the determination of antigen-specific T cells, which is a validated parameter for immunosuppression.]

Synopsis

[Overall, few studies were available to the Working Group. Patients receiving talc through thoracic injection (i.e. pleurodesis) showed a decrease in peripheral blood lymphocyte and eosinophil cell counts; however, the studies had several limitations. One study in rats showed that subcutaneous injection of talc altered leukocyte count and morphology of lymphoid organs, and increased allogenic graft survival.]

4.2.8 Modulates receptor-mediated effects

(a) Humans

A case–control study by Cramer et al. (2016) (described in Section 2.1.5(b)) involved 2041 women with epithelial ovarian cancer and 2100 women who served as age- and residence-matched controls; menopausal status and use of postmenopausal hormone therapy were considered to be potential modifiers for the observed effects. In fact, menopausal status is relevant for the key characteristic "modulates receptor-mediated effects" because estrogen and progesterone levels decrease after menopause, and this might alter hormone interactions potentially relevant to cancer risk. In this study, women aged 18–80 years were recruited using tumour boards and registries from eastern Massachusetts and New Hampshire, USA, and potential associations with talc use were investigated. Cases and controls recalled several risk factors that occurred for > 1 year before the cancer diagnosis, including whether they "regularly" or "at least monthly" applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital–rectal area. Lifetime talc-years, according to self-reported exposure, were estimated, and data were collected on potential confounders and effect modifiers, including menopausal status. Stronger associations between talc use and ovarian cancer risk were observed for premenopausal women (OR, 1.41; 95% CI, 1.13–1.75) and postmenopausal women who used hormonal therapy (OR, 2.21; 95% CI, 1.63–3.00) than for postmenopausal women who did not use hormonal therapy (OR, 0.97; 95%, 0.78–1.20). [The Working Group noted that the positive associations for these subgroups may indicate a role for estrogen- and/or progesterone-related pathways in cancer risk. However, owing to limitations in the study design, i.e. the lack of specific mechanistic end-points relevant to the modulation of receptor-mediated effects, decrease in the number of participants during the study, and lack of information on the nature of the talc used, the study was not considered to be relevant to the present evaluation. Also, contamination of the talc with asbestos could not be ruled out.]

(b) Experimental systems

Two studies in experimental systems were evaluated and reported in Table 4.10. First, Khawaja et al. (1990) created a model of surgical stress by surgically exposing male rats to talc peritonitis. A significant increase in mitochondrial α-glycerophosphate dehydrogenase (αGPD) activity in the liver was reported after administration of triiodothyronine (T3), and there was a transient decrease in hepatic T3 nuclear receptor-binding capacity compared with controls. These results suggested an interaction between the surgical application of talc, increased αGPD, and binding capacity of the T3 nuclear receptor.

In a study conducted by Frazier-Jessen et al. (1996), ovariectomized female mice (as a model for postmenopausal status) were given food

Table 4.10 End-points relevant to receptor-mediated effects in non-human mammalian systems exposed to talc

End-point	Assay	Species, strain (sex)/cell line	Tissue	Results[a]	Dose	Route, duration, dosing regimen	Comments	Reference
αGPD activity	Optical density	Rat, Charles River CD (M)	Liver	↑ at 1 d and 2 d after surgical stress	50 mg	Surgical administration in peritoneal cavity (n = 9 at time zero; control group, n = 9); co-treatment with T3 for > 6 d; killed at 1, 2, 3 d after surgery	Autoclaved talc; purity, NR.	Khawaja et al. (1990)
T3 nuclear receptor binding	Commercial kit		Serum	↓ only at 1 d after surgery with T3 treatment No change without T3 treatment	50 mg	Surgical administration in peritoneal cavity (n = 6); control group, n = 6; killed at 1, 2, 3 d after surgery		
GH mRNA	Dot blot hybridization		Anterior pituitary	No change	50 mg	Surgical administration in peritoneal cavity (n = 6); control group: n = 6; with or without T3 treatment; killed at 1, 2, 3 d after surgery		
JE/MCP-1 mRNA	Northern blot	Mouse, C57BL/6 (F)	Abdominal wall tissue	+	30 mg of talc in saline solution	Single intraperitoneal injection; killed 14 d after injection Mice were ovariectomized	Purity, NR; from Sigma Chemical Co., St Louis, Missouri, USA.	Frazier-Jessen et al. (1996)

αGPD, alpha glycerophosphate dehydrogenase; bw, body weight; d, day(s); F, female(s); GH, growth hormone; h, hour(s); M, male(s); MCP-1, monocyte chemotactic protein 1; NR, not reported; T3, triiodothyronine; USA, United States of America.

[a] +, positive; ↑, increase; ↓, decrease.

containing a placebo or 17β-estradiol and then injected with talc or saline alone in the intraperitoneal cavity. [The Working Group noted that the talc was not contaminated with asbestos.] The talc-treated mice receiving 17β-estradiol had a greater loss of abdominal connective tissue deposition (measured as connective tissue thickness in trichrome-stained tissue sections) than did talc-treated mice receiving the placebo. Additionally, 4 out of 5 talc-treated mice not given 17β-estradiol expressed mRNA for the murine monocyte chemoattractant protein-1 (JE/MCP-1), whereas only 1 mouse in the talc-treated group receiving 17β-estradiol expressed this protein, which is important for connective tissue deposition. [The Working Group noted that the findings indicated a potential effect of talc application on the role of 17β-estradiol in the formation of connective abdominal tissue, and the effect of talc is altered in the presence of treatment with 17β-estradiol.]

Synopsis

[Few studies were available to the Working Group. A case–control study in women showed that premenopausal status and postmenopausal hormone replacement could modify associations between lifetime talc exposure and ovarian cancer risk, suggesting potential interplay with endogenous and exogenous hormones; however, the study had several limitations. In two experimental systems, an interaction between talc, T3, and 17β-estradiol was reported for various parameters.]

4.2.9 Alters cell proliferation, cell death, or nutrient supply

(a) Humans

(i) Exposed humans

Three studies were available to the Working Group (Table 4.11). In one study, morphological tissue changes were observed in 10 out of 28 patients with mesothelioma after receiving talc pleurodesis, where biopsies were available at diagnosis and postmortem examination over a 7-year period (Attanoos and Gibbs, 2004). Fibroblastic spindle cell proliferation was observed in 70% of the mesothelioma biopsies (7/10); spindle cells were located around the talc crystals, and there was a variable admixture of chronic inflammatory cells. [The Working Group noted that this study included a small number of patients.]

In a prospective study, increased levels of basic fibroblast growth factor (bFGF) were detected in the pleural effusion of patients (n = 23) with malignant disease receiving talc pleurodesis when compared with pleural effusion of patients (n = 6) with non-malignant pleural effusion who had not received talc (Antony et al., 2004). [The Working Group noted that this difference could be related to the underlying state – one group being patients with malignancy and the other patients without. This study included a small number of patients.]

Finally, many scars embedding crystals with talc-like characteristics were observed in the lung in a case report of pulmonary Langerhans cell histiocytosis (Weinberg and Mark, 1992) in a woman aged 34 years. The woman was admitted to the hospital because of a pruritic rash, cough, myalgia, and low-grade fever, and had a complex clinical history, including smoking habits, infectious diseases, and suspected drug abuse. [The Working Group noted that the causal association between talc and the disease was uncertain.]

(ii) Human cells in vitro

[Considering the available evidence from experimental studies in humans in vitro, in non-human mammals in vivo, and in in vitro studies reporting on end-points relevant to the key characteristic "alters cell proliferation, cell death, or nutrient supply", the Working Group analysed which studies used talc known to be not contaminated by asbestos. A similar stepwise approach was used to that described in Section 4.2.6(a)(ii).]

Table 4.11 End-points relevant to cell proliferation, cell death, or nutrient supply in humans exposed to talc

End-points	Assay	Biosample, tissue, or cell type	Location, setting or study design	Exposure level, no. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments	Reference
Proliferation of Langerhans cells	Immunohistochemistry (protein S100)	Lung	Massachusetts General Hospital, Boston, USA Case report	Unknown, presence of embolic talc, possibly because of suspected drug abuse	↑	None	Uncertain association between embolic talc and pulmonary Langerhans cell histiocytosis. Suspected association between talc and periarteriolar sclerosis.	Weinberg and Mark (1992)
bFGF	ELISA	Pleural effusion	Florida, USA Prospective cohort study (n = 29) Baseline, 2, 4, 12, and 24 h after thoracoscopy followed by talc pleurodesis	Thoracoscopic talc poudrage, 2–4 g per malignant pleural effusion 23 patients who had talc pleurodesis, 6 control patients with non-malignant pleural effusion and no talc pleurodesis who had congestive heart failure	↑ bFGF in patients with successful pleurodesis at 2 h (P < 0.001) and in patients with unsuccessful pleurodesis at 4 h No change in control group (who did not respond to pleurodesis)	None	Talc, mean particle diameter = 2.1 µm; sterile, lipopolysaccharide-free; from Humco Laboratory.	Antony et al. (2004)

Table 4.11 (continued)

End-points	Assay	Biosample, tissue, or cell type	Location, setting or study design	Exposure level, no. of exposed and controls	Response (significance)[a]	Covariates controlled	Comments	Reference
Fibroblastic spindle cell proliferation	Morphological analysis by histology	Mesothelioma biopsies	UK Retrospective cohort study (n = 48)	Talc pleurodesis Non-talc-exposed patients (n = 20), talc-exposed patients (n = 28) of which 10/28 patients had ante- and postmortem biopsies	+ in 7/10 patients with variable admixture of chronic inflammatory cells; no mitotic activity identified in the spindle cell component	None	No details on talc, no statistical assessment. Contamination with asbestos could not be ruled out.	Attanoos and Gibbs (2004)

bFGF, basic fibroblast growth factor; ELISA, enzyme-linked immunosorbent assay; h, hour(s); UK, United Kingdom; USA, United States of America.

[a] ↑, increase; +, positive.

Several studies were available (Table 4.12). Five studies (Antony et al., 2004; Nasreen et al., 2007; Lee et al., 2010; Fletcher et al., 2019; Harper et al., 2023) were performed in primary mesothelial, endothelial, or ovarian epithelial cells, or fetal lung fibroblasts, and other studies were performed in immortalized mesothelial cells (Gan et al., 1993; Nasreen et al., 2007), immortalized epithelial or cancer ovarian cells (Buz'Zard and Lau, 2007; Fletcher et al., 2019), or mesothelioma or lung cancer cell lines (Nasreen et al., 2000; Lee et al., 2010).

Antony et al. (2004) investigated the role of bFGF produced by primary PMCs exposed to talc. Stimulation of fibroblastic proliferation was described in human fetal lung fibroblasts (HFLF) exposed to PMC-conditioned medium or pleural fluids from patients who had undergone talc pleurodesis. In another study in which the talc sample (Bryan Corporation, Woburn, Massachusetts, USA) tested had a mean particle diameter that was 10 times the usual value (< 10 µm) (Nasreen et al., 2007), inhibition of endothelial cell proliferation was observed after exposure to patient pleural fluids or talc-exposed PMC medium. The inhibition of secretion of endostatin was also reported in PMCs treated with talc.

In primary ovarian epithelial cells, exposure to talc (a commercial brand of talcum baby powder) at a concentration of 5, 20, or 100 mg/mL for 72 hours, was shown to increase secretion of the ovarian cancer marker CA125 and overall cell proliferation, and also to decrease the activity of caspase-3 at a talc concentration of 100 µg/ml (estimated to correspond to 18 µg/cm^2), thus suggesting a decrease in apoptosis (Fletcher et al., 2019). Conversely, Lee et al. (2010) observed no change in generic death of PMCs. [The Working Group noted that data were poorly reported, and information was missing.]

