IARC MONOGRAPHS

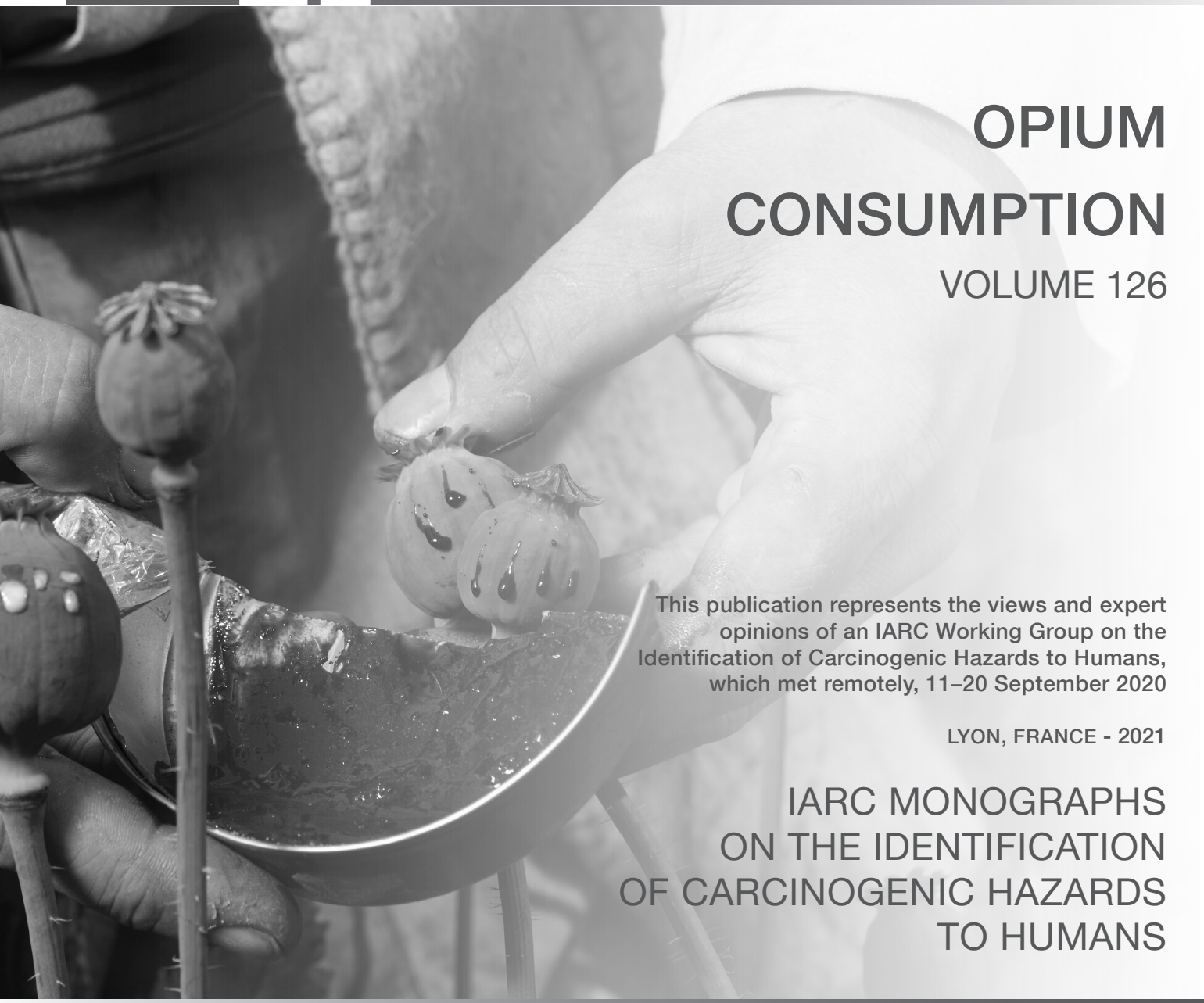
OPIUM CONSUMPTION

VOLUME 126

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS



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This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 11–20 September 2020

LYON, FRANCE - 2021

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

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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: A blunt-bladed instrument is used to scrape the solidified latex from the opium poppy seedpod. Source: © Couperfield/Shutterstock

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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, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, or via email at imo@iarc.fr, 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.fr/).

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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.fr/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. 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 & 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

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.

searching the literature and performing title and abstract screening, organizing conference calls to coordinate the development of pre-meeting 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).

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

The Working Group meets at IARC for approximately eight days to discuss and finalize the scientific review and to develop summaries 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, 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 end-point). 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 (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, lifecycle, 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 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 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 & Steenland, 1988; Richardson et al., 2014).

- **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 & 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 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 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 pre-neoplastic 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 & Bailer, 1989; Bieler & 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

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).

effects", are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by 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 & 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 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. s*ufficient 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 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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GENERAL REMARKS

This one-hundred-and-twenty-sixth volume of the *IARC Monographs* contains an evaluation of the carcinogenic hazard to humans of opium consumption. Due to the coronavirus disease (COVID-19) pandemic, this meeting, which was scheduled to be held in Lyon, France, in March 2020, was held remotely in September 2020.

This agent has not been previously evaluated by the *IARC Monographs* programme. The Advisory Group to Recommend Priorities for the *IARC Monographs* programme that met in 2014 accorded high priority to the evaluation of opium consumption on the basis of new studies of cancer in humans (Straif et al., 2014).

A summary of the findings of this volume appears in *The Lancet Oncology* (Warnakulasuriya et al., 2020).

Definition and scope of the agent

The Working Group carefully considered the applicable scope of the agent under evaluation in this monograph. The agent was therefore defined as the consumption (via ingestion or smoking) of minimally processed forms of opium, including raw, dross, and "refined" opium. Opiates (narcotics derived from opium, such as codeine, heroin, and morphine) and opioids (narcotics not derived from opium, such as fentanyl and oxycodone) were expressly excluded from this evaluation.

The Working Group noted inconsistencies in the published literature in descriptions of the agent with respect to opium as a subcategory of opiates. Terms for "opium" and "opiates" are sometimes used interchangeably in scientific publications, making it difficult to understand what was studied. Sometimes "opium" is used erroneously to refer to opiates – see, for example, the publication by Hosseini et al. (2010), which includes heroin as a category under "types of opium" and "intravenous injection" as a category under opium consumption. It is generally accepted that opium is not consumed intravenously because it contains a high proportion of insoluble material. Heroin, on the other hand, is readily consumed by intravenous injection. In another example, Ketabchi et al. (2005) discuss opium use throughout their article, but – in some instances – indicate that they studied opium and its derivatives. This imprecision in agent definition creates issues both for identifying studies for inclusion and for characterizing the exposure. There are additional uncertainties in agent definition in some hospital-based case–control studies, for example, due to the secondary use of data captured from hospital records, resulting in questions about agent definition and reporting in these records.

Comments on exposure assessment

The Working Group noted numerous data gaps in the characterization of the composition of opium forms that are predominantly used throughout the world. For example, little information was available on the constituents of illicitly traded ("street") opium, and the role of the potentially carcinogenic components of street opium in contributing to its carcinogenicity was therefore unclear. Accordingly, the Working Group considered that lead and other heavy metals were part of the complex mixture that is opium, rather than co-exposures or confounders. No information was found on whether lead is a contaminant in soil used to grow poppies or is added as an adulterant to increase the weight of the traded product.

The impact of routes of opium consumption on carcinogenic hazard is not well understood, nor is the carcinogenic hazard posed by licit opium use (usually in the forms of tincture or syrup). Biomarkers of opium are not well-characterized and have seldom been directly employed in studies.

The Working Group noted the use of non-standard units (non-SI, International System of Units) in most research studies, which sometimes led to difficulties in directly comparing quantitative estimates of risk per unit of consumption across different studies.

The Working Group concluded that updating the opium consumption data for participants in the Golestan Cohort Study would add value to this already important study.

Gaps in the epidemiological literature on opium consumption and cancer

Minimally processed opium is consumed by millions of people worldwide, especially in populations concentrated in the Middle East and south-eastern Asia. Despite this widespread use, the Working Group noted substantial gaps in the epidemiological literature on opium consumption. The studies of cancer in humans were conducted almost entirely in the Islamic Republic of Iran, where approximately 40% of global consumption of opium occurs. While no other country has consumption at this level, the lack of epidemiological evidence from the countries responsible for the remaining 60% of consumption was notable, particularly in Afghanistan (responsible for > 80% of opium production), Pakistan, India, and south-eastern Asia. Although most of the studies were conducted in the Islamic Republic of Iran, where opium use is common, considering the totality of evidence the Working Group concluded that data generated from these cancer epidemiology studies were likely generalizable to other populations that consume opium in similar forms.

The Working Group considered it likely that combustion of opium would produce different levels and profiles of potential carcinogens, such that the observed carcinogenic hazards might be different for smoked and for ingested opium. However, the cancer evidence in humans did not support this view, and the overall evaluation, accordingly, did not differ by either route of consumption or form of opium consumed.

The Working Group noted that in some of the available epidemiological studies a substantial effort had been made to differentiate the carcinogenic effect of opium consumption from that of tobacco consumption, in order to control for potential confounding. However, a substantive gap in studies on the interactive effect of both

tobacco and opium consumption was noted. Joint effects of opium and tobacco smoking that are greater than additive could have important public health implications. Beyond confounding by tobacco consumption, several other potential specific methodological sources of bias in the identified literature, of relevance for the evaluation here, were also outlined by the Working Group, with detailed consideration given to their impact on the identification of the carcinogenic hazard presented by opium consumption (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer).

Specific data gaps in the available studies included a general lack of evaluation of latency, including differences between cancer sites and the impact on study conclusions and evaluation (for example, including irrelevant exposure in unlagged analyses may tend to bias results towards the null). Most epidemiological studies could not differentiate between important morphological subtypes (e.g. squamous cell carcinoma and adenocarcinoma of the oesophagus or urinary bladder). The identification of mutational signatures of opium exposure in different cancer tissues is an area of active research, but published findings were not available to the Working Group. Data gaps were also noted regarding the relative potency of opium consumption in different tissues or organs, as well as the need for an updated systematic review and meta-analysis including newly published literature at multiple cancer sites.

Role of evidence from bioassays in experimental animals

There was sparse evidence on carcinogenicity of opium consumption from bioassays in experimental animals. The Working Group considered that, because such studies are typically conducted to identify hazards to humans, additional bioassay studies may not be warranted for an agent classified in Group 1 as *carcinogenic to humans*. However, additional bioassays may be useful in identifying the specific components of the complex mixture of opium, or aspects of route of consumption, that contribute most to its carcinogenicity.

Scope of systematic review

Standardized searches of the PubMed database (National Library of Medicine, 2021) were conducted for the agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). The Web of Science database (Clarivate, 2021) was also searched for studies of tumours in humans and experimental animals. The literature trees for the agent, including the full set of search terms for the agent name and each outcome type, are available online.[1]

[1] The literature searches for the present volume are available from: https://hawcproject.iarc.who.int/assessment/612/.

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1. EXPOSURE CHARACTERIZATION

1.1 Identification of the agent

1.1.1 Introduction to the agent

Opium is a highly addictive narcotic drug obtained from the juice (latex) of the unripe seedpod of the poppy plant (*Papaver somniferum*). The latex requires minimal processing before it can be consumed. The traditional practices of latex processing vary from place to place and may include air-drying, heat-drying, or boiling (DEA, 1992, 2020a; Ray et al., 2006).

Chemically, opium is a complex mixture; notably, it contains several alkaloids, including morphine, codeine, noscapine, thebaine, and papaverine. After extraction and purification (Kalant, 1997), the alkaloids may also be used as base material for the manufacture of semisynthetic opiate derivatives, such as heroin (from morphine) and oxycodone (from thebaine) (Kalant, 1997; Yaksh & Wallace, 2018). The alkaloid components of opium or their derivatives are responsible for its analgesic, hypnotic, antitussive, and antidiarrhoeal effects when consumed (Labanca et al., 2018). There are also many wholly synthetic opioid drugs available, for example, fentanyl and methadone. These drugs mimic the effects of opium on consumers but are not manufactured from opium or its alkaloids and may have chemically unrelated structures.

The agent considered in the present monograph is "opium consumption". In this context, the term opium includes raw, minimally refined, and dross types, which are derived from the poppy latex and comprise a complex chemical mixture. The agent definition also includes contaminants that are integral to the complex mixture (see Section 1.4.2(g)). The agent definition does not include the pure alkaloids that can be extracted from opium (for example, morphine or codeine), their semisynthetic modifications such as heroin, or wholly synthetic opioid compounds such as fentanyl.