Talc was also shown to increase anchorage-independent growth (at the same concentration of 100 µg/mL, and further increasing at 500 µg/mL) in primary ovarian epithelial cells (Harper et al., 2023). PMCs exposed to talc at a concentration range of 3–12 µg/mL did not show significant apoptosis (Nasreen et al., 2000).

Commercial talc (at a concentration as low as 5 µg/mL) was also able to induce anchorage-independent growth in immortalized ovarian epithelial cells (Buz'Zard and Lau, 2007). Apoptosis was described in mesothelioma cell lines exposed to talc at concentrations as low as 6 µg/cm^2 (Nasreen et al., 2000), and a decrease in cell death, probably apoptosis, was also described in ovarian and fallopian cell lines (Fletcher et al., 2019). Cell death was observed in immortalized mesothelial cells (Gan et al., 1993), lung cancer cells (Lee et al., 2010), and in sensitive mesothelioma cell lines (Nasreen et al., 2000), but not in primary culture of human PMCs (Nasreen et al., 2000; Lee et al., 2010). [The Working Group noted that the comparison between studies was not straightforward owing to the different sources of talc; contamination from asbestos could not be excluded.]

(b) Experimental systems

See Table 4.13.

(i) Non-human mammals in vivo

After intratracheal exposure to talc, hyperplasia of the alveolar epithelium and adenomatous changes were observed in chinchillas (Trautwein and Helmboldt, 1967) and rats (Friemann et al., 1999). Hyperplasia was also described in the alveolar epithelium in a lifetime study of whole-body inhalation in rats and mice treated for 6 hours per day, 5 days per week, for > 110 weeks (rats) or 102 weeks (mice) with talc at 0, 2, 6, and 18 mg/m^3 (see also Section 3) (NTP, 1993). [The Working Group noted that this was a well-conducted GLP study.] Hyperplasia of the alveolar epithelium was observed in or near loci of inflammation in many exposed rats, but not in mice, reaching a frequency of 94% in female rats at the highest dose (NTP, 1993). [The Working Group noted that interim analysis of a small

Table 4.12 End-points relevant to cell proliferation, cell death or nutrient supply in human cells in vitro exposed to talc

End-points	Assay	Cell type	Result[a]	Treatment, duration,	Comments	Reference
Primary cells						
bFGF secretion	ELISA	PMCs	↑ ($P < 0.001$)	4 μg/cm² for 4 h	Talc particle, mean diameter = 2.1 μm. From Humco Laboratory.	Antony et al. (2004)
bFGF-induced fibroblast proliferation	[³H]thymidine incorporation	Fetal lung fibroblasts (HFLF)	↑ 2× incorporation of [³H] thymidine compared with control	Cells exposed to conditioned medium from PMCs exposed to talc	Partially dependent on bFGF (reversion tested by neutralizing antibodies).	
bFGF-induced fibroblast proliferation	[³H]thymidine incorporation	Fetal lung fibroblasts (HFLF)	Incorporation of [³H] thymidine was higher in pleural fluid from patients with successful pleurodesis	20 h incubation with pleural fluids collected after 4 h from talc pleurodesis in patients with malignant effusion (16 successful and 7 unsuccessful pleurodeses)	Partially dependent on bFGF (reversion tested by neutralizing antibodies).	
Endostatin secretion	ELISA	PMCs, primary (Clonetics Corp)	↑, LEC, 10 μg/cm² Highest effect at 25 and 50 μg/cm²	0, 10, 25, 50, 100, and 200 μg/cm² for 24 h	Talc particle, mean diameter = 26.6 μm; Sclerosol, from Bryan Corporation, USA. No dose-dependency and no cytotoxicity. Contamination with asbestos could not be ruled out.	Nasreen et al. (2007)
Cell proliferation	BrdU colorimetric cell proliferation assay	HUVEC	↓ with pleural fluid after 4 and 24 h	Incubation with patient pleural fluid at 0, 4, and 24 h after thoracoscopy	Partially dependent on endostatin (reversion tested by neutralizing antibodies).	
			↓ with conditioned medium	Incubation with conditioned medium from talc-exposed PMCs (unspecified concentration)		

Table 4.12 (continued)

End-points	Assay	Cell type	Result[a]	Treatment, duration,	Comments	Reference
Cell death	Propidium iodide staining and flow cytometry	PMCs from thoracocentesis of patients with congestive heart failure	No change in PMCs, 75 µg/mL (HIC), 72 h	0, 25,50, 75 µg/mL, for 24, 48, and 72 h	Talc particle, diameter = 2 µm. Lack of experimental details. Contamination with asbestos could not be ruled out.	Lee et al. (2010)
CA-125 expression (ovarian cancer biomarker)	ELISA	Primary ovarian epithelial cells	↑ $P < 0.05$	100 µg/mL,[b] for 72 h	Talcum baby powder from Johnson & Johnson, New Brunswick, New Jersey, USA; no. 30 027 477, lot no. 13717RA.	Fletcher et al. (2019)
Cell proliferation	MTT		↑ $P < 0.05$	100 µg/mL,[b] for 24 h		
Caspase-3 activity	Colorimetric assay		↓ $P < 0.05$; LEC, 5 µg/mL[c]	5, 20, 100 µg/mL,[b] 72 h	Dose-dependency.	
Anchorage-independent cell growth	Abcam ab235698	Primary ovarian epithelial cells	↑ $P < 0.05$	100[b] and 500 µg/mL, 72 h	Talcum baby powder (Johnson & Johnson, New Brunswick, New Jersey, USA; no. 30 027 477, lot no. 13717RA).	Harper et al. (2023)
Proliferation index	Ki-67, IHC		↑		Statistical analysis of IHC was weak and the results were dubious.	
Apoptosis	TUNEL	PMCs	No change; HIC, 12 µg/mL	0, 3, 6, 12 µg/cm^2 at 24, 48, 72 h	Talc particle, mean diameter = 2.1 µm. From Humco Laboratory. No cytotoxicity.	Nasreen et al. (2000)

Table 4.12 (continued)

End-points	Assay	Cell type	Result[a]	Treatment, duration,	Comments	Reference
Cell lines						
Endostatin Secretion	ELISA	Mesothelioma cell line (CRL-2081)	↑ at 50 μg/cm^2	0, 10, 25, 50, 100, and 200 μg/cm^2 for 24 h	Talc, Sclerosol, mean particle diameter = 26.6 μm[c] from Bryan Corporation, USA. Contamination with asbestos could not be ruled out.	Nasreen et al. (2007)
Cell death	Propidium iodide staining and flow cytometry	Lung cancer cell line (A549)	↑ 50 μg/mL (LEC) at 24 h	0, 25, 50, 75 μg/mL for 24, 48, 72 h	Talc particle, diameter = 2 μm Lack of experimental details. Contamination with asbestos could not be ruled out.	Lee et al. (2010)
CA-125 expression (ovarian cancer biomarker)	ELISA	Macrophages (kEL-1), fallopian tube cells (FT33), and ovarian cancer cells (SKOV-3, TOV112D, and A2780)	↑ $P < 0.05$	100 μg/mL,[b] for 72 h	Talcum baby powder from Johnson & Johnson, New Brunswick, New Jersey, USA; no. 30 027 477, lot no. 13717RA.	Fletcher et al. (2019)
Cell proliferation	MTT		↑ $P < 0.05$	100 μg/mL,[b] for 24 h		
Caspase-3 activity	Colorimetric assay		↓ $P < 0.05$; LEC, 5 μg/mL[b]	5, 20, 100 μg/mL,[b] for 72 h		
Anchorage-independent cell growth	Growth in soft agar for 14 d	Immortalized normal ovarian epithelial cells (OSE2a) Immortalized normal ovarian granulosa cells (GC1a)	LEC, 5 μg/mL ↑ $P < 0.05$ in OSE2a ↑ $P < 0.01$ in GC1a	5, 20, 100 μg/mL, for 72 h	Talc from Sigma, no further details. Dose–response relation observed.	Buz'Zard and Lau (2007)
Catalysis of DNA incorporation into cells	Transfection of a reporter gene after cell seeding	Immortalized mesothelial cells (Met5A)	No effect on reporter but 50% cytotoxicity 6 d after treatment at 0.2 μg/cm^2	0.020 and 0.2 μg/cm^2 [d]	Talc no. 8476 from Mallinckrodt plc, USA.	Gan et al. (1993)

Table 4.12 (continued)

End-points	Assay	Cell type	Result[a]	Treatment, duration,	Comments	Reference
Apoptosis	TUNEL	Mesothelioma cell lines (CRL-2081, CRL-5820, and CRL-5915)	↑ at 6 μg/cm² with corresponding TUNEL positivity	0, 3,6,12 μg/cm² at 24, 48, and 72 h	Talc particle, mean diameter = 2.1 μm. From Humco Laboratory.	Nasreen et al. (2000)

bFGF, basic fibroblast growth factor; BrdU, 5-bromo-2′-deoxyuridine; d, day(s); ELISA, enzyme-linked immunosorbent assay; h, hour(s); HIC, highest ineffective concentration; HUVEC, human umbilical vein endothelial cell; IHC, immunohistochemistry; LEC, lowest effective concentration, MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; PMC, pleural mesothelial cell; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling; USA, United States of America.

[a] ↑, increase; ↓, decrease.

[b] Estimated to correspond to about 18 μg/cm².

[c] Gilbert et al. (2018).

[d] Estimated on the basis of seeding in a 10 cm² dish.

Table 4.13 End-points relevant to cell proliferation, cell death, or nutrient supply in non-human mammalian systems exposed to talc

End-points	Assay	Species, strain (sex)	Tissue, cell lines	Results[a]	Route, duration, dosing regimen	Comments	References
In vivo							
Hyperplasia	Histology H&E	Chinchilla (M, F)	Lung, alveolar epithelium Lymph nodes	+ +	Repeated dose of 40 mg, 5 intratracheal injections at 0, 20, 50, 70, and 90 d; killed 11 mo after last injection $n = 2$ (control); $n = 12$ (talc)	Talcum powder, purified ($Mg_3Si_4O_{11}$. H_2O). From Fisher Scientific Co., Boston, Massachusetts, USA. No statistics reported. Metaplastic changes (to cuboidal and columnar types) observed proximal to the talc-induced granulomas, in all lungs.	Trautwein and Helmboldt (1967)
Cell proliferation of transformed cells	Histology H&E		Lung, alveolar epithelium	↑ of cuboidal to columnar cells in alveoli with talcum powder deposits	Single intratracheal dose of 40 mg; killed 5 d after injection $n = 5$ (control); $n = 24$ (talc)		
Hyperplasia and reticular-cell proliferation	Histology H&E		Lymph nodes	↑	Repeated intratracheal injections, one per week for 9 wk; killed at 1, 2, and 3.5 mo after injection $n = 4$ (control); $n = 13$ (talc)		
Type II cell hyperplasia	Morphometry (IHC)	Wistar rats (F)	Lung, alveolar epithelium	↑ number and surface of type II cells/mm alveolar wall at only 1 mo after administration ($P < 0.01$)	Single intratracheal injection of 25 mg; observations at 1, 6, or 12 mo after injection $n = 38$ (control); $n = 30$ (talc)	Contamination with asbestos could not be ruled out.	Friemann et al. (1999)
Proliferation index	Feulgen (DNA) staining			↑ at 1 mo after administration ($P < 0.01$)			

Table 4.13 (continued)

End-points	Assay	Species, strain (sex)	Tissue, cell lines	Results[a]	Route, duration, dosing regimen	Comments	References
Hyperplasia	H&E	Rat, F344/N (M, F)	Lung, alveolar epithelium	↑	Cumulative dose 633 (2.8 mg/kg per day) and 1899 mg (8.4 mg/kg per day) for male rats, 390 (3.2 mg/kg per day) and 1170 mg (9.6 mg/kg per day) for female rats. Inhalation of 6 or 18 mg/m^3, 5 d/wk until mortality in any exposure group reached 80%, for up to 113 wk for males, 122 wk for females; *n* = 50/group	Talc MP 10-52 grade. Talc was asbestos-free.	NTP (1993)
		Mouse B6C3F$_1$ (M, F)		–	Cumulative dose, 34 (2 mg/kg per day) and 102 (6 mg/kg per day) mg for male mice, 24 (1.3 mg/kg per day) and 72 mg (3.9 mg/kg per day) for female mice, for up to 104 wk. *n* ~50/group (47–49 males; 48–50 females)		
Count of mesenteric mesothelial/ histiocytes vs dendritic/ other elongated cells and labelling index	Morphometric and [^{3}H]thymidine incorporation	Mouse, ICR (sex not reported)	Mesentery	↑ 3× for mesothelial/ histiocytes at 72 h vs 1.5× for dendritic/other elongated cells. ↑ labelling index with peak at 24 h	Single intraperitoneal injection at 20 mg; administration of [^{3}H] thymidine 30 min before, killed at 24, 48, and 72 h	Talc powder prepared according to Deutsches Arzneibüch (German Pharmacopoeia, 1973).	Dreher et al. (1978)
Chondrocyte cloning	H&E	Rabbit (F)	Femoral head cartilage	↑ chondrocyte clone number	Single unspecified[b] dose, intra-articular injection in the right side (hip) of the animal, then observations until 11 wk post-injection Left side used as control	Talc injection-induced synovitis. Talc of unknown origin ("surgical talc").	Gershuni et al. (1979)

Table 4.13 (continued)

End-points	Assay	Species, strain (sex)	Tissue, cell lines	Results[a]	Route, duration, dosing regimen	Comments	References
Bone marrow hyperplasia	Quantitative histology	Rat, Fischer		↑ megakaryocytes ($P < 0.01$) ↓ osteoblasts ($P < 0.01$)	Single dose at 400 mg Marrow-free bone implanted into syngeneic rats at day 0; talc administered on days 7, 14, and 21 ($n = 6–9$)	Talc described as magnesium silicate, from Kemika, Zagreb, Croatia.	Vukicević et al. (1988)
Inhibition of sarcoma xenograft growth	Implantation of sarcoma 180 fragment into the flank of mice	Mouse, Swiss albino	Subcutaneous implant	↓ tumour growth	Unknown, tumour fragment rolled in talc before implantation; $n = 40$ (20 controls, 20 treated)	Talc described as magnesium silicate with no further details given, dose unknown.	Kerr and de Mesquita (1975)
In vitro							
Nucleotide incorporation in DNA-synthesizing cells	[^{3}H]thymidine incorporation	Mouse, CBA	Bone marrow-derived macrophage	Dose-dependent ↑ [^{3}H]thymidine incorporation starting at 50 µg/mL	0–500 µg/mL for 48 h, 24 h after CSF-1 withdrawal, which induced bone marrow-derived macrophage growth arrest	Talc of USP grade.	Hamilton et al. (2001)
Secretion of VEGF	ELISA	Rabbit, New Zealand	Primary PMCs	↑ starting at 6 h	25 µg/cm^2 for 6, 24, 48 h	Talc, Magnesita, São Paulo, Brazil.	Acencio et al. (2007)
Apoptosis	Flow cytometry (Annexin V-FITC/PI) and IHC			↑ starting at 6 h			

CSF-1, colony-stimulating factor 1; h, hour(s); d, day(s); F, female(s); FITC, fluorescein isothiocyanate; h, hour(s); H&E, haematoxylin and eosin staining; IHC, immunohistochemistry; M, male(s); min, minute(s); MP, micronized powder; mo, month(s); PI, propidium iodide; USP, United States Pharmacopeia; VEGF, vascular endothelial growth factor; vs, versus; wk, week(s).

[a] ↑, increase; ↓, decrease; +, positive; –, negative.

[b] Gershuni et al. (1979).

subset of animals at 6, 11, and 18 hours showed a pattern towards a time-dependent increase in hyperplasia in talc-exposed rats.]

In ICR mice, a single dose of talc (20 mg suspended in 2 mL of 0.9% saline solution, administered by intraperitoneal injection) induced a marked increase in the number of round histiocytes and/or mesothelial cells, and dendritic and other elongated cells at 24, 48, and 72 hours, as measured by incorporation of [^{3}H]thymidine (Dreher et al., 1978). [The Working Group noted that the talc was prepared according to the Deutsches Arzneibüch, 7th edition (German Pharmacopoeia, 1973).]

In female rabbits, a single dose of surgical talc (magnesium tetrasilicate), administered by intra-articular injection into the hip, seemed to induce the formation of clones of chondrocytes from 2 weeks after injection and to an increasing extent at 4 and 5 weeks (Gershuni et al., 1979). Clonal chondrocyte proliferation was shown to promote cartilage repair (Brittberg et al., 2005). [The Working Group noted that these observations suggested talc-induced mitogenic stimulation of chondrocytes; however, important details such as the talc dose and origin were missing.] Bone marrow hyperplasia was observed in a study in which marrow-free bone was implanted into syngeneic rats that had received 400 mg of talc (Vukicević et al., 1988).

Inhibition of sarcoma xenograft growth was described in Swiss albino mice in a model of foreign-body type reaction when the fragment of tumour was pre-embedded in talc (magnesium silicate) (Kerr and de Mesquita, 1975). [The Working Group considered that this study was of low relevance because of limitations concerning lack of detail on the amount and nature of talc used in the experiments.]

(ii) Non-human mammalian systems in vitro

A dose-dependent increase in the proliferation (measured as DNA synthesis by [^{3}H]thymidine incorporation) of murine bone marrow-derived macrophages that had been pretreated with macrophage colony-stimulating factor (CSF-1) was observed with talc at doses starting from 50 µg/mL (Hamilton et al., 2001). [The Working Group noted that the talc used was USP grade.]

In contrast, exposure of rabbit primary mesothelial cells to talc (25 µg/cm^2) resulted in secretion of VEGF and increased apoptosis (Acencio et al., 2007).

Synopsis

[Overall, the above studies indicated that talc appears to alter cell proliferation, cell death, or nutrient supply. In patients undergoing thoracoscopic procedures with talc, spindle cell proliferation in the lungs was observed. Two in vitro studies using multiple models of human primary or immortalized ovarian epithelial cells showed that talc promoted anchorage-independent growth. In addition, conditioned medium of primary mesothelial cells exposed to talc promoted the growth of fibroblasts, assessed by incorporation of [^{3}H]thymidine. Talc promoted the growth of primary ovarian cells assessed by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Furthermore, several studies in vivo showed the development of hyperplasia in the respiratory system of rodents exposed to talc chronically by inhalation or acutely by intratracheal administration. Considering the number of studies (human in vitro, and experimental in vivo and in vitro) reporting end-points relevant to the key characteristic of "alters cell proliferation, cell death, or nutrient supply", the Working Group analysed which studies used talc known not to be contaminated by asbestos. The additional screening step served to determine the extent to which the strength-of-evidence evaluation may be influenced by potential contamination. The results of this analysis did not change the Working Group's conclusions about the strength of the evidence.]

4.2.10 Multiple key characteristics

Three studies reported on end-points potentially relevant to multiple key characteristics. Emi et al. (2021) exposed phagocytic murine macrophages (J774) to certified asbestos-free talc (10 µg/well in 100 mm Petri dishes, ~1 µg/mL) for 24 hours (see Section 4.2.4). Talc alone or in combination with estradiol induced and increased gene expression in pathways related to cell division or proliferation, macrophage phagocytosis or particle phagocytosis, immune response signalling, major histocompatibility complex MHC class I presentation, oxidative stress or ROS-induced signalling, estrogen/estrogen receptor alpha (ESR1) signalling, apoptosis, and epigenetic control of gene transcription. [The Working Group identified several methodological limitations of this study.]

Shukla et al. (2009) exposed human mesothelial cells (LP9) to nonfibrous talc for 8 or 24 hours. Genome-wide gene expression microarray analysis was carried out. Nonfibrous talc at a low concentration (15 μm^2/cm) caused an increase in the expression of a single gene at 8 hours, activating transcription factor 3 (*ATF3*). [The Working Group noted that the results for talc-treated cells were reported for only one time point and one treatment concentration.] However, the expression of 30 genes increased at 8 hours when a higher concentration (75 $\mu m^2/cm^2$) of talc was administered, with the greatest increase (13-fold) seen for *ATF3*. Data were confirmed by polymerase chain reaction (PCR) and suggested that there was dose–response activation. An increase in expression of at least twofold compared with controls was observed for other genes related to chemotaxis, inflammation (interleukins), and blood coagulation. Of these upregulated genes, a high number were ontologically related to inflammation.

Hillegass et al. (2010) furtherly analysed the array data from the above study in human mesothelial cells (LP9). In addition, they exposed human ovarian epithelial cells (IOSE) to nonfibrous talc for 8 or 24 hours and measured gene expression genome-wide using a microarray. Using global gene expression clustering, human mesothelial cells were shown to be more sensitive (as shown by fold-change increases in transcript levels) to nonfibrous talc than were ovarian epithelial cells. [The Working Group noted that results were not reported at the individual transcript level, but only for aggregated results.] [Overall, a single study in vitro provided some evidence that talc exposure could elicit a transcription signature related to inflammation in human mesothelial cells.]

4.3 Other relevant evidence

Very rare hypercalcaemia was associated with a talc granuloma reported in an individual with occupational talc exposure > 20 years previously (Woywodt et al., 2000). Elevated 1,25-dihydroxyvitamin D3 ($1,25[OH]_2D3$) was reported to stimulate the proliferation of monocytes and differentiation into epithelioid cells in vitro (Ohta et al., 1986), while inhibiting dendritic cell maturation and increasing apoptosis (Penna and Adorini, 2000; Gwadera et al., 2019); however, the net impact on immune function remained to be determined. One case report described severe hypercalcaemia in an infant after a talc pleurodesis for recurrent dialysis-related hydrothorax (Aujla et al., 2008). This hypercalcaemia was characterized by persistently elevated levels of $1,25[OH]_2D3$ and osteocalcin, resulting from extrarenal production of $1,25(OH)_2D3$ by macrophages in a large thoracic talc granuloma, which appeared as a large right-side calcified mass upon chest CT (Aujla et al., 2008).

5. Summary of Data Reported

5.1 Exposure characterization

The agent evaluated in this monograph is talc, which includes both naturally occurring mineral talc and synthetic talc. Talc containing asbestos was not evaluated in the present volume. However, it is well documented that asbestos is a common contaminant of talc. Talc is a hydrated magnesium silicate – $Mg_3(OH)_2Si_4O_{10}$ – and normally occurs in nature as lamellar or, more rarely, fibrous particles. Depending on its purity, talc is described as industrial, cosmetic, or pharmaceutical grade, of which pharmaceutical talc has the highest purity with a minimum of 98% talc. In 2023, about 7 000 000 metric tonnes were mined worldwide, with the main producers being India, China, and Brazil. To date, synthetic talc has little commercial relevance. Talc has been exploited commercially because of its outstanding chemical, physical, and technological properties of affinity for organic molecules, high specific surface, hydrophobicity, insolubility, lamellar morphology, and softness. Talc is a common component of plastics, ceramics, paint, paper, roofing materials, rubber products, animal feed, food, fertilizers, cosmetics, and pharmaceuticals. It is also used as a sclerosing agent for pleurodesis. Talc is present in air, water, and soil as a result of natural and anthropogenic processes.