1.1.2 Botanical and chemical data

(a) Nomenclature of opium and its source plant

Botanical name: *Papaver somniferum*

Family: Papaveraceae

Subfamily: Papaveroideae

Common names: opium poppy, breadseed poppy (Mahr, 2017; Labanca et al., 2018)

Opium (*lachryma papaveris* or "poppy tears", also called "raw opium") is the dried latex obtained from the unripe seedpods of the opium poppy plants (INCB, 2019).

Although, as a complex mixture, minimally processed opium has no chemical structure or formula, a highly purified form of opium does have a Chemical Abstracts Service (CAS) registry number of 8008-60-4 (Drugs.com, 2019a).

European Community/List No.: 232-368-5 (ECHA, 2019), also known as "crude opium"

WHO Anatomical Therapeutic Chemical codes: A07DA02, N02AA02 (WHOCC, 2019)

The nomenclature of certain opium products (e.g. as described in Section 1.4.1(c)) has varied over time and by country (USDA, 2020). For example, opium is called *teriak* in Persian, *afeen* in Hindi, and *afiyoon* in Urdu, while (minimally) refined (i.e. further processed, for example, condensed) opium is known as *chandu* in India and Myanmar (DEA, 1992). In the Islamic Republic of Iran (hereafter referred to as "Iran"), different types of opium are known by different terms: *teriak* for raw opium, *sukhteh* or *sookhteh* for opium dross, and *shireh* or *shire* for refined opium (Khademi et al., 2012; Nikfarjam et al., 2016). There is also a multitude of "street names", such as Aunti, Aunti Emma, Big O, Black Pill, Chinese Molasses, Dopium, Dream Gun, Fi-do-nie, Gee, Guma, Midnight Oil, and Zero (DEA, 2020a).

(b) Description of the plant and its cultivation

P. somniferum (Fig. 1.1) is a dicotyledonous, dialypetalous, superovaried annual herb, 30–150 cm long with a stem between 0.5 and 1.5 cm thick, blue-green leaves, and four white, violet, or purple petals, which is cultivated in temperate and subtropical regions. It is hardy and may be grown without fertilizers or pesticides (UNODC, 1953a; Ray et al., 2006; Pushpangadan et al., 2012). Traditionally, most highland and upland farmers in south-eastern Asia have not used fertilizers for any of their crops, but opium poppy farmers have started using both natural and chemical fertilizers to increase opium poppy yields in recent years. Chicken manure, human faeces, or bat droppings are mixed into the planting soil. Opium poppy seeds are planted by the end of October. After 1 month, some plants are removed and 8–18 plants/m^2 are left. Most opium poppy varieties in south-eastern Asia produce three to five mature pods per plant. Harvesting is done in February, about 2 weeks after the flower petals fall from the pods (DEA, 1992). All parts of plants of the *Papaver* genus are characterized by watery and milky latex, except the seeds.

1.1.3 Opium composition and forms

(a) Opium composition

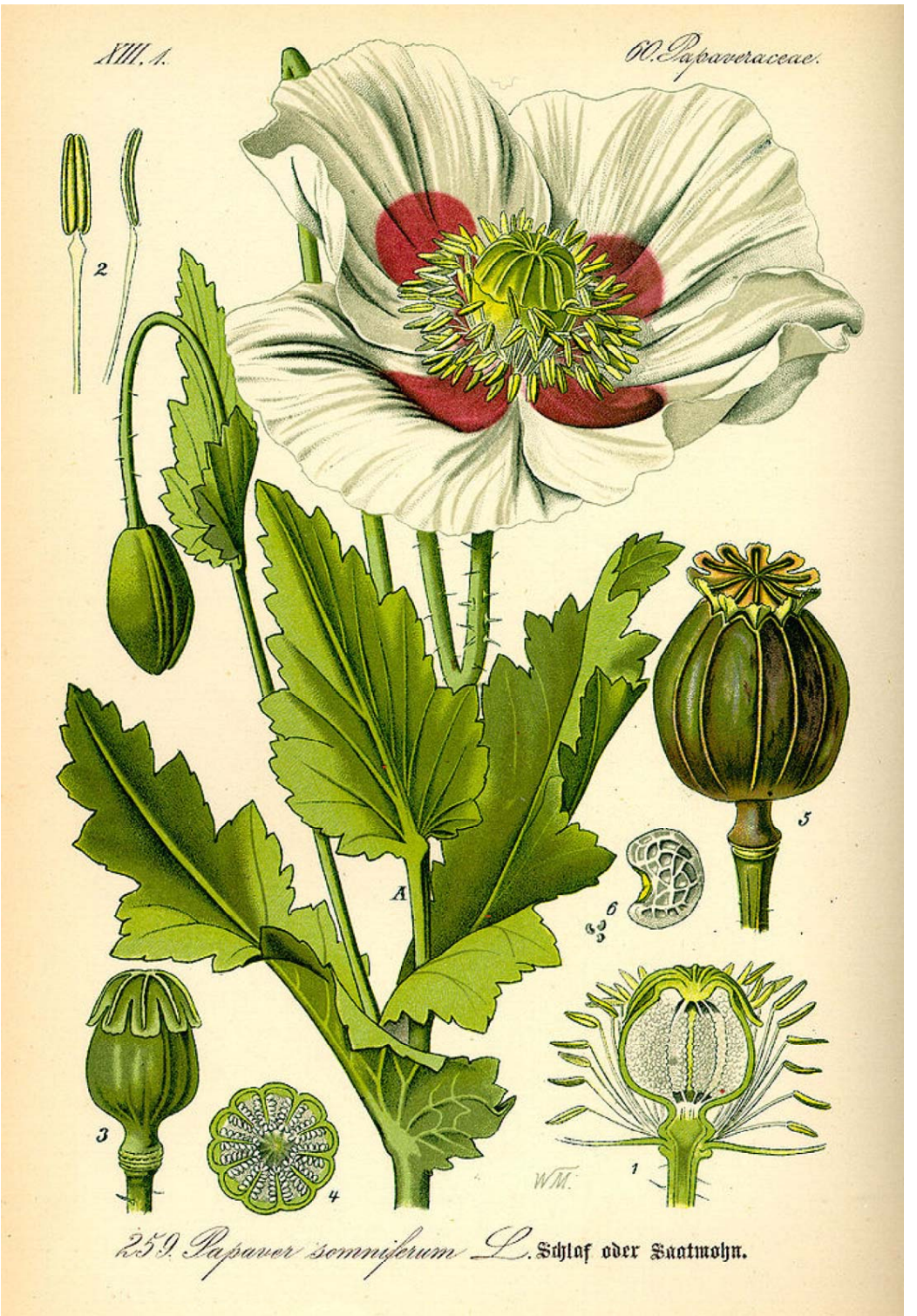
Opium has a complex chemical composition consisting of sugars, proteins, fats, water, meconic acid, plant wax, latex, gum, ammonia, sulfuric and lactic acids, and at least 25 alkaloids (Fig. 1.2; Pushpangadan et al., 2012; Labanca et al., 2018). The composition of opium is further discussed in Section 4.1. The alkaloids are categorized into two main chemical classes: phenanthrenes and benzylisoquinolines (Yaksh & Wallace, 2018). The types and percentages of these alkaloids differ widely in different poppy cultivars. Also, differences in seed yield per plant and latex yield per plant have been reported (Solanki et al., 2017; Labanca et al., 2018). The principal phenanthrenes are morphine, codeine, and thebaine (Yaksh & Wallace, 2018). Morphine is the most abundant phenanthrene in opium. The metabolites of thebaine, an intermediate of morphine biosynthesis in poppy plants, include thebaol and oripavine (WHO, 2006; Megutnishvili et al., 2018).

The principal benzylisoquinolines are papaverine and noscapine (Frick et al., 2005; Beaudoin & Facchini, 2014; Labanca et al., 2018; Yaksh & Wallace, 2018).

(b) Composition of different forms of opium

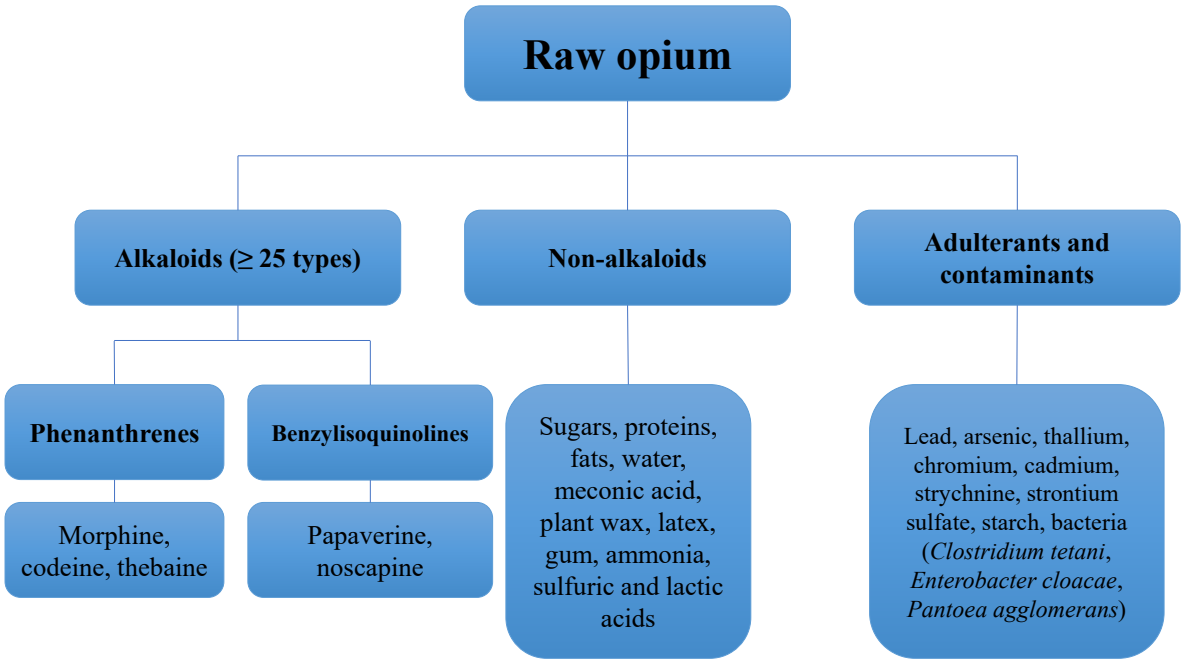
The main forms of opium are raw or crude opium, opium dross, refined opium, and other derivatives.

Fig. 1.1 Opium poppy, *Papaver somniferum*



Professor Dr Otto Wilhelm Thomé, *Flora von Deutschland, Österreich und der Schweiz*, 1885, Gera, Germany. Courtesy of Wikimedia Commons. Released under public domain.

Fig. 1.2 Schematic view of the composition of raw opium



Created by the Working Group.

(i) Raw or crude opium

Raw or crude opium is the unprocessed dried latex of the poppy seedpod and is a dark and sticky substance (Fig. 1.3; Khademi et al., 2012). Alkaloids are major components of crude opium. Among all alkaloids, the most abundant is morphine (10–12% of crude opium by weight). The other alkaloids – including thebaine, codeine, papaverine, noscapine, narcotine, and narceine (UNODC, 1953a; Labanca et al., 2018), together with morphine – make up about 25% of the weight of crude opium, as shown in Table 1.1. Sterols such as cycloartenol and β-sitosterol (Malaveille et al., 1982) are also present in raw opium. [The Working Group noted that the expression of the morphine content of opium as a percentage depends in part on the moisture content.] After the opium has been collected, the moisture content is usually ~30%. Commercial opium usually has a moisture content of ~10–15%. Opium that is apparently dry still retains considerable moisture (~6%) (UNODC, 1953a). Raw opium is often adulterated with other substances, for example, starch (37%) and strontium sulfate were reported in Mexican opium (Sodi Pallares & Meyran Garcia, 1954); arsenic in Indian opium (Datta & Kaul, 1977; Narang et al., 1987); and arsenic and strychnine in Sri Lankan opium (Wijesekera et al., 1988). More recently, traded opium in Iran has been shown to be contaminated with heavy metals such as lead, chromium, cadmium, and thallium, and bacteria such as *Clostridium tetani*, *Enterobacter cloacae*, and *Pantoea agglomerans* (Ghaderi & Afshari, 2016; Aghababaei et al., 2018; Ghane et al., 2018).

(ii) Opium dross

Dross is produced by scraping away the tarry residues that accumulate on the inside walls of the opium pipe as a result of incomplete

Fig. 1.3 Dried latex obtained from the opium poppy

DM Trott. Courtesy of Wikipedia. Released under Creative Commons Attribution-Share Alike 4.0 International.

combustion of raw opium. The dross is black, dry, and granular (Meysamie et al., 2009). Each gram of opium yields 0.3 g of dross (Siassi & Fozouni, 1980). The summary content of the five main alkaloids in opium dross is less than their summary content in raw opium (see Table 1.1). This pyrolysed opium (Meysamie et al., 2009), unlike raw opium, contains primary aromatic amines, heterocyclic (nitrogen-containing) aromatic compounds, and polycyclic aromatic hydrocarbons.

(iii) Refined opium or opium sap

Refined opium or opium sap is the (minimally) refined product of opium and is prepared by boiling opium dross with or without raw opium in water for several hours. The solution is then filtered, insoluble parts are separated, and the excess water is left to evaporate. The final product is brown, sticky, and shiny (Kalant, 1997; Meysamie et al., 2009; Khademi et al., 2012; Nikfarjam et al., 2016). The summary alkaloid content in minimally refined opium is about the same as in raw opium (see Table 1.1).

(iv) Other opium derivatives

Other opium derivatives include the pure alkaloids like morphine and codeine; semi-synthetic opiates like heroin, compact-heroin, and buprenorphine; and crystal and synthetic opioids like fentanyl, methadone, and pethidine. This group of opium derivative drugs is outside of the scope of this monograph (see Section 1.1.1, Introduction to the agent).

Table 1.1 Alkaloid content of raw, prepared, and dross illicit opium from south-eastern Asia: analysis after initial drying (weight %)

Component	Raw (n = 15)		Dross (n = 15)		Prepared[a] (n = 15)	
	Range	Mean	Range	Mean	Range	Mean
Morphine	9.8–15.0	12.2	6.8–15.4	10.2	10.5–22.7	16.2
Codeine	1.6–3.2	2.2	0.9–1.7	1.2	1.8–4.4	2.7
Thebaine	1.8–4.4	2.8	0–0.1	0.1	1.1–3.4	1.9
Papaverine	0.02–0.52	0.21	0.04–0.14	0.09	0.08–0.20	0.14
Narcotine	5.0–8.0	6.4	Not detected	NR	1–2[b]	1.5[b]
H_2O	28–36	NR	6–9	NR	7–27	NR

NR, not reported.
[a] Prepared opium is a 30–50% mixture of raw and dross opium [the Working Group noted that "prepared" opium in this reference is likely to be similar to the "refined" opium described elsewhere in the present monograph].
[b] Estimated.
From Lim & Kwok (1981). ©1981. United Nations. Reprinted with the permission of the United Nations.

1.2 Methods of measurement, detection, and analysis

Biological marker detection techniques

Biomonitoring of opium derivatives in urine, blood, hair, or other tissues provides a direct marker of an individual's opium exposure. Interindividual differences in the absorption and metabolism of opium, and the temporality or cumulative dose of opium or opium derivatives (e.g. morphine, codeine, or poppy seed paste), among other factors, can influence concentrations in body fluids or tissues.

Opium metabolites are present in urine or blood for 2–4 days after the opium is consumed (Hasselström & Säwe, 1993; Abnet et al., 2004; Rashidian et al., 2017). Methods to detect opium alkaloids in blood and urine include gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and thin-layer chromatography, among others (Dams et al., 2002; Sabzevari et al., 2004; Shamsipur & Fattahi, 2011; Gholivand et al., 2015; Bagheri et al., 2017; Rashidian et al., 2017; Megutnishvili et al., 2018). Dispersive liquid–liquid microextraction is a fast, reproducible, cost-effective, and simple technique to preconcentrate opium alkaloids in human urine or plasma, enabling subsequent quantification via HPLC or GC-MS (Rezaee et al., 2006; Ahmadi-Jouibari et al., 2013; Farahani & Sereshti, 2020).

Opium use can be determined by a rapid urine drug screen, followed by confirmatory testing methods including thin-layer chromatography, HPLC, or GC-MS (Rashidian et al., 2017). Microfluidic technologies have emerged as useful tools in solid-phase extraction methods, enhancing their simplicity, portability, and extraction yields, while reducing testing times and cost. Farahani & Sereshti (2020) recently outlined the use of microfluidic devices for solid-phase and spectrophotometric detection of opium alkaloids (morphine, codeine, and papaverine) in urine samples for point-of-care testing. Their method yielded extraction recoveries of between 66.7% and 85.0%, with limits of quantitation of 4, 4, and 1 ng/mL, and limits of detection of 1.4, 1.3, and 0.3 ng/mL for morphine, codeine, and papaverine, respectively. For blood, use of an ultrasensitive electrochemiluminescent immunoassay for morphine yielded a limit of detection of 67 pg/mL and a limit of quantification of 0.2 ng/mL (Fei et al., 2013).

Thebaine is an opium alkaloid that, if found in the body, indicates consumption of opium

or its derivatives. Thebaine can be quantified in hair using GC-MS with high validity (Lee et al., 2011). Likewise, morphine can be measured in hair at concentrations as low as 0.016 ng/mg using GC-MS. Hair may be suitable for assessing past exposure to opium by evaluating morphine or thebaine concentrations, but these measures are dependent on hair length (hair grows at a rate of 0.9–1.2 cm/month) and hair colour (higher morphine concentrations have been documented in dark hair) (Sabzevari et al., 2004). Toenails may also be suitable for the biomonitoring of opium use. A study assessing cocaine and morphine concentrations in toenails and hair showed higher concentrations in toenails than in hair. Toenails grow at a rate of about 1–2 mm/month (Yaemsiri et al., 2010), so concentrations in toenails could document past exposure to opium (Cingolani et al., 2004). To date, no studies on opium and cancer incidence have been identified that used hair samples or toenail clippings to biomonitor opium exposure, although samples were collected in some studies (Pourshams et al., 2010; Ashrafi et al., 2018). [The Working Group noted that these methods are not specific for opium exposure and may also reflect exposure to other opiates.]

1.3 Production

1.3.1 Legal production

As described in Section 1.4.1, legal opium production occurs in a few countries, as prescribed by international protocols. Such cultivation (e.g. Fig. 1.4) is used to produce the global supply of more highly processed forms of opium, such as opium tincture and morphine. India was the main producer and only licit exporter of raw opium in 2017, accounting for 432.5 tonnes (47.5 tonnes in morphine equivalent) or 98.4% of total global licit production. It was followed by China, which produced 6.4 tonnes (0.7 tonnes in morphine equivalent) and where poppy straws (dried seedpod capsules) have replaced opium as the main raw material used in the manufacture of alkaloids since 2000. The Democratic People's Republic of Korea also produced smaller amounts of opium in 2017, but exclusively for domestic consumption and use. Japan produces very small amounts for scientific purposes only (INCB, 2019). [The Working Group noted that there are large annual variations; for example, Australia was the largest producer in 2016, with 180 tonnes, followed by France, Turkey, Spain, Hungary, and India, in descending order (INCB, 2017). Most substances resulting from licit opium production are outside of the scope of this monograph (e.g. morphine and codeine). However, as noted above, opium tincture and opium syrup are within the scope of this monograph.]

1.3.2 Illicit production

Opium is illicitly produced in some 50 countries worldwide, and the area of land under illicit opium poppy cultivation (240 800 hectares in 2019, preliminary estimate) has increased substantially over the last 10 years. In addition, global potential production of oven-dry opium has shown a long-term upward trend and has increased over the last decade from 4950 to 7610 tonnes (UNODC, 2020). Afghanistan is currently the world's largest producer of illicit opium (UNODC, 2019b, 2020). Over 80% of the world's opium comes from Afghanistan, but less than 1% [0.35% in 2018, calculated by the Working Group] is seized there (UNODC, 2020), and massive volumes of illicit opiates are smuggled out of the country (Beyrer, 2011).

As noted above, opium poppies can be grown without artificial irrigation or fertilizers, and the product does not need refrigeration, can be transported by mule or camel without decaying, and has a high market price (Goodhand, 2000; Beyrer, 2011). Myanmar (7%) and Mexico (6%) are the second and third major global producers of illicit opium, respectively (UNODC, 2019b,

Fig. 1.4 Poppy field in Tasmania, Australia

2020). Of the 7610 tonnes of opium produced worldwide in 2019, it was estimated that some 1180–1480 tonnes remained unprocessed for consumption as opium, while the rest was processed into heroin (UNODC, 2020).

1.3.3 Harvesting of opium

Opium is harvested, about 2 weeks after the petals fall, in two phases: the incision of the capsule and the collection of the latex. Opium harvesting is labour-intensive (Ray et al., 2006) and poppies are still processed manually in many producer countries. The incision of the capsule requires a high level of skill: the latex is found between the epicarp and the mesocarp, and the juice channels are cut so that they run upwards from below (Fig. 1.5). A great many channels must be made, but the wall of the capsule must not be cut right through or the latex will run down inside and be lost (UNODC, 1953b). The immature seedpods (fruits) of the opium poppy are scratched and incisions are made by a special lancet called (in Afghanistan) a *nushtar* or *nishtar*. A *nishtar* carries three or four blades, 3 mm apart, and is scored upward along the seedpod. Incisions are made at sunrise or sunset, and it takes from 8 to 14 hours for the latex to exude and solidify (UNODC, 1953b). Incisions are made three or four times, 2–3 days apart. Each time, the sticky brown resin (latex) is scraped

Fig. 1.5 Poppy capsule with opium latex ("poppy tears") flowing from the immature seedpod

From iStockphoto.com/sadikgulec.

off the following morning with a blunt-bladed instrument and collected (Fig. 1.6). The latex is dehydrated by air-drying, boiling, or heating. In the legal processing of opium, scratching the pods is not done and the dried capsules (poppy straws) are processed to extract alkaloids (Ray et al., 2006).

1.4 Use and consumption

1.4.1 Opium history and description

(a) History

Opium use has been reported from several centuries BCE from several areas in the world, mainly around Mesopotamia (UNODC, 2008). The medicinal and adverse effects of opium were well described by Avicenna, the famous Persian physician, in his textbook *The Canon of Medicine* in the early 11th century CE (Heydari et al., 2013). Avicenna described analgesic,

Fig. 1.6 Harvesting of raw opium from the poppy seedpod in the field

A blunt-bladed instrument is used to scrape the solidified latex from the opium poppy seedpod.

hypnotic, antitussive, gastrointestinal, and cognitive medicinal effects, listed adverse effects such as respiratory depression, neuromuscular disturbances, and sexual dysfunction, and explained the potential toxicity of opium. Opium was used for headache, joint pain, earache, toothache, labour, and kidney and urinary bladder pain. Other indications for use included insomnia, severe cough, severe diarrhoea, and high libido. Opium was applied as oral, topical, rectal, and intranasal treatments. Forms such as syrups, tablets, smoke, and ear drops were popular (Heydari et al., 2013). From the Middle East, opium use spread to Europe, China, and India between the 11th and 15th centuries (Aragón-Poce et al., 2002), and later to the USA and Australia.

In the 17th century, the habit of opium smoking, linked to the spread of tobacco smoking, presented greater addiction potential than when the opium was ingested, which was the traditional means of consuming the drug (UNODC, 2008). After the Opium Wars of the mid-19th century, China fully legalized the importation of opium (UNODC, 2008). According to official Chinese figures, about 3.5% of the total population of China and 25% population of adult men smoked opium in 1906 (UNODC, 2008). In the USA, about 0.18% of

the adult population and up to 10% of people in the medical profession were addicted to opium in 1907–1908 (UNODC, 2008). In some other countries (e.g. Iran, Viet Nam, Laos, Cambodia, Thailand, Myanmar, Indonesia, the Philippines, India, Canada), the proportions of opium users among the total populations were estimated to vary between 0.1% and 2.9% in 1907–1908 (UNODC, 2008).

(b) Historical regulation

In Iran, royal orders for the restriction of opium use were documented as many as 400 years ago (Razzaghi et al., 2000). In China, the importation and sale of opium were banned for the first time in 1729 (UNODC, 2008). Bans on some aspects of opium use were initiated early in the 20th century in several countries, including New Zealand, Australia, and Canada (New Zealand Legal Information Institute, 1901; Australasian Legal Information Institute, 1908; Canadian Senate Special Committee on Illegal Drugs, 2002). An International Opium Convention came into force in 1928 and was eventually signed and ratified by 56 countries, which agreed to prohibit the manufacture, import, sale, distribution, export, and use of narcotic drugs, except for medical and scientific purposes (UNODC, 2008).

In 1953, an Opium Protocol was proposed, in which only seven countries – Bulgaria, Greece, India, Iran, Turkey, the former Soviet Union, and the former Serbia and Montenegro – would be authorized to produce opium for export, and opium use was limited exclusively to medical and scientific needs (UNODC, 1953c). The Protocol did not receive enough international ratifications to bring it into force until 1963, and it was superseded by the 1961 Single Convention, which came into force in 1964 (Senate of Canada, 2001) (see Section 1.5).