Occupational exposure to talc dust occurs predominantly during mining and milling of talc ore, although exposures can occur among workers in downstream industries that use talc, such as rubber, paper, ceramics, pharmaceuticals, and cosmetics production. The main pathway of exposure in occupational settings is inhalation. Workers can be exposed to talc that contains asbestos and/or crystalline silica during extraction and processing, and in downstream production industries.

For the general population, there are many possible pathways of exposure to talc, including ingestion (foods, pharmaceuticals), inhalation (powder products), and application to skin and the perineal area (cosmetic products and body powder). Exposure to talc via the injection of pharmaceuticals intended for oral use has been reported. Exposure to talc via food and pharmaceuticals may be substantial in some cases, but data were very limited. Widespread use of talc-based body powders has been documented in many countries, particularly among women. However, exposure assessment typically relies on self-reports, which can be unreliable. There are no biomarkers or other markers for talc exposure. Some talc-based consumer products have been repeatedly shown to be contaminated with asbestos, making them a potential source of asbestos exposure. Industry standards used to assess talc in cosmetic and pharmaceutical products are currently not sufficiently sensitive to rule out asbestos contamination.

5.2 Cancer in humans

Two main bodies of evidence were available for consideration by the Working Group in its evaluation of the carcinogenicity of talc. These were: (i) occupational studies (mainly cohort) of talc mining and milling industries and downstream industries, such as rubber, pulp and paper production, and printing, which use talc in part of their process; and (ii) cohort and case–control studies (mainly of ovarian cancer) of women who were asked about their perineal use of talc-based body powder. A major overall consideration when evaluating both these groups of studies was the potential for contamination of the talc with asbestos, apart from a few of the mining and milling industry studies for which the use of asbestos-free talc has been verified, as judged by the Working Group. Contamination of talc with asbestos can act as a confounder for those cancers known to be caused by asbestos,

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in particular, cancers of the lung, larynx, ovary, and mesothelium. The Working Group considered the large number of studies on perineal use (including several informative studies that had been published since *IARC Monographs* Volume 93) and concluded that, within the body of evidence for ovarian cancer, there was a consistent association for ever (versus never) use. Some studies reported analyses relating to frequency and/or duration of use, which provide evidence of an exposure–response relation, even though there was variation in how these metrics were defined and used in different studies. Although most studies adjusted for personal confounding factors, adjustment for any confounding effect of asbestos contamination of the talc has not been possible in these studies. There were also two largely overlapping occupational studies on ovarian cancer among women exposed to talc in the pulp and paper industry that showed an excess risk of ovarian cancer for the whole cohort for incidence and mortality.

The Working Group concluded that there was evidence of a positive association between talc exposure (based upon the findings of studies on perineal application of talc-based body powder) and ovarian cancer and that this association was not likely to be explained by chance. Although there was adjustment for most risk factors for ovarian cancer, bias from differential exposure misclassification and confounding by asbestos contamination of the talc could not be ruled out with reasonable confidence.

Uterine cancer was also investigated in the studies on perineal use (four cohort studies and one case–control study). There were some positive findings for uterine cancer in the cohort studies, but a pooled study of ever (versus never) exposure did not find an association overall, although suggestive positive findings were seen for long-term use of talc for the non-endometrioid subtype. The Working Group judged that no conclusions could be drawn from these studies about a causal relationship between talc exposure and uterine cancer.

The Working Group considered the evidence from studies in the talc mining and milling industry and in particular the three cohorts in Austria, France, and Italy in which the ore used was documented to be asbestos-free. A meta-analysis for lung cancer conducted by the Working Group found no excess risk in these three cohorts. There was no evidence of an exposure–response relation, limited adjustment for smoking, and no accounting for co-exposure to silica, which is a potential confounding exposure in the industry. Therefore, the Working Group concluded that there was not convincing evidence of a causal association between talc exposure and lung cancer.

For stomach cancer, there was also some evidence of a small excess of deaths in a meta-analysis of the same three studies, but this meta-estimate was heavily influenced by a large number of deaths in one study and a small number in the other two, and there was lack of adjustment for possible confounders. There was also a single study on consumption of talc as part of a Chinese traditional medicine treatment, which showed a positive association with stomach cancer; however, there were concerns about asbestos contamination of the talc before 2005, short follow-up, and confounding by indication. Therefore, the Working Group concluded that there was no convincing evidence of a causal association between talc exposure and stomach cancer, based on the findings in those studies.

The Working Group also considered the evidence for several other cancers, including urinary tract, other organs in the digestive tract, mesothelioma, brain, cervix uteri, prostate, breast, and haemopoietic cancers. There were usually too few studies, too few cases to perform a meta-analysis, poor exposure assessment, and/or other methodological limitations, and the Working Group concluded that there was no

convincing evidence of an association between talc exposure and any of these cancer types.

5.3 Cancer in experimental animals

Treatment with talc caused an increase in the incidence of malignant neoplasms (adrenal medulla and lung) in females, and a combination of benign and malignant neoplasms (adrenal medulla) in males of a single species (rat) in one study that complied with Good Laboratory Practice (GLP). The occurrence of tumours in this study was considered unusual because of the following findings: (i) the significant increase in the incidence of bilateral benign pheochromocytoma and bilateral malignant pheochromocytoma of the adrenal medulla in females; and (ii) the development of tumours in the adrenal medulla after exposure to talc by inhalation in both sexes.

Talc was administered by inhalation in the one study that complied with GLP, in male and female F344/N rats. In females, talc caused malignant pheochromocytoma, benign or malignant pheochromocytoma (combined), bilateral benign pheochromocytoma, and bilateral malignant pheochromocytoma of the adrenal medulla; and bronchioloalveolar carcinoma, and bronchioloalveolar adenoma or carcinoma (combined). In males, talc caused benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla.

5.4 Mechanistic evidence

No relevant data on metabolism of talc could be identified. The existing available human and experimental data on absorption, distribution, and excretion suggested that inhaled talc is retained in the lungs, while intravenous injection of talc leads to systemic distribution. Evidence from several individuals showed persistence of inhaled talc in the human lungs years after cessation of exposure.

Intrapleural exposure to talc leads to translocation and deposition in the lungs, according to one study in humans. In biopsies in humans, talc was identified at multiple pelvic sites distant from the perineum, lodged in distal structures in the female reproductive tract, and was associated with reported perineal use of talc.

In rabbits and rats, several studies suggested that intrapleural exposure to talc leads to translocation and deposition in the lungs and other organs. However, in two studies in rodents, intrapleural exposure to talc in general did not lead to relevant systemic distribution. In rodents, alveolar clearance of talc was reported to be essentially complete 4–12 months after exposure for up to 4 weeks. Orally ingested talc was excreted shortly after dosing, and no or negligible intestinal absorption or translocation of talc to the liver and kidneys was observed in rats, mice, and guinea-pigs. In most studies in experimental animals, no translocation from the perineal region to the ovaries was reported.

There is consistent and coherent evidence that talc exhibits key characteristics of carcinogens.

Talc induces chronic inflammation. The evidence in exposed humans is suggestive. Talc causes strong acute inflammation, which may persist to become chronic inflammation and evolve into chronic fibrosis. Therapeutic talc pleurodesis is an example from medical interventions demonstrating this process. Numerous case reports, which describe an association between prolonged external exposure to talc and granulomatous inflammation in different organs, provide support for the hypothesis that talc causes chronic inflammation. None of the reviewed studies directly evaluated mechanistic end-points of chronic inflammation per se, which were caused by exposure to talc independent of other known risk factors for chronic inflammatory lung disease. There is a paucity of evidence in human primary cells. Consistent

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and coherent evidence of chronic inflammation comes from numerous studies in experimental systems with varying exposures, up to 2 years. In vivo exposures of non-human mammals to talc at a variety of body sites has been associated with inflammation after various routes of exposure. Upregulation of interleukin 8 (IL-8) was observed across a few studies in human and non-human mammalian cells in vitro.

Talc alters cell proliferation, cell death, or nutrient supply. There is a paucity of data in exposed humans. Consistent and coherent evidence comes from studies in human primary cells and experimental systems. Two in vitro studies using multiple models of human primary or immortalized ovarian epithelial cells showed that talc promoted anchorage-independent growth. Primary mesothelial cells exposed to talc secreted factors that promoted the growth of fibroblasts. Talc induced the growth of primary ovarian cells. Multiple studies showed the development of hyperplasia in the respiratory system of rodents exposed chronically by inhalation or acutely by intratracheal administration.

Evidence from the available studies reporting outcomes relevant to the key characteristics of "induces chronic inflammation" and "alters cell proliferation, cell death or nutrient supply" were further evaluated by the Working Group to determine which studies used talc known not to be contaminated by asbestos. This additional screening, in a stepwise approach, was undertaken to determine the extent to which the strength-of-evidence evaluation may be influenced by potential contamination by asbestos. The results of this analysis did not alter the Working Group's judgement about the strength of the evidence for talc.

There is suggestive evidence that talc induces oxidative stress in experimental systems. There is a paucity of data in exposed humans and in human primary cells. Experiments in human cells were mostly limited to cancer cell lines whose nature (e.g. genome instability, heterogeneous cultures) makes the relevance of the outcomes difficult to interpret. There were several in vivo studies in rodents, describing induction of relevant end-points. In one in vivo study in dogs, the observed effects (decreased superoxide production) were not clearly described and may not have been specifically related to oxidative stress.

There is suggestive evidence that talc is immunosuppressive in experimental systems. There is a paucity of data in exposed humans and in human primary cells. In one study in rats, it was demonstrated that subcutaneous injection of talc alters leukocyte counts and thymus and spleen morphology and increases allogenic graft survival.

There was a paucity of data for the following key characteristics: "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "alters DNA repair or causes genomic instability", "induces epigenetic alterations", and "modulates receptor-mediated effects". No data were available as to whether talc exhibits the key characteristic "causes immortalization".

6. Evaluation and Rationale

6.1 Cancer in humans

There is *limited* evidence in humans for the carcinogenicity of talc. Positive associations have been observed between exposure to talc and cancer of the ovary.

6.2 Cancer in experimental animals

There is *sufficient* evidence in experimental animals for the carcinogenicity of talc.

6.3 Mechanistic evidence

There is *strong* evidence that talc exhibits key characteristics of carcinogens in human primary cells and experimental systems.

6.4 Overall evaluation

Talc is *probably carcinogenic to humans* (Group 2A).

6.5 Rationale

The Group 2A evaluation of talc is based on three different evidence combinations, any one of which would have led to a Group 2A classification:

(a) the combination of *limited* evidence for cancer in humans and *sufficient* evidence for cancer in experimental animals;

(b) the combination of *limited* evidence for cancer in humans and *strong* mechanistic evidence in human primary cells and experimental systems;

(c) the combination of *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in human primary cells.

There is *limited* evidence that exposure to talc causes cancer of the ovary in humans. Among the available studies of cancer in humans, consistent findings of increased risk of ovarian cancer were observed in several cohort and many case–control studies that assessed ever perineal use of talc-based body powder, and evidence that risk increased with increasing exposure was seen in some studies. These studies were considered informative for the evaluation of talc. However, contamination of talc-based body powder by asbestos has been documented; therefore, confounding by asbestos contamination of the talc cannot be ruled out. Bias resulting from differential exposure misclassification also could not be ruled out. Occupational studies on ovarian cancer risk and talc exposure were scarce, since only studies conducted in the pulp and paper industry included a sizeable proportion of women. Although some positive associations were observed, the occupational studies were considered less informative because of concerns about asbestos contamination of the talc used in this industry and the low number of observed cancers.

For all other cancers, including lung and stomach, the evidence was considered *inadequate*, because associations were not seen consistently across the available studies or were imprecise, studies were few in number, or there was co-exposure to other carcinogens.

The *sufficient evidence* in experimental animals is based on an increase in the incidence of malignant neoplasms (adrenal medulla and lung) in females, and a combination of benign and malignant neoplasms (adrenal medulla) in males of a single species (rat), in one study that complied with Good Laboratory Practice. This *sufficient evidence* is also based on unusual results of this study: (i) the significant increase in the incidence of bilateral benign pheochromocytoma and bilateral malignant pheochromocytoma of the adrenal medulla in females; and (ii) the development of tumours in the adrenal medulla after exposure to talc by inhalation in both sexes.

There is *strong* evidence that talc exhibits key characteristics of carcinogens. The evidence is based on consistent and coherent evidence that talc induces chronic inflammation in experimental systems, and alters cell proliferation, cell death or nutrient supply in human primary cells and experimental systems.

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LIST OF ABBREVIATIONS

AACES	African-American Cancer Epidemiology Study
ACGIH	American Conference of Governmental and Industrial Hygienists
ADI	acceptable daily intake
afu	atoms per formula unit
AHERA	Asbestos Hazard Emergency Response Act
ANECS	Australian National Endometrial Cancer Study
ASTM	American Society for Testing and Materials
AUS	Australian Cancer Study
B[a]P	benzo[*a*]pyrene
BCG	bacille Calmette-Guérin
bFGF	basic fibroblast growth factor
BMI	body mass index
BOM	Bureau of Mines
BrdU	5-bromo-2′-deoxyuridine
bw	body weight
CANJEM	Canadian Job Exposure Matrix
CAS	Chemical Abstracts Service
CAT	catalase
CCCS	Cook County (Chicago) Case Study
CI	confidence interval
CIS	conical inhalable sampler
CN	commercial nanotalc
CON	Connecticut Ovary Study
CRP	C-reactive protein
CSF-1	colony-stimulating factor
CT	computed tomography
CTFA	Cosmetic, Toiletry and Fragrance Association
CTPA	Cosmetic, Toiletry and Perfumery Association Limited
1CyHEMA	*N*-acetyl-*S*-(1-cyano-2-hydroxyethyl)-L-cysteine
2CyEMA	*N*-acetyl-*S*-(2-cyanoethyl)-L-cysteine
DOV	Diseases of the Ovary and their Evaluation Study
DTA	differential thermal analysis
DTH	delayed-type hypersensitivity
DU	decision unit

EC	European Commission
EDS	energy-dispersive X-ray spectroscopy
EDX	energy-dispersive X-ray analysis
EDXA	X-ray diffraction microanalysis probe
EFSA	European Food Safety Agency
EELS	electron energy loss spectroscopy
ELISA	enzyme-linked immunosorbent assay
EPMA	electron probe microanalysis
ESR	estrogen receptor alpha
FDG	fluorodeoxyglucose
FTIR	Fourier transform infrared spectroscopy
GLP	Good Laboratory Practice
GM	geometric mean
GMP	Good Manufacturing Practice
αGPD	α-glycerophosphate dehydrogenase
GPx	glutathione peroxidase
GRF	glutinous rice flour
GSD	geometric standard deviation
GSR	glutathione reductase
HAW	Hawaii Ovarian Cancer Study
2HEMA	*N*-acetyl-*S*-(2-hydroxyethyl)-L-cysteine
HFLF	human fetal lung fibroblast
HHE	Health Hazard Evaluation
HOP	Hormones and Ovarian Cancer Prediction Study
HPV	human papillomavirus
HR	hazard ratio
HRCT	high-resolution computed tomography
HR-ICP-MS	high-resolution inductively coupled plasma mass spectrometry
HRR	hazard rate ratio
hr-SOD	human recombinant superoxide dismutase
HSE	Health and Safety Executive
HUVEC	human umbilical vein endothelial cells
HWE	healthy-worker hire effect
HWSB	healthy-worker survivor bias
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IN	indigenous nanotalc
iNOS	inducible nitric oxide synthase
INPS	National Institute for Social Security (Istituto Nazionale Previdenza Sociale)
IOM	Institute of Occupational Medicine
ISO	International Organization for Standardization
IRR	incidence rate ratio
ISM	incremental sampling methodology
JEM	job-exposure matrix
LACOCS	Los Angeles County Ovarian Cancer Study
LDH	lactate dehydrogenase
LLDPE	linear low-density polyethylene

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LOD	limit of detection
LPS	lipopolysaccharide
MAL	Malignant Ovarian Tumor Study
MESA	Mining Enforcement and Safety Administration
miRNA	microRNA
MMAD	mass median aerodynamic diameter
mppcf	million particles per cubic foot
MSHA	Mine Safety and Health Administration
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCGIH	National Conference of Governmental Industrial Hygienists
NCO	North Carolina Ovarian Cancer Study
NEC	New England Case–Control Study of Ovarian Cancer
NHIRD	National Health Insurance Research Database
NHL	non-Hodgkin lymphoma
NHS-I	Nurses' Health Study
NHS-II	Nurses' Health Study II
NIOSH	National Institute for Occupational Safety and Health
NIRS	near-infrared spectroscopy
NMAM	NIOSH manual of analytical methods
NMRD	non-malignant respiratory disease
NMTC	natural mixture of talc and chlorite
NOES	National Occupational Exposure Survey
NOS	Newcastle–Ottawa scale
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
OCAC	Ovarian Cancer Association Consortium
OCMAP	Occupational Cohort Mortality Analysis Program
OCWAA	Ovarian Cancer in Women of African Ancestry
OEL	occupational exposure limit
OPCMIA	Operative Plasterers' and Cement Masons' International Association
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PAPDEM	pulp and paper department-exposure matrix
PBL	peripheral blood lymphocyte
PCOM	phase contrast optical microscopy
PCPC	Personal Care Products Council
PEL	permissible exposure level
PET	positron emission tomography
PLOM	polarized light optical microscopy
PMC	pleural mesothelial cell
PMR	proportionate mortality ratio
ppm	parts per million
PROVAQ	PRevention of OVArian Cancer in Quebec
RR	rate ratio
PSD	particle size distribution
ROS	reactive oxygen species
RT-PCR	reverse transcription-polymerase chain reaction
RT-qPCR	reverse transcription-quantitative polymerase chain reaction
SAED	selected area electron diffraction

SAM	spectral angle mapper
SCE	sister-chromatid exchange
SCF	European Scientific Committee for Food
SEER	Surveillance, Epidemiology, and End Results
SEM	scanning electron microscopy
SD	standard deviation
SFA	super-fine asbestos
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SOD	superoxide dismutase
SON	Southern Ontario Ovarian Cancer Study
SRR	standardized rate ratio
STEM	transmission electron microscopy fitted with a scanning attachment
SWIR	short-wavelength infrared
T3	triiodothyronine
TBARS	thiobarbituric acid-reactive substances
TEM	transmission electron microscopy
TEM-EDX	transmission electron microscopy coupled to X-ray energy dispersive spectrometry
TGA	thermogravimetric analysis
TGFβ	transforming growth factor beta
TLV-TWA	threshold limit value-time weighted average
TNFα	tumour necrosis factor alpha
TOT	two tetrahedral layers surrounding one octahedral layer (2:1)
TWA	time-weighted average
UCI	University of California, Irvine Ovarian Cancer Study
UK	United Kingdom
US	United States
USA	United States of America
USC	University of Southern California Study of Lifestyle and Women's Health
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VCRP	Voluntary Cosmetic Registration Program
VEGF	vascular endothelial growth factor
VNIR	visible and near-infrared
VPSEM	variable pressure scanning electron microscopy
vs	versus
WAXS	wide angle X-ray scattering
WDS	wavelength-dispersive X-ray spectrometry
WHI	Women's Health Initiative
WHI-OS	Women's Health Initiative Observational Study
w/w	weight per weight
%wt	percentage by weight
WHO	World Health Organization
XRD	X-ray diffraction
XRF	X-ray fluorescence
XRPD	X-ray powder diffraction
ZTO	zedoary turmeric oil

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ANNEX 1. SUPPLEMENTARY MATERIAL FOR SECTION 1, EXPOSURE CHARACTERIZATION

These supplementary online-only tables are available from: https://publications.iarc.who.int/646.

Please report any errors to imo@iarc.who.int.

Talc

The following tables were produced in draft form by the Working Group and were subsequently fact-checked, but not edited:

Table S1.6	Composition of selected glazes and slips containing talc
Table S1.12	Dust measurements in talc mines and mills (liquid impinger, all values in mppcf)
Table S1.13	Exposure to respirable dust in talc mines and mills (personal sampling, all values in mg/m^3)
Table S1.19	Exposure assessment review and critique for epidemiological studies on cancer in humans with occupational exposure to talc
Table S1.20	Exposure assessment review and critique for epidemiological studies on cancer in humans with non-occupational exposure to talc

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ANNEX 2. QUANTITATIVE BIAS ANALYSIS FOR EXPOSURE MISCLASSIFICATION FOR THE EFFECTS OF EVER VERSUS NEVER USE OF TALC ON OVARIAN CANCER

In studies on talc powder personal use and ovarian cancer, exposure has been assessed on the basis of participant recall, leading to concern about exposure misclassification. Cohort studies, which assess talc exposure before disease occurrence, have the potential for non-differential exposure misclassification, whereas case–control studies, which assess exposure after disease status is known, have the potential for both differential and non-differential exposure misclassification. In the present annex, the Working Group examined the potential bias resulting from misclassification of talc exposure when assessing its effects on ovarian cancer. We limited our analysis to ever versus never use of talc (including body powder) and to the studies included in the pooled analyses of cohort studies (O'Brien et al., 2020) and case–control studies (Terry et al., 2013; Davis et al., 2021). When evaluating cohort studies, we included all women, regardless of whether their reproductive tracts were patent or not.

The extent of bias caused by misclassification is determined by the sensitivity and specificity of exposure classification. No validation studies on the self-reporting of talc use were identified by the Working Group. To quantify sensitivity and specificity, we relied on the expert opinion of Working Group members, particularly the exposure scientists and epidemiologists who had studied perineal use of talc. We conducted an iterative procedure to estimate sensitivity and specificity. First, the purpose of a bias analysis and the process involved were described to the Working Group experts participating in the bias assessment. Next, the experts were asked to quantify their beliefs about the sensitivity and specificity of misclassification, providing a best guess for the sensitivity and specificity values associated with cohort studies and an interval within which they were 95% certain about these estimates (Table A2.1). For case–control studies, these experts were asked to provide separate sensitivity and specificity estimates for cases and controls (Table A2.1).

The experts then met to compare their estimates of sensitivity and specificity and agreed on a range of sensitivities and specificities (separately for cohort and case–control studies) that encompassed the minimum and maximum values that they jointly agreed were plausible. Finally, the members were given the opportunity to review their personal best guesses and 95% certainty intervals and revise them.

Table A2.1 Experts' best guesses for the sensitivity and specificity values

Expert identity	Cohort studies			Case–control studies		
		Best guess (%)	95% Range (%)		Best guess (%)	95% Range (%)
Expert 1	Sens	90	85–95	Sens cases	96	94–98
	Spec	90	85–95	Spec cases	85	80–90
				Sens controls	90	85–95
				Spec controls	90	85–95
Expert 2	Sens	80	75–85	Sens cases	75	65–85
	Spec	90	85–95	Spec cases	90	85–95
				Sens controls	65	60–70
				Spec controls	90	85–95
Expert 3	Sens	80	75–85	Sens cases	90	85–95
	Spec	80	78–82	Spec cases	85	80–90
				Sens controls	80	75–85
				Spec controls	90	85–95

sens, sensitivity; spec, specificity.

This process resulted in the following ranges of values for cohort studies:

- Sensitivity: 0.80–0.95;
- Specificity: 0.80–0.94.

The following ranges were specified for case–control studies:

Cases:

- Sensitivity: 0.80–0.95;
- Specificity: 0.75–0.90.