(c) Opium consumption and description of its forms

Globally, an estimated 1100–1500 tonnes of opium are consumed each year [76% of which is consumed in Asia] (UNODC, 2009, 2020). Annually, an estimated 450 tonnes of opium are consumed in Iran (42% of total global opium consumption) (UNODC, 2010), making this country the world's largest per capita consumer of opium (Dolan et al., 2011). After Iran, the next highest consumption occurs in Afghanistan and Pakistan, with an estimated 80 tonnes of opium (7% of the globally consumed opium) consumed annually in each of these two countries (UNODC, 2009). Among individual opium users, historical average daily doses have varied between 0.5 and 2.6 g in India and between 3.8 and 15 g in China (UNODC, 2008). In recent epidemiological (case–control) studies, the median daily consumption quantity among control groups who used opium was less than 2 g (Khademi et al., 2012; Mohebbi et al., 2021), and in a recent survey of 8696 daily opium users the mean daily dose was 3 g (Rafiei et al., 2019); these data are further described in Section 1.4.2(c) and Section 2. [The Working Group noted that few published data were found on the quantities of daily opium consumption in Iran and other countries.]

There are two main methods of consuming opium; ingestion (sometimes referred to as "eating" in the literature) and smoking (Khademi et al., 2012). Opium can be ingested through chewing, drinking, and swallowing (UNODC, 1953d). Opium can be chewed or eaten raw, dried, or after boiling or heating, and with or without being combined with substances including spices, amber, aloes, cochineal, musk, saffron, sugar, or rice (UNODC, 1953d; Westermeyer & Neider, 1982). Opium can also be ingested by pounding and mixing it with liquids – including water, tea, or wine – and then drinking (Fig. 1.7; UNODC, 1953d, 2014; Fernandez & Libby, 1998). In rural

Fig. 1.7 Preparing opium tea

north-western India, opium is traditionally consumed in the form of nuggets or powder. In contrast to the powder, which is usually smoked, the nuggets are dissolved in water, filtered, and then the extract is drunk (Ray et al., 2006). Finally, some individuals ingest opium by swallowing it in the crude form in which it is sold or as a pill (Richards, 1877; UNODC, 1953d). Liquids for oral use include opium tincture, opium wine, and opium syrup (Ray et al., 2006; Heydari et al., 2013). Opium tincture, also known as laudanum, is an antidiarrhoeal prescription drug. As a solution sold as oral drops, it is authorized in 17 European Union Member States (EMA, 2020). Opium tincture usually contains 10 mg/mL morphine and 19–33% ethanol (Drugs.com, 2019b; EMC, 2020). It is also used for the management of opium withdrawal in adults (Rahimi-Movaghar et al., 2018) and neonates (Ghazanfarpour at al., 2019) and for maintenance therapy in the treatment of opioid addiction (Jittiwutikarn et al., 2004), and has, in this context, also been referred to as opium syrup (Dahmardehei & Rafaiee, 2012). Opium wine is a solution of opium in

Fig. 1.8 A man smokes opium using a traditional tobacco pipe, Lao People's Democratic Republic

From Ivoha/Alamy Stock Photo.

aromatized sherry or diluted alcohol and has the same strength as ordinary laudanum (Merriam-Webster, 2020).

In ancient times, opium was usually taken orally (Swift et al., 1997; Heydari et al., 2013); however, after the introduction of the tobacco pipe during the 17th century, smoking opium became a popular method of opium consumption, particularly in China (Swift et al., 1997). Opium smoking (Fig. 1.8) remains a common and preferred method of consuming opium in many countries, including Afghanistan and Iran (UNODC, 2014; Sheikh et al., 2020), which could be due to the pleasurable effects of opium being achieved more rapidly by smoking opium than ingesting it (Westermeyer, 1978). Raw opium and opium dross can be ingested, or smoked with special devices (an opium pipe, called a *vafoor* in Persian), after direct heating with burning charcoal or sometimes with a hot metal rod (Siassi & Fozouni, 1980; Khademi et al., 2012; Rafiei et al., 2019). Opium is placed in a pipe, the head of the pipe is heated with charcoal, and then the smoke from the heated opium is inhaled through the pipe. Refined opium can be ingested or smoked by indirect heating using a special type of opium pipe. When the refined opium is heated indirectly, the user inhales the opium vapour, not its smoke (Khademi et al., 2012).

1.4.2 Prevalence, levels, and trends

(a) Global patterns

While the estimated global number of opiate users has increased from 15–21 million in 2007 to 30 million in 2019 (UNODC, 2009, 2016, 2020), the proportion of opiate users who used opium in 2007 is unknown. In 2008, there were an estimated 4.1 million opium users (UNODC, 2010). Currently, there are approximately 5 million regular users of opium worldwide (Rahimi-Movaghar et al., 2018), 80% of whom reside in Asia (UNODC, 2010). In opium-cultivating countries and some of their neighbours, opium is more commonly used than other opiates (UNODC, 2019b).

(b) Afghanistan

In Afghanistan, a significant increase in the use of opium was observed between 2005 and 2015 (Afghanistan Ministry of Counter Narcotics, 2015). The 2005 drug-use survey estimated that there were ~150 000 regular opium users (0.6% of the total population) in the country (UNODC, Afghanistan Ministry of Counter Narcotics and Afghanistan Ministry of Public Health, 2005); by 2009, this number had increased to 230 000 (UNODC, Afghanistan Ministry of Counter Narcotics and Afghanistan Ministry of Public Health, 2009).

In 2015, the countrywide national drug-use survey – involving 2757 randomly selected households in 11 urban centres and 52 rural villages – sampled 10 549 people, including 2711 men, 3723 women, and 4110 children (The Colombo Plan Secretariat, 2015). Biological specimens (hair, urine, and/or saliva) from 8.5% of the adults (10.3% of men and 6.7% of women) and 6% of the children tested positive for opioids. No more than 9% of children with positive results were estimated to be active users; it was estimated that 46–48% of positive results derived from adult administration and 44–45% from environmental exposure. Parents may give opium to their children to calm them down or to numb their hunger (Afghanistan Ministry of Counter Narcotics, 2013). The survey confirmed that opioids are the most common illicit drug used in Afghanistan (Afghanistan Ministry of Counter Narcotics, 2015). Similar findings were reported in a study conducted in Afghanistan between 2010 and 2012, which included 2187 randomly selected urban households representing 19 025 household members in 11 provinces. In addition to self-reported questionnaires and interviews on past and current drug use among members of their household, hair, urine, and saliva samples from 5236 people in the households were obtained and tested for metabolites of 13 drugs (Cottler et al., 2014). Not all these individuals may have been opium users. Passive opium smoke exposure in Afghan homes was assessed using hair samples, revealing high concentrations of opium products and drug metabolites in the systems of family members of opium users, including women and children (Goldberger et al., 2010).

(c) India

In India, according to a national survey conducted in 2018, 0.52% of the population, or ~1.1 million people, had used opium in the last 12 months (Ambekar et al., 2019); these results are similar to those reported in a national survey conducted in 2002 (Ray, 2004). However, there are areas with higher levels of opium use. In several provinces, it has been reported that 4.8–6.6% of individuals aged 15 years or older are current opium users (Chaturvedi et al., 2003, 2013; Chaturvedi & Mahanta, 2004). In India, ingestion of opium is more common than opium smoking. In rural areas of India, raw opium is consumed in nugget form; the nugget is dissolved in water, filtered, and then the extract is drunk (Ray et al., 2006). Among opioid-dependent patients, 27% in one state and 33% in another were found to be using opium (Gupta et al., 2019).

(d) Islamic Republic of Iran

In Iran, opium has been the most widely used illicit drug for decades. Opium use is seen across different age groups, socioeconomic classes, and regions (see Section 1.4.3). In 2001, a national survey on drug use showed that 5.5% of the adult population were current opium users and 1.5% were opium-dependent (Iranian Ministry of Health, 2002). Ten years later, the 2011 national household survey showed that opium was the main illicit drug used and led to substance-use disorders (Rahimi-Movaghar et al., 2014; Amin-Esmaeili et al., 2016). Of the population aged 15–64 years, 4.4% and 2.3% were reported to have used raw opium (*teriak*) and minimally refined opium (*shireh*), respectively, in the last 12 months, and 1.2% and 0.3% had used them daily in the last 12 months. Opium had been used in the last 12 months by 7.9% and 0.8% of men and women, respectively, which represents [2 300 000] people in the adult population. Two surveys of a rural population showed that daily raw opium and *shireh* use by people aged 12 years and above increased from 5% and 1.3% in 2000 to 15.7% and 9% in 2012, respectively (Ziaaddini et al., 2013). In two studies that assessed weekly use of opium in the population aged 40–75 years, 17% of respondents in Gonbad in 2006 and 8.4% in Valashahr in 2016 were opium ever-users. Both studies included urban and rural areas (Pourshams et al., 2010; Gandomkar et al., 2017). Opium use is also frequent among high school and university students (Rahimi-Movaghar et al., 2006; Menati et al., 2016). Opium is one of the most common substances for which individuals seek treatment for drug dependency (Jafari et al., 2010; Akbari et al., 2019; Rafiei et al., 2019). There are regional differences in the extent of opium use in Iran (Amin-Esmaeili et al., 2016; Alizadeh et al., 2020; Naghibzadeh-Tahami et al., 2020; Sheikh et al., 2020). In the Golestan Cohort Study (GCS), which was conducted in the north-east of Iran, the median cumulative amount of opium used among the cohort population was 21 nokhod-years [about 4.2 gram-years] (a *nokhod* is the standard unit of opium supply and is approximately equivalent to 0.2 g) (Sheikh et al., 2020), while in another study conducted in Kerman Province in the south-east of Iran, the median cumulative amount of opium used among the control group was 87.5 gram-years (Naghibzadeh-Tahami et al., 2020).

Comparison of the results of four national studies on drug users from 1998 to 2018 (Razzaghi et al., 2000; Narenjiha et al., 2005, 2009; Rafiei et al., 2019) shows that traditional use of opium has remained the main form of illicit drug use. In the fourth national study on drug users carried out in 2018 (n = 20 175) (Rafiei et al., 2019), daily use of opium (raw opium, opium dross, and/or *shireh*) was reported by 37.5% of participants ("drug abusers" recruited from 16 outpatient and inpatient centres, drop-in centres, shelter, prisons, and homes). Moreover, 67.1% of participants reported opium to be their dominant drug of use at the time of the interview. For those who reported daily use of opium, 85% of opium consumed was raw opium; 25% and 5% reported daily use of *shireh* and opium dross, respectively.

In Iran, the most common method of opium consumption is smoking (90.9%), followed by oral ingestion (8.8%). Smoking of *sukhteh* and *shireh* is reported to be the dominant route of use by three quarters of participants in the survey described above. The other one quarter reported ingestion as the dominant route of *sukhteh* and *shireh* use (Rafiei et al., 2019).

(e) Pakistan

In Pakistan, opium consumption has decreased over recent decades. A national survey conducted in 2013 estimated that there were 320 000 regular opium users in the previous year (0.3% of the population aged 15–64 years). In Pakistan-administered Kashmir, 0.4% of the population was using opium regularly, and the

highest proportion of opium users (1%) was in the province of Balochistan (UNODC and Government of Pakistan, 2013). Opium users were mostly married, slightly older (mostly aged 40–54 years), and were more likely to live in rural areas than were heroin users. Also, 84% of opium users versus about 60% of heroin users lived in a home (rather than a park, road, shrine, or other location). Many of the opium users had also used heroin and cannabis (UNODC and Government of Pakistan, 2013).

(f) Other countries

In China, the proportion of people consuming opium is small. In 2000, a national survey on drug use showed that ~0.14% of individuals aged 15 years and older had used opium in the previous 12 months, which showed a decreasing trend compared with surveys conducted in 1993 and 1996 (Hao et al., 2004). In China, opium is consumed mainly by smoking (Ray et al., 2006).