Controls (the same values as for participants in cohort studies):

- Sensitivity: 0.80–0.95;
- Specificity: 0.80–0.94.

In addition, the experts agreed on the following constraints for the sensitivities and specificities:

A: The sensitivity for cases is greater than or equal to the sensitivity for the controls;

B: The specificity for cases is less than or equal to the specificity for the controls;

C: The extent of differential misclassification does not exceed 10%; that is (sensitivity for cases minus sensitivity for controls) is less than or equal to 10%, and (specificity for controls minus specificity for cases) is less than or equal to 10%.

In addition to these ranges, three experts in subgroups 1 and 2 provided their personal estimates and 95% certainty ranges for the sensitivity and specificity parameters, as follows.

We used the ranges and expert specifications in two sets of analyses:

1. A multidimensional bias analysis to quantify the extent to which the misclassification-adjusted effects change over a range of sensitivity/specificity values;
2. Three separate expert-specific bias analyses that used the bias parameters provided by three experts in the Working Group.

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Analysis

We chose six evenly spaced points between the lower and upper boundaries of the estimates and conducted a bias analysis on each of the 15 cohort and case–control studies indicated in Table A2.2, for every permutation of the sensitivity and specificity values. We always kept the cohort sensitivity and specificity equal to the control sensitivity and specificity in the multidimensional bias analyses (i.e. the misclassification was always non-differential for cohort studies). We only considered permutations of sensitivity and specificity that were consistent with constraints A, B, and C listed above, and this resulted in 306 permutations, on which we conducted bias analyses. Below, we also provide the results of bias analyses for the lowest, midpoint, and highest values for each range (consistent with the constraints) for ease of interpretation.

Each permutation of sensitivity and specificity was used to conduct a bias analysis in the following manner. First, we extracted the observed contingency data for each of the 15 studies (4 cohort and 11 case–control studies), then adjusted the observed data from each study for misclassification. Misclassification-adjusted effects were calculated using formulae from Greenland (1988). These formulae differ according to study design and the desired effect. They also incorporate uncertainty in the sensitivity and specificity parameters in the final interval estimates. For the multidimensional bias analysis, we assumed that there was no uncertainty in the sensitivity and specificity estimates. For the expert-specific bias analyses, we used the variance around the sensitivity and specificity parameters specified by the experts.

Second, the misclassification-adjusted data were adjusted for the impact of confounding. The results from step 1, above, could have been confounded, because unadjusted crude cell counts were used. However, a set of confounders was adjusted-for in each study. We estimated the extent of confounding in each study by computing the ratio of the confounding-adjusted effect to the crude effect for each study, both of which were misclassified. Next, we multiplied the misclassification-adjusted results in step 1 by this factor to produce results adjusted for both misclassification and confounding.

These two steps were repeated for each individual study (4 cohort and 11 case–control), resulting in 15 misclassification- and confounding-adjusted effect estimates and associated variances. These study-specific effects were then combined in a random effects meta-analysis.

For the multidimensional meta-analysis, this procedure was repeated for all 306 sensitivity and specificity permutations. For the expert-specific bias analysis, this procedure was repeated for each expert.

The data abstracted from the 15 studies included in this quantitative bias analysis are shown in Table A2.2, along with the study design and main (identified as "confounder-adjusted") effects. The results of the multidimensional bias analysis for 15 scenarios that represent the extremes of each range and the midpoint (and satisfy constraints A, B, and C above) are presented in Table A2.3. The effects presented in this analysis have been adjusted for both misclassification and confounding. The summary estimates (meta-relative risks, meta-RRs) obtained from meta-analyses for the 15 scenarios ranged from 1.00 to 1.22. The largest meta-RR, of 1.22, is the result that would have been obtained if the sensitivities in cohort and case–control studies were 80%, the specificity in cohort studies was 80%, and the specificity in case–control studies was 75%. The results shown in Table A2.3 are a subset of the 306 analyses that were conducted, which generated meta-RRs ranging from 0.81 to 1.30. The smallest adjusted effects, such as a meta-RR of 0.81, were associated with a large amount of differential misclassification. There was little between-study heterogeneity in any

Table A2.2 Characteristics of the studies included in the quantitative bias analysis for talc and ovarian cancer

Study (reference)	Case-exposed	Case-unexposed	Control-exposed	Control-unexposed	Study design	Effect measure (RR or OR)	Lower limit of 95% CI	Upper limit of 95% CI
NHS-I (O'Brien et al., 2020)	514.08	709.92	32 412.55	46 642.45	Cohort	1.07	0.95	1.20
NHS-II (O'Brien et al., 2020)	18.24	57.76	15 720.64	44 743.36	Cohort	0.81	0.47	1.38
SIS (O'Brien et al., 2020)	63.51	155.49	10 852.11	29 340.89	Cohort	1.02	0.76	1.38
WHI-OS (O'Brien et al., 2020)	363.44	285.56	37 558.45	33 306.55	Cohort	1.11	0.95	1.30
AUS (Terry et al., 2013)	705	300	658	305	CC	1.13	0.92	1.38
DOV (Terry et al., 2013)	272	1293	297	1544	CC	1.13	0.93	1.36
HAW (Terry et al., 2013)	74	326	112	489	CC	0.99	0.7	1.41
HOP (Terry et al., 2013)	194	439	316	989	CC	1.34	1.07	1.67
NCO (Terry et al., 2013)	195	469	122	391	CC	1.37	1.05	1.8
NEC (Terry et al., 2013)	755	1129	636	1239	CC	1.28	1.12	1.47
SON (Terry et al., 2013)	197	252	200	364	CC	1.35	1.03	1.76
USC (Terry et al., 2013)	208	435	170	494	CC	1.36	1.06	1.74
AACES_B (Davis et al., 2021)	119	196	202	394	CC	1.16	0.85	1.57
CCCS_B (Davis et al., 2021)	14	30	15	65	CC	1.51	0.52	4.4
CCCS_W (Davis et al., 2021)	53	180	75	346	CC	1.19	0.77	1.84

AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CC, case–control; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; OR, odds ratio; RR, relative risk; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W, in White women; WHI-OS, Women's Health Initiative Observational Study.

of the meta-analyses reported in Table A2.3. Of note, not every set of sensitivity and specificity values was compatible with every study, and therefore studies with data that were not compatible were excluded from the analyses. The total number of studies included is shown in the table.

Table A2.4 presents the results of the three expert-specific bias analyses. The estimate generated in the crude analysis, which was adjusted for confounding but subject to misclassification, was a meta-RR of 1.17 (95% confidence interval, CI, 1.10–1.25). The adjusted estimates (meta-RRs) provided by the three experts were all attenuated and ranged from 1.04 to 1.12. Little heterogeneity was noted between studies after adjusting for misclassification. Figs A2.1, A2.2, A2.3, and A2.4 present forest plots for the meta-analyses, based on the reported effects (adjusted for confounding but subject to misclassification), as well as the results provided by the three experts. Table A2.5 presents study-specific point estimates of the misclassification-adjusted effects calculated using the sensitivity and specificity parameters provided by each expert. Table A2.6 presents study-specific point estimates of the misclassification- and confounding-adjusted effects from

Table A2.3 Multidimensional quantitative bias analysis conducted at the extremes and midpoint of the sensitivity and specificity ranges

Cohort studies or controls[a]		Cases		Meta-RR[b]	*P*[c]	N[d]
Sens	Spec	Sens	Spec			
0.8	0.8	0.8	0.75	1.22	0.77	14
0.8	0.8	0.875	0.75	1.1	0.29	14
0.8	0.87	0.8	0.825	1.17	0.99	14
0.8	0.87	0.875	0.825	1.05	0.71	14
0.8	0.94	0.8	0.9	1.13	0.53	15
0.8	0.94	0.875	0.9	1	0.23	15
0.875	0.8	0.875	0.75	1.19	0.74	14
0.875	0.8	0.95	0.75	1.1	0.28	14
0.875	0.87	0.875	0.825	1.14	0.99	14
0.875	0.87	0.95	0.825	1.04	0.74	14
0.875	0.94	0.875	0.9	1.11	0.58	15
0.875	0.94	0.95	0.9	1	0.26	15
0.95	0.8	0.95	0.75	1.16	0.69	14
0.95	0.87	0.95	0.825	1.13	0.99	14
0.95	0.94	0.95	0.9	1.1	0.61	15

RR, relative risk; sens, sensitivity; spec, specificity.
[a] The sensitivity and specificity for the cohort studies are the same as for the controls in the case–control studies.
[b] Meta-analysis relative risk (meta-RR) estimate obtained from the misclassification- and confounding-adjusted estimates.
[c] Heterogeneity *P* value.
[d] Number of studies included in the meta-analysis. The number is < 15 because not all of the sensitivity/specificity values were compatible with the data for each study.

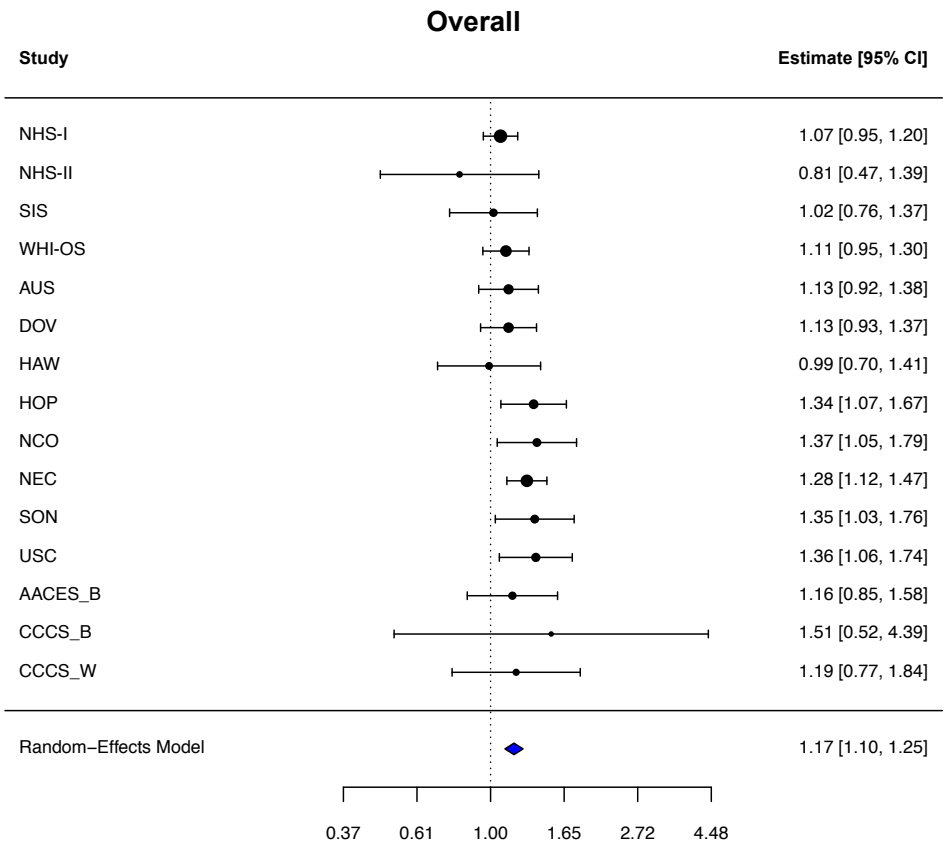
Table A2.4 Quantitative bias analysis using the best guesses by three experts for the sensitivity and specificity, incorporating uncertainty in the sensitivity and specificity estimates

Expert	Meta-RR[b]	Lower limit of 95% CI	Upper limit of 95% CI	*P*[c]
Crude[a]	1.17	1.1	1.25	0.48
Expert 1	1.06	0.97	1.16	0.97
Expert 2	1.12	1	1.25	1
Expert 3	1.04	0.92	1.18	0.85

CI, confidence interval; RR, relative risk.
[a] Assumes perfect sensitivity and specificity.
[b] Meta-analysis of the bias-adjusted estimates, except for the "crude" estimate, which is a meta-analysis of the reported effects from each study.
[c] *P*-value for the heterogeneity of the effects in the meta-analysis.

Fig. A2.1 Forest plots of the confounding-adjusted, but not misclassification-adjusted, study effects using estimates from the original paper

(A) Cohort and case–control studies



AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

each expert. Of note, there is little difference between the results in Table A2.5 and Table A2.6, indicating that there is relatively little observed confounding in the published studies.

We note several limitations of these analyses. First, quantitative bias analysis relies on sensitivity and specificity parameters, and the results of these bias analyses are only as valid as these parameters. Second, the adjustment for confounding is an approximation, rather than an exact result. However, given the very modest levels of confounding, this approximation is likely to be very good. Third, this approach does not incorporate the additional variance caused by the incorporation of confounding. This could result in final interval estimates that are too narrow. Fourth, the misclassification adjustments do not incorporate correlations between the sensitivities and specificities associated with case–control studies. This would probably result in interval estimates that are too wide.

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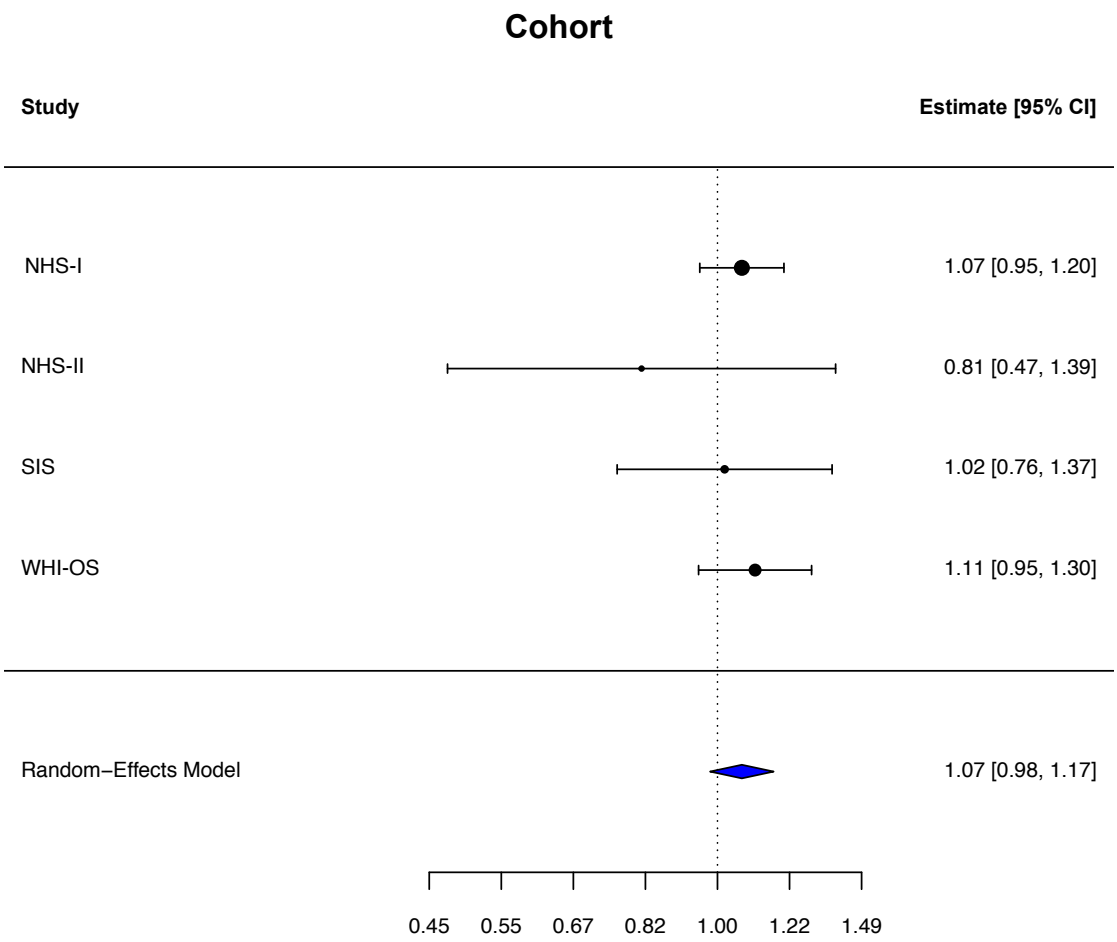
Fig. A2.1(B) Cohort studies only



AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

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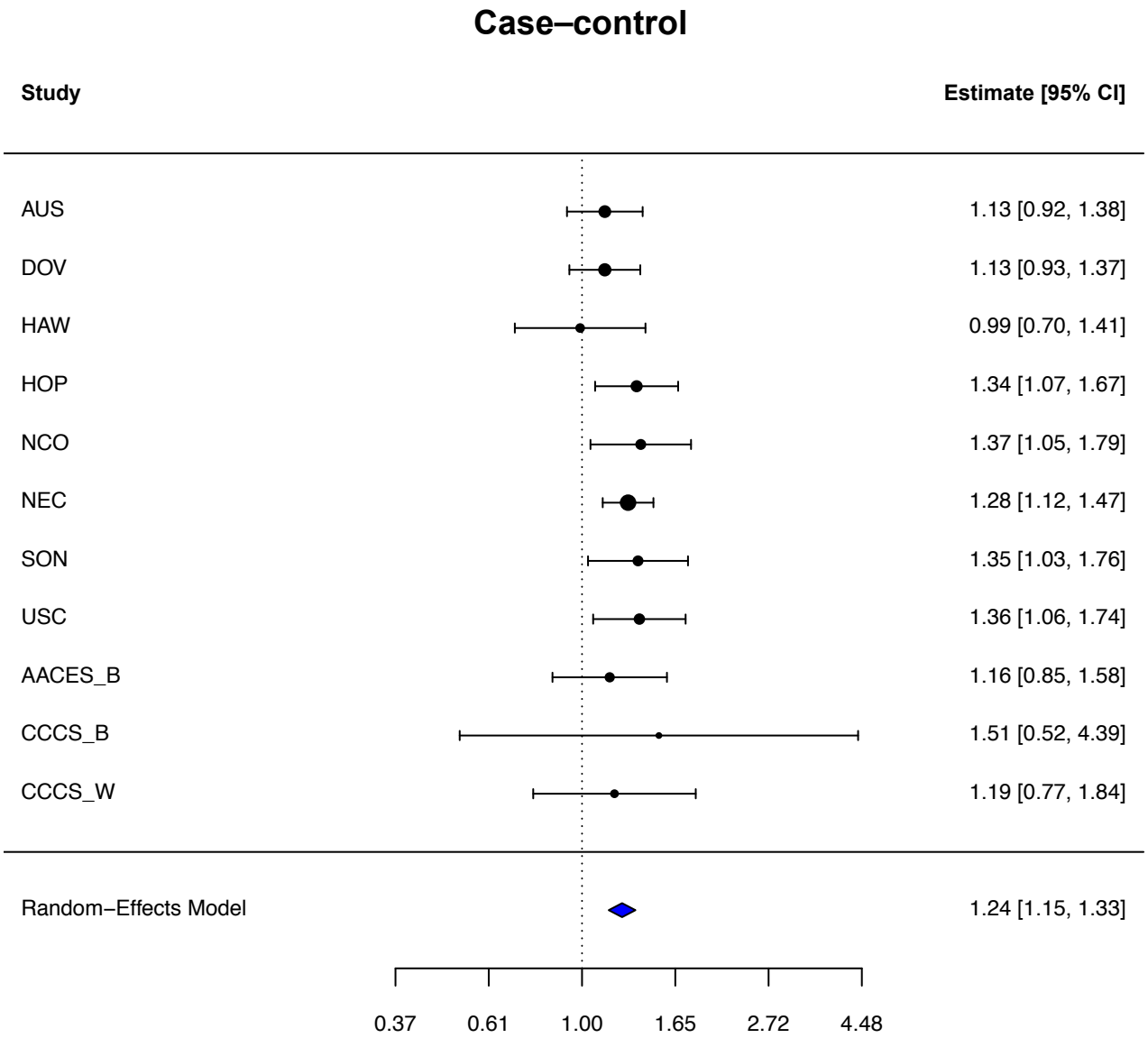
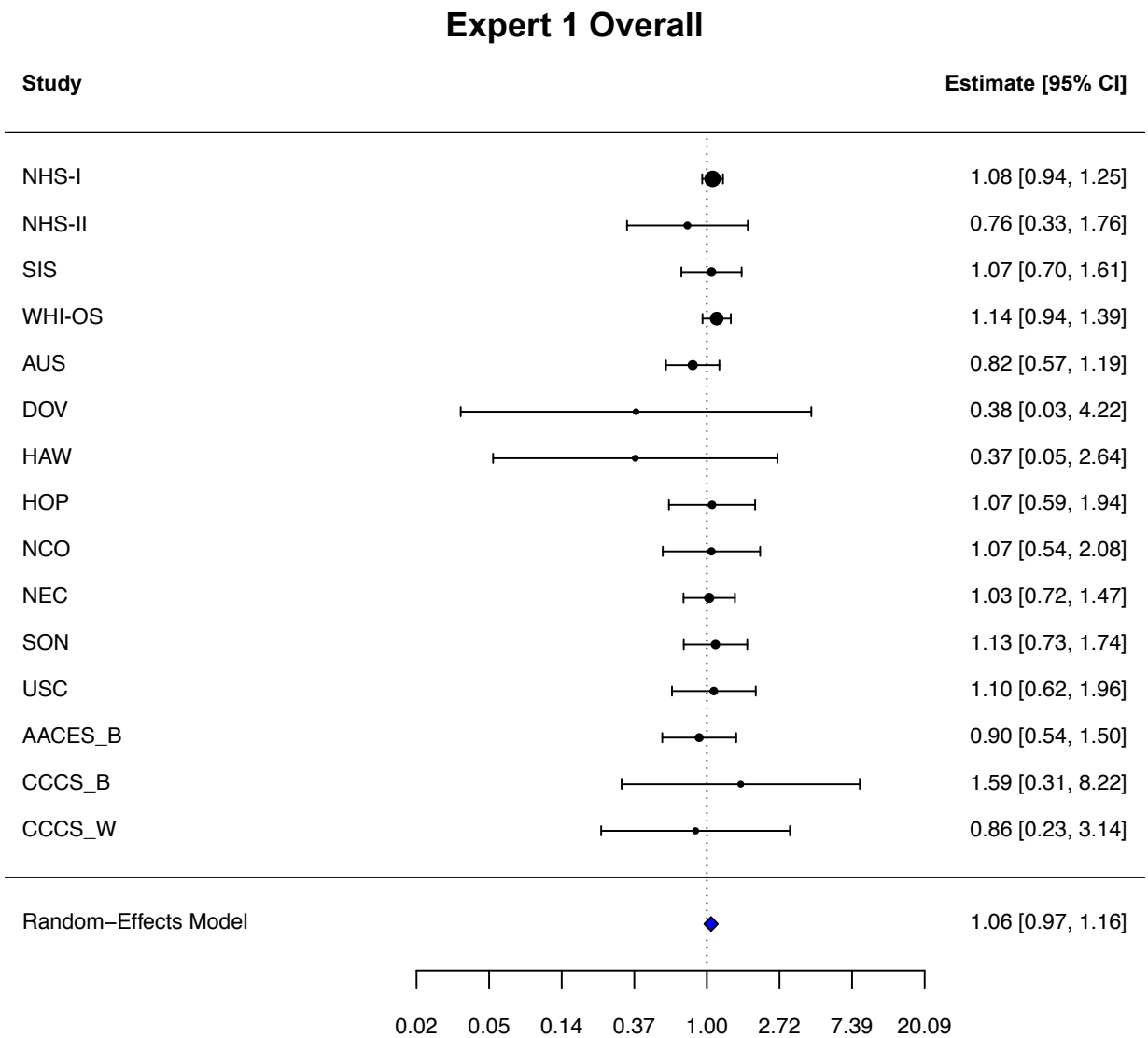
Fig. A2.1(C) Case–control studies only