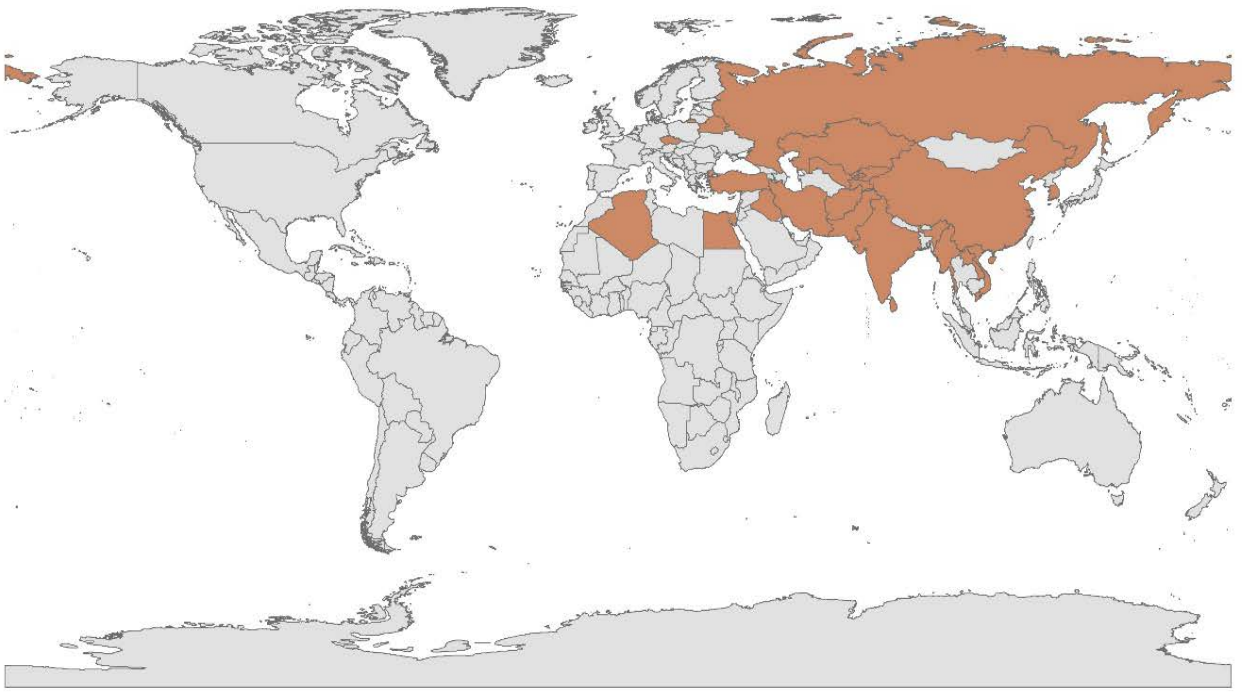
In 2018, there were 43 511 registered drug users [including more than 3100 registered opium users] in central Asia, excluding Turkmenistan (for which no data were available) (INCB, 2020). In addition, opium use has been reported in a small percentage of the population in Sri Lanka (Sri Lanka National Dangerous Drugs Control Board, 2018), Algeria (Abdennouri, 2014), Viet Nam (Thao et al., 2006), and the Democratic People's Republic of Korea (Yun & Kim, 2015). Recent data on the extent and pattern of opium use in these countries and for other parts of the world are lacking. Although most of the data on opium use come from southern and south-western Asia, the high number of countries all around the world that produce opium (either legally or illegally), the many countries that report opium seizures annually, and reported cases of opium poisoning (both in adults and in children) in other countries (Martínez & Ballesteros, 2019), suggest that opium use exists to a greater or lesser degree in many areas of the world. Fig. 1.9 indicates countries with reports of opium use during the past 20 years. Fig. 1.10 illustrates countries with reported opium seizures in 2018.

(g) Exposure to lead and other adulterants and contaminants as part of opium exposure

In the present monograph, contaminants and adulterants of opium are considered integral parts of the complex mixture to which opium users are exposed. Several studies have indicated the presence of different levels of lead contamination in tested opium samples (Aghaee-Afshar et al., 2008; Aghababaei et al., 2018; Akhgari et al., 2018; Rahimi et al., 2020). Some other studies have shown higher concentrations of lead in the blood of opium users than in non-users (Salehi et al., 2009; Amiri & Amini, 2012; Khatibi-Moghadam et al., 2016; Nemati et al., 2016; Ahmadinejad et al., 2019). Although all these reports originate from Iran, there is huge variation in the reported lead concentrations measured in opium samples, with values ranging from 1.88 ± 0.35 μg/g (Aghaee-Afshar et al., 2008) to 138.10 ± 75.01 μg/g (Aghababaei et al., 2018). Similarly, there is significant variation in reported mean blood lead concentrations among opium users (Alinejad et al., 2018; Soltaninejad & Shadnia, 2018), with major differences between opium users in different provinces of Iran (Amiri & Amini, 2012; Khatibi-Moghadam et al., 2016; Soltaninejad & Shadnia, 2018). The exact source of this contamination is not clear; however, water and soil contamination of opium poppy cultivation farms (Salamon & Fejer, 2011; Chizzola, 2012; Moghaddam et al., 2020), the use of inappropriate methods and equipment in opium production, and adulteration of opium with lead to increase its weight to raise profits are among the suggested mechanisms (Aghababaei et al., 2018; Akhgari et al., 2018; Alinejad et al., 2018; Zamani et al., 2020).

There are also reports from some countries that show other types of adulterants in opium, including arsenic (between 25 μg/100 g and 29 mg/100 g) in India and Sri Lanka (Datta &

Fig. 1.9 Countries with reports of opium use during the past 20 years, according to United Nations Office on Drugs and Crime reports, country reports, and published studies



Countries that are highlighted in the map are: Afghanistan, Algeria, Belarus, China, Czechia, Egypt, India, Iran (Islamic Republic of), Iraq, Kazakhstan, Kyrgyzstan, Lao People's Democratic Republic, Myanmar, Pakistan, the Russian Federation, Democratic People's Republic of Korea, Sri Lanka, Tajikistan, Turkey, Uzbekistan, and Viet Nam.
Data from Fan et al. (2004); Klusonová et al. (2005); Ray et al. (2006); Thao et al. (2006); UNODC (2010, 2020); UNODC and Government of Pakistan (2013); Abdennouri (2014); The Colombo Plan Secretariat (2015); Yun & Kim (2015); Amin-Esmaeili et al. (2016); Rahimi-Movaghar et al. (2018); Sri Lanka National Dangerous Drugs Control Board (2018); Ambekar et al. (2019); INCB (2019); Martínez & Ballesteros (2019).

Kaul, 1977; Wijesekera et al., 1988), strontium sulfate in Mexico (Sodi Pallares & Meyran Garcia, 1954), strychnine in Sri Lanka (Wijesekera et al., 1988), and chromium in Iran (Aghababaei et al., 2018).

1.4.3 Factors that are associated with opium use

The objective of this section is to provide information on the determinants of opium use and co-exposures to carcinogenic agents among opium users. The literature shows that sex and socioeconomic characteristics are associated with ever-using opium, and/or the intensity and duration of opium consumption (see Sections 1.6.1 and 1.6.2 for more information about these terms).

The average age of starting opium use is usually below 25 years (Haidary, 2015; Rasekh et al., 2018; Rafiei et al., 2019). Globally, opium use is much more prevalent in men than women (Dolan et al., 2011; UNODC, 2018). Surveys conducted in countries with high numbers of opium users – including Iran (Najafipour et al., 2015; Amin-Esmaeili et al., 2016), India (Mohan et al., 1986; Chaturvedi et al., 2013), and Afghanistan (Cottler et al., 2014) – have shown that men are 5- to 12-fold more likely to use opium than are women. There are also studies that show earlier age at initiating opium use (Ghaderi et al., 2017), higher cumulative opium use (Moossavi

Fig. 1.10 Seizures of opium, 2018

Created by the Working Group, with annual seizure data from UNODC (2019a)

et al., 2018), and higher rates of multiple drug use (Mohan et al., 1986; Chaturvedi et al., 2003; Ghaderi et al., 2017) among men who are opium users than among women opium users.

Opium is used across the spectrum of society. Reports from India and Iran show that opium use typically starts in social gatherings for pleasure and entertainment (Ray et al., 2006; Rahimi-Movaghar et al., 2018). Many users consume opium only occasionally and at such social events. Some people self-medicate with opium taken as a painkiller or sedative; however, this might result in regular use and dependence (Ray et al., 2006; Rahimi-Movaghar et al., 2018). Cessation of opium use by an individual who is opium-dependent gives rise to a classical opiate withdrawal syndrome of mild to moderate intensity. Opium dependence is not a benign disorder; however, opium costs less, requires fewer doses per day, and has less severe withdrawal symptoms than heroin (Westermeyer & Peng, 1977). Moreover, reports from several countries show that opium users have a more stable lifestyle and lesser degree of psychopathology than heroin users. A high proportion of opium users are married and live with their families (UNODC and Government of Pakistan, 2013; Rahimi-Movaghar et al., 2018; Gupta et al., 2019; Rafiei et al., 2019).

Reports from Afghanistan, India, and Iran indicate that opium use is more prevalent in populations with lower socioeconomic status (Gobar, 1976; Afghanistan Ministry of Counter Narcotics, 2013; Chaturvedi et al., 2013; Amin-Esmaeili et al., 2016). Socioeconomic status is a complex concept, and it has traditionally been defined by education, wealth, and occupation. Therefore, the selection of the socioeconomic indicator of the study population varies in different studies. Some indicators that have revealed significant correlations with opium use include income (Griffith & La France, 2018), employment (Chaturvedi et al., 2013; Haidary, 2015; Amin-Esmaeili et al., 2016; Griffith & La France, 2018), education (Chaturvedi et al., 2013; Haidary, 2015; Amin-Esmaeili et al., 2016), marital status (Chaturvedi et al., 2013; Amin-Esmaeili et al., 2016), wealth score (Sheikh et al., 2020), and urban or rural residence (Shiri et al., 2006; Khademi et al., 2012; Sheikh et al., 2020). There are also reports from Iran that have shown higher opium consumption among specific occupations, such as those involving long-distance driving (Rajabizade et al., 2004; Souri et al., 2016) and welding (Saberi-Zafarghandi et al., 2010).

Many opium users are also tobacco smokers; however, the percentages of opium users who also smoke tobacco vary across subgroups of men and women in the studied populations. In the GCS, which includes more than 50 000 residents of Golestan Province in the north-east of Iran, 8486 participants reported using opium, and of these 4475 (52.7%) also reported smoking cigarettes (Sheikh et al., 2020). In the GCS, opium users who also smoked cigarettes had significantly higher levels of cumulative opium use than opium users who did not smoke cigarettes (Moossavi et al., 2018). Similarly, in other studies that were conducted in different populations and geographical regions, the prevalence of ever-smoking tobacco among opium users was reported to be as high as 60–70%, and was more common among men than women (Mohan et al., 1986; Chaturvedi et al., 2003; Nasrollahzadeh et al., 2008; Ghaderi et al., 2017).

Evidence from the GCS shows that opium users are more likely to chew tobacco (Sheikh et al., 2020) and drink alcohol than non-users (Sheikh et al., 2020). The GCS also shows some evidence of slightly higher rates of drinking very hot tea (Islami et al., 2020), having an unhealthy diet, burning biomass as the main household fuel, and using water pipes to smoke tobacco among opium users than among non-users (Sheikh et al., 2020).

1.5 Regulation and legislation

The first international conference to discuss the global narcotics problem was the Opium Commission in Shanghai in 1909 (UNODC, 2008). Subsequent international conferences were held in 1924–25 and 1953 to prohibit the manufacture, import, sale, distribution, export, and use of narcotic drugs, except for medical and scientific purposes (UNODC, 2008). More information on international regulations before 1961 is presented in Section 1.4.1.

The current Single Convention on Narcotic Drugs (UNODC, 1961), which came into force in 1964 and was subsequently ratified by 190 countries (INCB, 2020), aims to prohibit the production and supply of named narcotic drugs and prevent drug abuse by coordinated international action (United Nations Treaty Collection, 1975). This Convention includes opium in Schedule I of international control. Parties to the Convention are committed to limit the possession, use, trade, distribution, import, export, manufacture, and production of opium exclusively to medical and scientific purposes. Morphine and thebaine, the main alkaloids that can be purified from opium, are also listed independently in Schedule I. Preparations of opium or morphine containing not more than 0.2% morphine are included in Schedule III of the Convention.

After endorsement of the Single Convention, countries individually developed national legislation to regulate access to the internationally controlled substances. Differences in substance classifications in these national laws may slightly affect the status of opium. For example, the UK has placed opium in class A of its three classes (UK Government, 2019), Canada in Schedule I of its six classes (Minister of Justice Canada, 2019), the USA in Schedule II of its five classes of controlled substances (DEA, 2020b), and Iran in class II of its two classes for illicit substances (Drug Control Law, 2010). However, all countries can prosecute individuals for illegal production, trafficking, and distribution of opium, and most countries can prosecute for possession of opium.

Global licit production of opium was about 30 000 tonnes in 1907–1908 before the international commitment to limit opium production to medical and scientific purposes (UNODC, 2004, 2008). Global illicit opium production decreased by about 25% between 2017 and 2019 (UNODC, 2020). The reduction might reflect the effectiveness of control measures in restricting the production and availability of opium and other opiates for use. Nevertheless, the continuing production of opium and the high number of users reflect partial effectiveness of the international conventions and national laws.