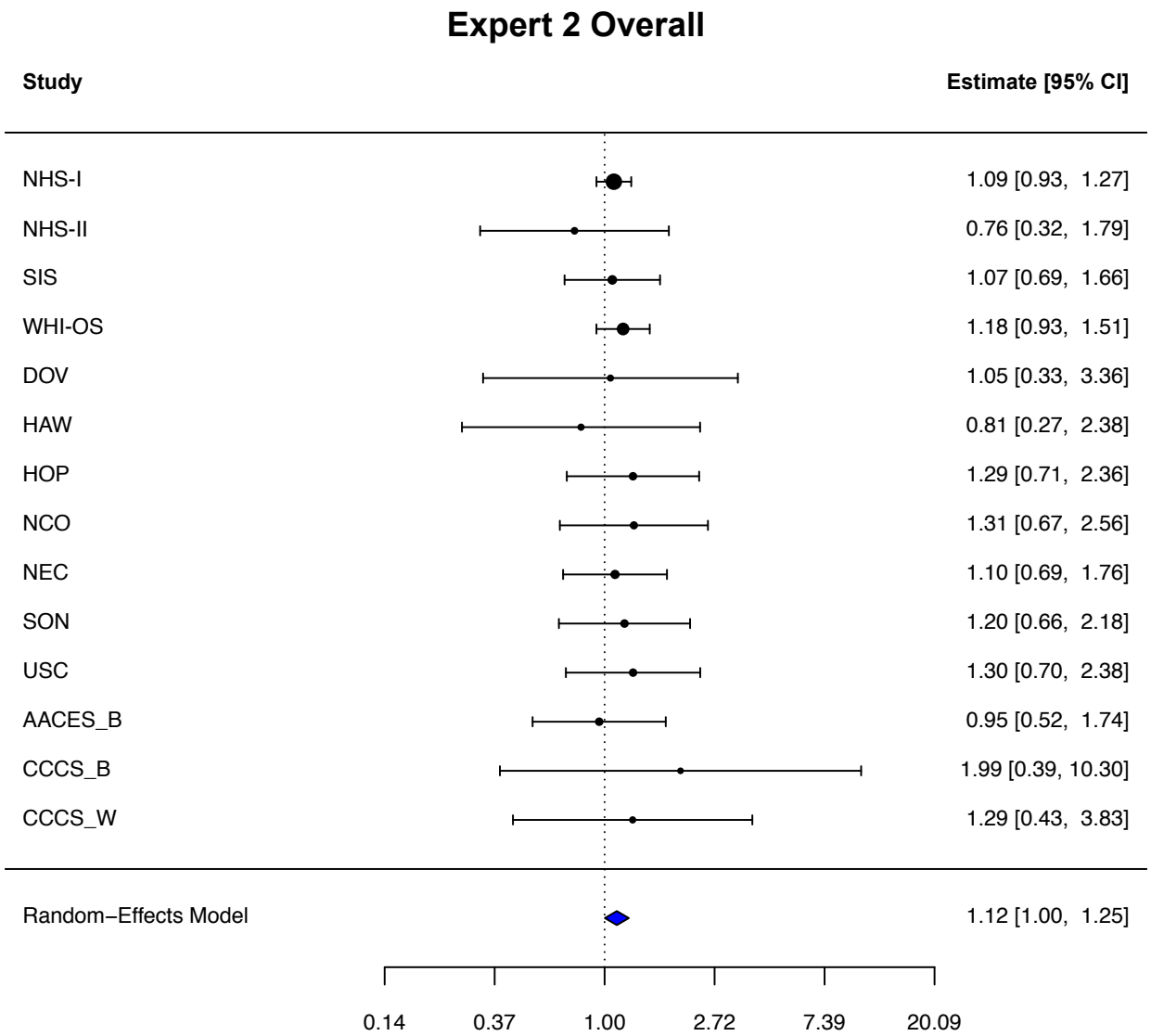
AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

Fig. A2.2 Forest plot of misclassification- and confounding-adjusted study effects, using the estimates from Expert 1



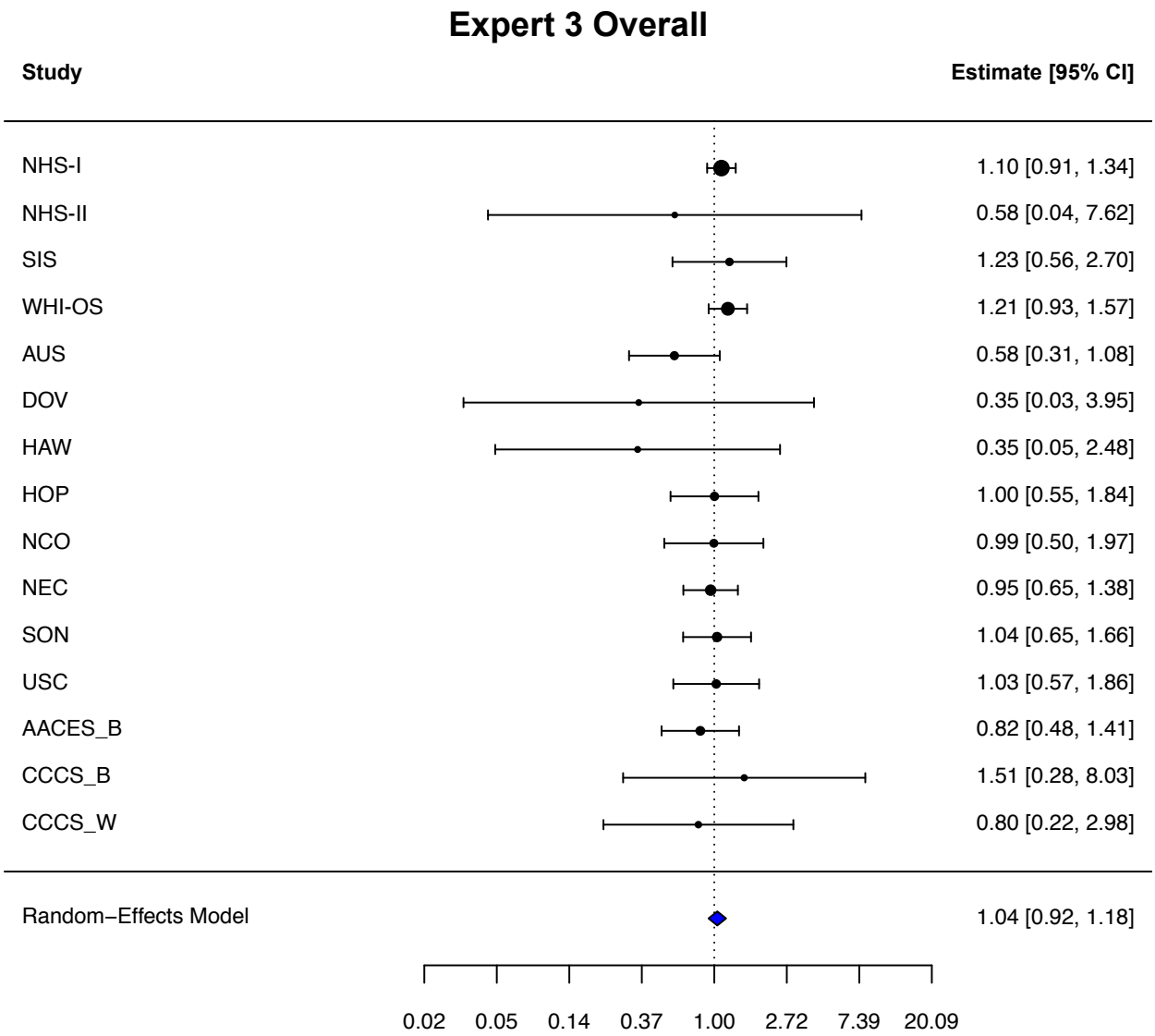
AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

Fig. A2.3 Forest plot of the misclassification- and confounding-adjusted study effects, using the estimates from Expert 2



AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

Fig. A2.4 Forest plot of the misclassification- and confounding-adjusted study effects, using the estimates from Expert 3



AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; CI, confidence interval; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; RE, random effect; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

Table A2.5 Misclassification-adjusted effects, based on the sensitivity and specificity values posited by the three experts, compared with the crude effect assuming perfect sensitivity and specificity

Study	Crude[a]	Expert 1	Expert 2	Expert 3
NHS-I	1.04	1.05	1.06	1.07
NHSII	0.9	0.85	0.84	0.64
SIS	1.1	1.15	1.16	1.33
WHI-OS	1.13	1.16	1.2	1.23
AUS	1.09	0.79	NA[b]	0.56
DOV	1.09	0.36	1.02	0.34
HAW	0.99	0.37	0.81	0.35
HOP	1.38	1.11	1.34	1.03
NCO	1.33	1.04	1.27	0.97
NEC	1.3	1.05	1.12	0.97
SON	1.42	1.19	1.26	1.1
USC	1.39	1.12	1.32	1.05
AACES_B	1.18	0.92	0.97	0.84
CCCS_B	2.02	2.13	2.67	2.02
CCCS_W	1.36	0.98	1.47	0.92

AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

[a] Crude analysis, assuming no misclassification of the data and not involving adjustment for confounding.

[b] NA indicates that the ranges of sensitivity and specificity were not compatible with these data.

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Table A2.6 Misclassification- and confounding-adjusted effects, based on the sensitivity and specificity values posited by the three experts, compared with the crude effect, in which perfect sensitivity and specificity was assumed

Study	Crude[a]	Expert 1	Expert 2	Expert 3
NHS-I	1.04	1.08	1.09	1.1
NHS-II	0.9	0.76	0.76	0.58
SIS	1.1	1.07	1.07	1.23
WHI-OS	1.13	1.14	1.18	1.21
AUS	1.09	0.82	NA[b]	0.58
DOV	1.09	0.38	1.05	0.35
HAW	0.99	0.37	0.81	0.35
HOP	1.38	1.07	1.29	1
NCO	1.33	1.07	1.31	0.99
NEC	1.3	1.03	1.1	0.95
SON	1.42	1.13	1.2	1.04
USC	1.39	1.1	1.3	1.03
AACES_B	1.18	0.9	0.95	0.82
CCCS_B	2.02	1.59	1.99	1.51
CCCS_W	1.36	0.86	1.29	0.8

AACES, African American Cancer Epidemiology Study; AUS, Australia Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer); _B, in Black women; CCCS, Cook County Case Study; DOV, Diseases of the Ovary and their Evaluation; HAW, Hawaiian Ovarian Cancer Study; HOP, Hormones and Ovarian Cancer Prediction; NCO, North Carolina Ovarian Cancer Study; NEC, New England Case–Control Study of Ovarian Cancer; NHS-I, Nurses' Health Study; NHS-II, Nurses' Health Study II; SIS, Sister Study; SON, Southern Ontario Ovarian Cancer Study; USC, University of Southern California Study of Lifestyle and Women's Health; _W in White women; WHI-OS, Women's Health Initiative Observational Study.

[a] Crude analysis, assuming no misclassification of the data and not involving adjustment for confounding.

[b] NA indicates that the ranges of sensitivity and specificity were not compatible with these data.

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