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

Epidemiological studies have used various exposure assessment methods to investigate the association between opium and cancer incidence. Optimal exposure assessment should consider:

- the type of epidemiological study
- the source of the opium exposure data, such as from a validated and structured interview, a clinical interview, or from patients' records, etc.
- a clear definition of opium use
- the age or date of first use of opium
- the average daily dose of opium (intensity)
- the duration of exposure in months or years
- the cumulative exposure (intensity multiplied by duration)
- the temporality of the exposure (when it occurred relative to the study end-point)
- the type(s) of opium consumed (raw, dross, or minimally refined; see Section 1.1.2)

- the mode of consumption (smoking or ingestion).

The intensity, modes, and type of opium use may change between data collection at baseline and at the time of end of follow-up, which is particularly important for cancers with long latency. The manner of data collection should minimize the potential for under-reporting of opium, which can occur because of its illicit nature. Where possible, the accuracy of the exposure ascertainment should be checked (see Section 1.2). However, opium metabolites in urine can only indicate recent exposure to opium (Abnet et al., 2004). Furthermore, as outlined in Sections 1.1.3(b), 1.4.2(g), and 1.6.2, the opium product may be adulterated or contaminated by potentially carcinogenic impurities [the Working Group noted that the extent of and components of adulteration have varied by time and geographical area, which makes exposure assessment difficult].

1.6.1 Exposure assessment methods in epidemiological studies of cancer and mechanistic studies in humans

The Working Group evaluated 5 publications from cohort studies (4 of which were conducted within the same cohort), 27 case–control studies, and 1 meta-analysis investigating the association between opium consumption and cancer incidence or mortality (see Tables S1.6.2A–D, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600; and Section 2, Tables 2.1–2.5). One study did not mention how exposure data were ascertained (Khoo, 1981). The remainder of the studies ascertained data on opium exposure via patient records or by questionnaires or interviews.

The Working Group identified 13 mechanistic studies in humans. Most mechanistic studies compared opium users with non-users, and examined various biological outcomes other than cancer (e.g. Asgary et al., 2008; Ghazavi et al., 2013a, b; Hashemipour et al., 2013; Nabati et al., 2013; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019).

As outlined in Section 1.2, biomarkers were used to evaluate the quality of the questionnaire data. The reliability of questionnaire data was assessed using test–retest methods.

The extent of exposure assessment varied across studies. Some studies incorporated "ever" versus "never" opium consumption without collecting other data on opium exposure (type, mode of ingestion, duration, intensity, or temporality of use) (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). In the GCS, comprehensive exposure assessment was obtained via an interview-based structured and validated questionnaire administered by trained staff, including general practitioners and nutritionists. Multiple studies used the GCS Questionnaire (GCSQ) (see Section 2).

The GCSQ ascertained information on age at starting opium use, daily amount consumed, frequency of use, route of administration (smoking or ingestion), opium type, and age at stopping use (Rahmati et al., 2017; Sheikh et al., 2019). "Ever" use of opium was defined as opium use at least once per week for at least 6 months (Malekzadeh et al., 2013). Opium was quantified via nokhods, and cumulative use was calculated in "nokhod-years" based on nokhods per day multiplied by the number of years of consuming opium (Moossavi et al., 2018; Sheikh et al., 2020).

In a case–control study of gastrointestinal cancers (oesophageal, gastric, pancreatic, and colon and rectum), Vazirinejad et al. (2020) defined opium use as mesghals per day. A *mesghal* (also known as a *mithkal*) is a unit of weight used to quantify precious materials such as gold and saffron. One mesghal is equal to 4.55 g (Houtsma et al., 1993).

In Golestan Province, opium is primarily either smoked or ingested. The GCS (Sheikh et al., 2020) evaluated opium consumption on

the basis of quartiles of cumulative nokhod-years of consumed opium compared with never consumption of opium (where "never" was defined as not having consumed opium at least once per week for at least 6 months). In addition, smoking opium and ingesting opium were separately evaluated in the GCS. Opium smoking was evaluated on the basis of quartiles of cumulative nokhod-years of smoking opium compared with never-smoking opium. Opium ingestion was evaluated on the basis of quartiles of cumulative nokhod-years of ingested opium compared with never-ingestion of opium. For individuals who smoked and ingested opium, cumulative exposure was calculated separately and included in the corresponding smoked and ingested exposure categories. A study by Mohebbi et al. investigated the validity of perceived and reported opium use across Iran using a modelling clay-like material to demonstrate the amount of opium used (Mohebbi et al., 2019). The study showed that estimating the amount of opium on the basis of nokhods or grams was inaccurate and varied by geographical region, and that people had a tendency to underestimate the actual amount of opium consumed (Mohebbi et al., 2019). Experimentally, the median perceived weight for 1 g of opium by the participants was lower than the expected standard (0.24 g instead of 1 g; interquartile range, 0.16) (Mohebbi et al., 2019). Similarly, the participants perceived the median weight of one nokhod as lower than the expected standard (0.16 g instead of 0.20 g; interquartile range, 0.16). (Mohebbi et al., 2019). [The Working Group noted that this suggests that the amounts of opium consumed may have been underestimated in studies reporting opium use in grams and in studies reporting exposure intensity as nokhods per day.]

Information on opium exposure from the GCSQ was validated for 150 participants by means of quantification of opium alkaloids (codeine and morphine) in urine (Abnet et al., 2004). The validity of self-reported opium use was high (sensitivity, 93%; specificity, 89%). The GCS study also assessed the reliability of the questionnaire by reinterviewing 130 participants 2 months after they initially completed the questionnaire. The comparison yielded kappa values of 0.96 for ever-use of opium and 0.74 for duration of opium use (Abnet et al., 2004). Tables S1.6.2A–D (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600) shows that a minority of case–control studies assessed opium exposure via structured, validated questionnaires. The remaining case–control studies ascertained exposure information from patient records, telephone calls, interviews, or public demographic information. The questionnaires were administered in various ways in the case–control studies. To minimize variation across interviews, some studies used a single interviewer for all study participants (see, for example, Naghibzadeh Tahami et al., 2014; Akbari et al., 2015). However, others used multiple interviewers, so may be prone to random variation in exposure assessment (Bakhshaee et al., 2017). To quantify the amount of opium used, some studies categorized opium exposure on the basis of never versus low versus high use, using median use in the control population as a cut-off point for low versus high, thereby reflecting levels in the background population.

To date, one meta-analysis has investigated the association between opium consumption and cancer risk: Afshari and colleagues investigated the association between opium use and the incidence of urinary bladder cancer, aiming to distinguish between exposure to opium alone and exposure due to concurrent use of opium and cigarettes (Afshari et al., 2017). Two researchers extracted data from the eligible studies; a third researcher acted as an adjudicator in case of disagreement. The meta-analysis included 11 case–control studies, 1 cohort study, and 5 cross-sectional studies, all from Iran. The included studies evaluated exposure on the basis of structured validated questionnaires

(Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Lotfi et al., 2016) or patient records (Sadeghi et al., 1979; Aliasgari et al., 2004; Nourbakhsh et al., 2006; Salehi et al., 2011; Karbakhsh et al., 2013; Aliramaji et al., 2015). One study had limited information on how exposure data were ascertained (Ketabchi et al., 2005). The five cross-sectional studies investigated the frequency of opium consumption. Two studies evaluated the dose of opium, and five studies included the duration of opium consumption. The meta-analysis did not provide a clear definition of opium use and did not distinguish the type of opium used or method of consumption. One study included in the meta-analysis (Tootoonchi et al., 2000) was excluded from the present monograph because it lacked sufficient detail for evaluation (see Section 2.2), and two studies were excluded from consideration for the present monograph because they were case series (Ghavam-Nasiri et al., 2002; Mohseni et al., 2005). The varying methods of exposure ascertainment in the meta-analysis should be considered when interpreting the study findings.

1.6.2 Critical review of exposure assessment

(a) Studies of cancer in humans

This section reviews the exposure assessment methods and quality in the cancer epidemiology and human mechanistic studies for the primary exposure of interest, opium consumption. It also provides an assessment of potential confounders of associations of opium use with cancer (notably tobacco) (see Section 1.4.3). The quality assessment findings are summarized in Tables S1.6.2A–E (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600) and, for cancer in humans, in Tables 2.1–2.5.

To assess the quality of the exposure assessment, the cancer epidemiology studies and mechanistic studies carried out in people exposed to opium were reviewed and tabulated (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). A high-quality exposure assessment would include the list of data elements provided at the start of Section 1.6.1. The presence of these data was tabulated for each study (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). It was noted whether the exposure data were collected before or after the disease outcome was identified, and whether the reference group might contain opium-exposed individuals. The study definition of the opium user was examined (e.g. "addict") and whether the study reported a minimum intensity or duration of exposure for an individual to be included as an exposed individual. Data relating to other exposures reported in the paper were also identified and are included in Tables S1.6.2A–E (Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). The reported co-exposures varied with each paper and could include smoking and chewing of tobacco, use of alcohol, tea temperature, food, cooking methods, occupational exposures, and others.

(i) Golestan cohort and case–control studies and opium exposure

The majority of the data relating to cancer and opium use that were identified were from Iran, particularly from the Golestan cohort of over 50 000 people recruited between January 2004 and June 2008 (Khademi et al., 2012). More detail about the GCS is provided in Section 2.1. This cohort examined opium use and reported that the consumption of *sukhteh* [opium dross] and use of opiates such as heroin were uncommon in this cohort (Khademi et al., 2012).

Each participant in the GCS was interviewed at baseline by a trained general physician (Pourshams et al., 2010; Sheikh et al., 2020), using a structured and validated questionnaire

(the GCSQ), which gathered exposure history, including that of opium use. Opium use was defined as ever-used, encompassing opium use at least weekly over a 6-month period (Abnet et al., 2004). Those who used opium occasionally were included in the unexposed group. The age of starting consumption, intensity, and duration at each dose level, type of opium, and mode of consumption (smoking only, ingestion only, or both) were collected.

[The Working Group considered the data collected using the GCSQ to be systematic, detailed, and comprehensive.] The GCSQ allows the assessment risk of average daily intensity in nokhods, duration of use, and cumulative exposure. Exposure metric(s) can be lagged for cancers with a long latent period because the temporality of the exposure is known. The prospective nature of the exposure assessment means that recall bias is less likely than when exposure data are collected after diagnosis. In addition, reverse causation and protopathic bias can be discounted (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer). This occurs, for example, when the development of a perhaps painful disease precipitates the use of opium. A minimum level of exposure (less than weekly over a 6-month period) was defined, and individuals with such low exposure were excluded from the exposed group because their inclusion could reduce the strength of any observed association. However, these individuals may have been included in the reference or unexposed group, which could also reduce the observed association. The daily opium dose was validated by comparing the questionnaire responses with measurements of urinary metabolites (Abnet et al., 2004). [The Working Group noted that the few Golestan cohort participants who reported using only heroin at the time of enrolment were past users of opium and were included in the exposed group.]

The GCSQ has been used in several publications from the GCS (Pourshams et al., 2005; Khademi et al., 2012; Malekzadeh et al., 2013; Rahmati et al., 2017; Moossavi et al., 2018; Sheikh et al., 2019, 2020). The GCSQ has also been used in several case–control studies, including some conducted in Golestan Province (Shakeri et al., 2012, 2013) and some in other regions in Iran (Naghibzadeh Tahami et al., 2014, 2016; Shakeri et al., 2016, in which the questionnaire was modified for pancreatic cancer; Akbari et al., 2015; Iankarani et al., 2017; Alizadeh et al., 2020). While the GCSQ differentiates between modes of opium consumption, some studies using this questionnaire combined the different modes for their analyses.

The GCS collected exposure data at baseline (Pourshams et al.; 2005). These prospectively collected data have been used in later studies (Khademi et al., 2012; Moossavi et al., 2018; Sheikh et al., 2019, 2020). Although the cohort exposure data, such as on opium smoking, have been updated since the data collection at baseline, they have not been published (Pourshams et al., 2010). [The Working Group noted that, while the duration of use and cumulative exposure to opium may increase after baseline, the study classified cohort members with respect to opium use at baseline.]

[The Working Group noted that, as discussed in Section 1.4.2, secondhand opium exposure can occur. Exposure among non-user family members of users has been observed in Afghanistan (Goldberger et al., 2010) and Iran (Ghadirian et al., 1985). Hair samples showed that non-users may be exposed if they are domiciled with opium users (Goldberger et al., 2010).]

Some studies that used the GCSQ were case–control studies, which were not nested in the Golestan cohort, and where the opium exposure data were collected after diagnosis (Nasrollahzadeh et al., 2008; Shakeri et al., 2013, 2016; Naghibzadeh Tahami et al., 2014, 2016). [The Working Group noted that if exposure data were collected at or after diagnosis, particularly in a clinical setting, cases may be more willing

to report opium use than controls. This would result in recall bias, and exposure among controls would be more likely to be underestimated than that of cases.]

Some of the illicit opium supply may have been adulterated (see Sections 1.1.2 and 1.4.2(g)), resulting in a reduced proportion of active ingredients (Aghababaei et al., 2018). The adulterants may themselves be toxic (e.g. lead, Aghababaei et al., 2018). [The Working Group considered it likely that long-term opium consumers could obtain supplies of less-adulterated opium and that they may adjust the amount of opium consumed to experience the effects of a standard amount of the active ingredients.]

(ii) Other studies

Some case–control studies have collected data on opium exposure by structured or semi-structured interview or questionnaire (Mousavi et al., 2003; Hosseini et al., 2010; Sadjadi et al., 2014; Ghadimi et al., 2015; Bakhshaee et al., 2017; Alizadeh et al., 2020; Vazirinejad et al., 2020); others have used data from patient records (Aliasgari et al., 2004; Aliramaji et al., 2015; Berjis et al., 2018).

The definition of what is meant by opium consumption was clear in some papers, for example, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as opium dependence and abuse, followed up with urinary testing for opiates (Hosseini et al., 2010). In other papers, the definition was "drug abuse" (Ghadimi et al., 2015), "opium addict" (Sadeghi et al., 1979), or "opium consumer" (Aliasgari et al., 2004).

[The Working Group noted that the lack of documented detail in some studies means that there is uncertainty about the systematic nature and reliability in the collection of opium exposure data. If exposure data were collected at or soon after diagnosis, particularly from an unstructured interview, then there is the possibility of information bias. Cases may have been probed more strongly and/or may have been more willing to report opium use than controls, particularly in a clinical setting. Therefore, the control group would be more likely to contain unidentified opium users. This would create differential misclassification and could lead to overestimation of any risk. However, according to investigators, opium in Iran is a "traditional medicine in this population, and possibly because of the setting and personnel completing the interview, we suspect that there was little social pressure to deny use" (Abnet et al., 2004). The extent to which this applies to all the studies presented here was not clear.]

[The Working Group noted the possibility of a further reporting bias in case–control studies, in that opium users may under-report the amount of opium use as the number of nokhods or grams per day (see Section 1.6.1 for a discussion of the accuracy of exposure estimates in nokhods and grams). It is less likely that they would over-report the extent of exposure. This could lead to misclassification, in that exposure may be higher than reported for at least some users. This misclassification would likely lead to overestimation of the risk associated with a particular level of opium consumption. If there is a threshold of exposure below which risk is undetectable, underestimation of exposure in cases and controls could result in identification of a lower than actual threshold.]

A case–control study by Vazirinejad et al. (2020) reported opium exposure as mesghals per day. [The Working Group noted that this measure was used in a single study, but that the validity of this unit of exposure is not clear.]

[The Working Group noted that opium consumption, like tobacco smoking, may extend over many years with varying intensity over the period. Data from investigation of the reliability of the recall of tobacco smoking show that recall over many years of duration or intensity may not be reliable (Bernaards et al., 2001).]

The differences in cancer risk arising from the mode of consumption have been examined in some studies (e.g. Nasrollahzadeh et al., 2008; Hosseini et al., 2010; Malekzadeh et al., 2013; Rahmati et al., 2017; Sheikh et al., 2020). [However, the Working Group noted that even where exposure is quantified and the mode of consumption considered, no difference in the amount of exposure between the different consumption modes has been considered. It is not clear whether ingested opium is more or less carcinogenic or biologically active than the same quantity of inhaled opium. When smoked, the dross is often eaten so that all the opium is consumed, but what proportion of the opium or its metabolites reaches a critical organ, for example, the urinary bladder, has not been considered.]

[The Working Group further noted that there is no agreed standard summary measure of exposure or agreed "ideal metric" for opium exposure. In epidemiological analyses, the exposure is often presented as ever/never, so individuals with long-term, low-level exposure may be combined with those with shorter-term, perhaps higher-intensity exposure; and opium smoking and ingestion are often combined in analyses, although it would be desirable to analyse these modes of exposure separately. The GCSQ data allowed analyses by intensity, duration, and cumulative exposure. Cumulative exposure was calculated in some studies (Khademi et al., 2012; Naghibzadeh Tahami et al., 2014; Akbari et al., 2015; Moossavi et al., 2018; Sheikh et al., 2019, 2020; Alizadeh et al., 2020).]

Cancers typically develop after long periods of latency; it is therefore important to evaluate associations between exposures and their effects by evaluating exposures occurring at different time periods before the onset of disease. Exposure lagging was possible with data from the GCSQ, but explicit lagging was not identified in any of the studies. Some studies separately examined risk from distant past exposure and from all exposure (e.g. Malekzadeh et al., 2013; Moossavi et al., 2018; and Sheikh et al., 2020) or from recent and all exposure (e.g. Pourshams et al., 2005).

Reverse causation or protopathic bias could occur if opium use started, or the extent of use increased, in response to disease symptoms such as pain (see Annex 2, Methodological considerations for epidemiological studies on opium consumption and cancer). This could have occurred in studies that included recent exposures (e.g. Hamrah et al., 2017), or where the whole exposure period was included or the period of opium use was not defined. Most analyses of the Golestan cohort have evaluated reverse causation in the sensitivity analyses by excluding the first 2 years of follow-up (Khademi et al., 2012; Rahmati et al., 2017; Sheikh et al., 2019, 2020).

Studies of cancer in humans have focused on individuals who deliberately consumed opium by smoking or ingestion (injection of opium is unusual). Section 1.4.1 presents some traditional and prescription medicines that contain opium, but these are not considered in most epidemiological studies. Secondhand exposure is not considered in the present monograph, although there is evidence for such exposure in family members of users (Ghadirian et al., 1985; Goldberger et al., 2010; Afghanistan Ministry of Counter Narcotics, 2013; Vazirinejad et al., 2020). As noted in Section 1.4.2, in a community survey in Afghanistan, 10.3% of men, 6.7% of women, and 6% of children tested positive for opioids (Afghanistan Ministry of Counter Narcotics, 2015).

[In summary, the Working Group noted that epidemiological studies on opium almost all rely on self-reported exposure, which may be more reliable when collected prospectively than when collected after diagnosis of cancer. Recall bias and reporting bias cannot be ruled out in these studies. The GCS stands out as having prospectively collected detailed data on the intensity and duration of exposure, and on the type of opium and modes of exposure. Several case–control

studies outside this cohort had limited data on when the exposure occurred relative to diagnosis and on the type of opium, and did not identify the mode(s) of use.]

(iii) Quality of co-exposure data

As outlined in Section 1.4.3, there are several other exposures that co-occur with opium consumption and that may increase or decrease cancer risk (for example, the use of tobacco, alcohol, consumption of hot tea, some occupational exposures, indoor air pollution, and some foods). Most of the studies reviewed here collected information about at least some of these risk factors. Some studies excluded participants with particular exposures and some studies used co-exposures as adjustment factors.

Most studies collected tobacco-smoking history, with some reporting cumulative exposure, such as pack-years (e.g. Akbari et al., 2015; Sheikh et al., 2019, 2020); and others reporting status as never/ever smoker (Khademi et al., 2012), or never/current/ex-smoker (Ghadimi et al., 2015). Some studies collected data on the use of a hookah, which may entail exposure to a large amount of tobacco (Nasrollahzadeh et al., 2008; Shakeri et al., 2013; Sadjadi et al., 2014; Pournaghi et al., 2019). Opium may also be smoked with a water pipe, not just with dedicated opium pipes (Chaouachi, 2009).

Some studies also gathered data on nass consumption. Nass is a tobacco, lime, and ash mixture that is chewed. The tobacco-smoking or nass use reported in the GCSQ correlated with urinary cotinine levels (Pourshams et al., 2005).

The validity and reliability of the Golestan food frequency questionnaire (FFQ) was tested. The FFQ was repeatable and was correlated with 24-hour food recall, but correlation with specific nutrients measured in urine and blood was lower (Malekshah et al., 2006). FFQ use was reported by Akbari et al. (2015) and Sheikh et al. (2019, 2020). Data on food were collected using other instruments in several other studies, but were not mentioned in the analyses except as a factor to be controlled for (e.g. Nasrollahzadeh et al., 2008; Iankarani et al., 2017; Vazirinejad et al., 2020). [The Working Group noted that details about these instruments were sparse.]

The temperature of tea is a possible risk factor for oesophageal cancer and was measured by Sheikh et al. (2019). Pourshams et al. showed that the reported tea temperatures from the GCSQ were repeatable despite interindividual variability (Pourshams et al., 2005).

A history of alcohol use was collected in most studies (see Tables S1.6.2A–E, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600), but is usually reported as ever or never, because it is a relatively uncommon exposure. [The Working Group noted that there could be under-reporting of alcohol use, because this is seen as socially undesirable (Naghibzadeh-Tahami et al., 2016).]

The job histories or occupational exposures gathered in the GCS do not appear to have been used in any analyses. Other studies are likely to have gathered occupational data using different questionnaires. One study of urinary bladder cancer excluded those with occupational risks (definition unclear) (Hosseini et al., 2010), while others coded jobs to International Standard Classification of Occupations codes and/or analysed risk for some industry groups (Shakhssalim et al., 2010; Ghadimi et al., 2015). A case–control study of lung cancer also excluded individuals if there had been a significant history of exposure to a list of known occupational carcinogens, such as arsenic, asbestos, and radon (Safari et al., 2016).

(b) Mechanistic studies in humans

Summaries of the exposure methods and exposure assessment quality of the human mechanistic studies are found in Tables S1.6.2E (Annex 1, Supplementary material for Section 1,

web only; available from: https://publications.iarc.fr/600).

There were limited details about how the opium exposure data were collected in many studies (e.g. Azarang et al., 2007). In most cases, data were drawn from a questionnaire and/or interview (Asgary et al., 2008; Nabati et al., 2013; Safarinejad et al., 2013a; Salarian et al., 2018). One paper used patient records (Firouzeh et al., 2016), while another used cases from the Golestan cohort and so probably used opium exposure data from the validated structured questionnaire (the GCSQ), but this was not explicitly stated in the paper (Abedi-Ardekani et al., 2011). [The Working Group noted that lack of information about how the exposure data were collected means that it is unclear how systematic the data collection was, and suggests that information bias, particularly under-reporting, and/or observer bias cannot be excluded.]

About one half of the evaluated studies used "opium user" or "opium addict" to define the exposed individuals, with no identified minimum opium exposure duration or intensity. Some studies had more specific definitions, e.g. clinic attendees (Dwivedi et al., 2019) or a DSM-IV diagnosis (Ghazavi et al., 2013a, b; Hashemipour et al., 2013). A few studies set a minimum exposure intensity and/or duration for the opium addiction (e.g. Ghazavi et al., 2013a, b; Hashemipour et al., 2013; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019). Some studies validated recent opium exposure by urine analysis (Nabati et al., 2013; Safarinejad et al., 2013a, b; Salarian et al., 2018). In all these studies, the non-exposed groups may have included people who used opium but did not meet the criteria for an exposed person.

A few studies reported intensity of exposure in nokhods per day (Safarinejad et al., 2013a, b). Others reported duration of addiction (Hashemipour et al., 2013; Safarinejad et al., 2013a, b). Ayatollahi-Mousavi et al. (2016) excluded those with less than 3 years of opium use, while others only included individuals who consumed more than 2 g of opium per day for at least 1 year (e.g. Ghazavi et al., 2013a, b; Hashemipour et al., 2013).

[The Working Group noted that a minimum exposure amount or time may be more important to some end-points than others. A wide range of cumulative exposure is likely between individuals in most studies; however, such individuals have been grouped in the analysis. Insufficient data were presented in most papers to evaluate this potential, but variability in intensity and duration can be seen in at least one study (Naghibalhossaini et al., 2004). Lack of a minimum exposure intensity or duration meant that individuals with a trivial intensity or duration of exposure could have been included in the exposed group. Inclusion of the intensity or duration means that the exposed individuals could be grouped and dose–response relations examined (e.g. Hashemipour et al., 2013). See also Section 1.6.1 for discussion of the relative inaccuracy of recalled grams or nokhods as weight measures of opium (Mohebbi et al., 2019). The Working Group also considered it possible that opium addicts may be exposed to opiates such as methadone when recruited from addiction clinics, but this was not identified in the literature.]

Few studies explicitly stated whether they considered temporality of exposure; Hashemipour et al. (2013) was the exception. Recent exposure was assumed when addicts were studied. [The relevance of recent or past exposure will vary depending on the outcome being assessed.]

Most of the mechanistic studies identified neither the type of opium nor the mode of consumption. Where these were identified, the analyses usually combined the different types and modes as "opium user" (Naghibalhossaini et al., 2004; Abedi-Ardekani et al., 2011; Ayatollahi-Mousavi et al., 2016; Dwivedi et al., 2019). [The Working Group noted that this was

the case even where it might be expected that there would be a difference in the effects from smoking and ingestion, for example, lesions in oral mucosa (Mansour Ghanaei et al., 2013).]

[Overall, the Working Group noted that the mechanistic studies seldom described the exposure data or collection methods in sufficient detail for them to be critically evaluated.]

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2. CANCER IN HUMANS

This section reviews studies of opium consumption in relation to cancer incidence or mortality in humans. The first documented suspicions that opium was a potential carcinogen originate from the Islamic Republic of Iran (hereafter referred to as "Iran") in the 1970s. A potential role for opium consumption in the etiology of oesophageal cancer was suggested on the basis of the results of a 2-year clinical observation study conducted in the Iranian province of Golestan (then, the eastern part of Mazandaran Province; Dowlatshahi et al., 1977; Dowlatshahi & Miller, 1985). Incidence rates of oesophageal squamous cell carcinoma (SCC) were extremely high in Golestan (up to 180 new cases per 100 000 population annually), despite low rates of alcohol consumption and cigarette smoking, the main known risk factors for this cancer. The study reported that 61% of men and 25% of women among 126 patients with documented oesophageal cancer had a 5- to 20-year history of opium addiction antecedent to the onset of their symptoms. In addition, brownish-black particles of burnt opium were noted on the oesophageal mucosa and the odour of the compound was detected during endoscopic examination of these patients (Dowlatshahi et al., 1977; Dowlatshahi & Miller, 1985). In parallel, a potential role for opium consumption in the etiology of urinary bladder cancer was proposed on the basis of observation of a male to female ratio in the Iranian province of Fars that was unusually high (9 : 1) compared with that typically seen (3 : 1) in many other areas of the world (Sadeghi & Behmard, 1978). The researchers were not able to identify any obvious reason(s) for such unusually high ratios, because there were no major factories or dye-production facilities in the area; tobacco-smoking prevalence and intensity were not unusually high among men; and schistosomiasis was virtually non-existent in the area. However, the authors noted that opium consumption was widespread in Fars, with a male to female ratio of 8 : 1 in registered addicts, and speculated that opium consumption played a role in bladder carcinogenesis (Sadeghi & Behmard, 1978).

The findings above led to several case–control or cross-sectional studies being undertaken in the 1970s and 1980s in Golestan (for oesophageal cancer) and Fars (for urinary bladder cancer), as well as in Singapore and Hong Kong Special Administrative Region, China (for laryngeal and lung cancers). They also led to the initiation of a small and limited number of mechanistic and experimental animal studies, primarily led by the International Agency for Research on Cancer (IARC).

Despite initial positive findings, published research on opium consumption ceased in the early 1980s. For studies in Iran, this was due to the sociopolitical changes that happened in 1979.

For the studies in eastern Asia, it is unclear why the research did not continue. [The Working Group considered it possible that the following factors were contributory: declining opium consumption due to changing drug preferences, including access to more potent alternatives such as heroin, and increased law enforcement.]

Epidemiological studies on opium and cancer in humans resumed in the 2000s, and have continued, exclusively in Iran, to the present day. Iran is a unique site for the investigation of opium as a potential human carcinogen because opium consumption is common and is socially tolerated despite being illegal, and there is a strong research infrastructure to support the conduct of epidemiological studies. Since research recommenced, studies have evaluated the role of opium consumption as a potential carcinogen for several organ sites, including the oesophagus, urinary bladder, lung, stomach, colon, pancreas, larynx, and other sites in the head and neck. These studies include one very large and well-conducted cohort study (the Golestan Cohort Study, GCS) undertaken in Golestan Province, and a large, multisite, multicentre case–control study (the Iranian Study of Opium and Cancer, IROPICAN), both of which have contributed evidence for several cancer sites.

An important consideration underlying the body of literature on opium consumption in relation to cancer incidence and mortality in humans is the largely illicit, and therefore unregulated, nature of opium as an agent. Natural variation in the chemical composition of opium occurs in different cultivars of the poppy flower, but may also be influenced by the growing conditions, including the increasing use of fertilizers and pesticides. Contaminants may also be introduced into the product, either intentionally or unintentionally, during the process of turning the poppy latex into a saleable and consumable product. [The Working Group recognized that "street opium" is not a standardized product; that variations in chemical composition are an innate part of the complex nature of the agent; and that the current body of evidence on cancer in humans does not allow the effects of different aspects of the mixture to be disentangled.]

Sections 2.1 to 2.5 summarize all available cohort and case–control studies on opium consumption in humans and form the majority of this section. The text presents a synthesis of the study findings with only the essential details included. More details on the analyses and results are included in the relevant tables. Specifically, for the sake of brevity, confounders are listed in full in the tables but mentioned in the text only when they have particular importance for the evaluation of study quality and informativeness, for example, if age and sex were *not* adjusted for. [The Working Group also noted that socioeconomic status was often adjusted for in the design (matching on neighbourhood of residence), rather than in the analysis, for many of these studies and is therefore often missing from the list of the confounders.] Instances where a matching design has particular importance for the evaluation of study quality and informativeness have been noted in the text.

Annex 2 describes some specific methodological considerations for the evaluation of the human cancer evidence related to opium consumption. While all observational epidemiological studies may present concerns about confounding, selection and information bias, and other sources of bias, the Working Group took the view that there were specific conditions related to consumption of opium that presented particular challenges for the evaluation of potential carcinogenicity. For example, the potential for reverse causation (the consumption of opium as a result of a cancer diagnosis) or protopathic bias (the consumption of opium as a result of prediagnostic symptoms of disease) necessitate consideration of the extent of control for, and impact of, these special sources of bias in observational studies of opium consumption

and cancer. The Working Group considered that an explicit discussion of the potential for, and impact of, these specific sources of bias would aid in the interpretation and synthesis of the evidence and would increase the transparency of the evaluations.

Other information relevant to the Working Group's consideration of bias and confounding more generally, including several directed acyclic graphs, is also outlined in Annex 2.

Finally, Section 2.6 presents the Working Group's synthesis of the body of evidence in relation to cancers at individual organ sites, including cancers of the oesophagus, urinary bladder, lung, larynx, pancreas, stomach, colon and rectum, and pharynx.

2.1 Cancer of the oesophagus

See Table 2.1.

Analyses from one cohort study and three case–control studies investigating the association between opium consumption and oesophageal cancer are presented below. Five descriptive studies, two investigating morphine metabolites in urine and three describing the prevalence of opium consumption among oesophageal cancer cases, were not considered informative by the Working Group and are not discussed further here (Joint Iran-International Agency for Research on Cancer Study Group, 1977; Ghadirian et al., 1985; Islami et al., 2004; Marjani et al., 2010; Hamrah et al., 2017). In studies discussed in this section, the large majority of the cases of oesophageal cancer were SCCs. Therefore, the results presented in this section are most applicable to oesophageal SCC.

2.1.1 Cohort study

Sheikh et al. (2020) is the most recent study arising out of the GCS. The GCS is a large-scale, population-based study that was initially established to explore possible etiological factors for the high rates of oesophageal SCC in the province of Golestan in Iran (Pourshams et al., 2005, 2010). The cohort was established in 2004 and, during 4 years of data collection, recruited 50 045 individuals aged 40–75 years from both rural and urban areas (Pourshams et al., 2010). Participation rates ranged from 50% for men in urban areas to 84% for women in rural areas (Sheikh et al., 2019). Data collection was via a structured questionnaire, the Golestan Cohort Study Questionnaire (GCSQ). Participants were asked about consumption of opium that occurred at least weekly for a minimum of 6 months, including the type of opium consumed (raw, refined, or dross), duration (years), ages started and stopped, frequency (per day), amount (in the local unit called a *nokhod*), and route of consumption (smoking or ingestion). The GCS also collected information on potential confounders including socioeconomic status, cigarette smoking, the use of water pipes to smoke tobacco, and consumption of nass (a tobacco product that is chewed), alcohol, and hot tea. Self-reported information on opium and tobacco consumption was found to be valid and reliable in this population (Abnet et al., 2004; Pourshams et al., 2005). Participants have been followed annually via telephone surveys, home visits, and regular reviews of provincial cancer and death registration data, and loss to follow-up is very low (< 1%) (Sheikh et al., 2019). GCS staff conduct follow-up on self-reports via medical record review or verbal autopsy, with around 90% of self-reported cancer diagnoses confirmed by expert physicians (Sheikh et al., 2019, 2020). Baseline data on exposure variables have not been updated during the follow-up period (Pourshams et al., 2010). [The Working Group noted that the lack of updated data on whether opium users quit during the follow-up period may be less of a concern than the lack of updated data on opium use in the referent population if they began using opium, or used opium more frequently, after baseline data had been collected.] [The Working

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus

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
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 342 oesophageal cancers (309 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus (mainly SCC), incidence Oesophagus (mainly SCC), incidence Oesophagus (mainly SCC), incidence	Opium use (HR): Never Ever Opium use, men (HR): Never Ever Opium use, women (HR): Never Ever	 249 93 NR NR NR NR	 1 1.38 (1.06–1.80) 1 1.31 (0.94–1.82) 1 1.40 (0.87–2.23)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; large sample size; minimal missing data; large group of regular opium users; validation of self-reported opium consumption; low prevalence of some confounders. *Limitations*: potential errors in exposure and outcome measurements (although steps taken to minimize such errors); presence of contaminants in opium unaccounted for (may have contributed to carcinogenicity); effects of residual confounding.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Cumulative opium use, any route (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	NR	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.34 (0.84–2.12)		
			2nd quartile (5.1–21 nokhod-years)	NR	1.18 (0.73–1.91)		
			3rd quartile (21.1–60 nokhod-years)	NR	1.42 (0.90–2.21)		
			4th quartile (> 60 nokhod-years)	NR	1.60 (1.06–2.42)		
			Trend-test *P* value, 0.0099				
		Oesophagus (mainly SCC), incidence	Cumulative opium use, by smoking (HR):				
			Never used	NR	1		
			1st quartile (≤ 4 nokhod-years)	NR	1.34 (0.78–2.31)		
			2nd quartile (4.1–18 nokhod-years)	NR	1.00 (0.54–1.85)		
			3rd quartile (18.1–60 nokhod-years)	NR	1.62 (1.00–2.61)		
			4th quartile (> 60 nokhod-years)	NR	1.79 (1.12–2.86)		
			Trend-test *P* value, 0.0046				

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Cumulative opium use, by ingestion (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	NR	1		
			1st quartile (≤ 9 nokhod-years)	NR	1.34 (0.71–2.54)		
			2nd quartile (9.1–30 nokhod-years)	NR	1.05 (0.51–2.14)		
			3rd quartile (30.1–78 nokhod-years)	NR	1.53 (0.83–2.84)		
			4th quartile (> 78 nokhod-years)	NR	0.91 (0.44–1.87)		
			Trend-test *P* value, 0.527				
		Oesophagus (mainly SCC), incidence	Opium type (HR):				
			Never used opium	249	1		
			Raw opium (*teriak*)	83	1.43 (1.09–1.89)		
			Refined opium (*shireh*)	5	0.92 (0.37–2.26)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	0	–		
			Combination of any of the above	5	1.58 (0.64–3.93)		
		Oesophagus (mainly SCC), incidence	Opium use status (HR):				
			Never used opium	249	1		
			Former user	8	1.05 (0.51–2.16)		
			Current user	85	1.44 (1.09–1.90)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	249	1		
			Only smoking	55	1.43 (1.04–1.95)		
			Only ingestion	29	1.20 (0.79–1.82)		
			Both routes	9	1.95 (0.98–3.87)		
		Oesophagus (mainly SCC), incidence	Route of opium use, never-users of tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Never used opium	NR	1		
			Only opium smoking	NR	1.58 (1.08–2.30)		
			Only opium ingestion	NR	0.90 (0.47–1.69)		
			Both routes	NR	2.34 (0.86–6.31)		
		Oesophagus (mainly SCC), incidence	Route of opium use, ever-users of tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	NR	1		
			Only opium smoking	NR	1.19 (0.69–2.07)		
			Only opium ingestion	NR	1.57 (0.85–2.89)		
			Both routes	NR	1.69 (0.64–4.46)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	220	1		
			Used opium but not tobacco	46	1.41 (1.02–1.96)		
			Used tobacco but not opium	29	1.07 (0.71–1.62)		
			Used both opium and tobacco	47	1.51 (1.07–[2.14][a])		
		Oesophagus (mainly SCC), incidence	Opium use, lower SES (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	1.28 (0.93–1.76)		
		Oesophagus (mainly SCC), incidence	Opium use, higher SES (HR):				
			Never	NR	1		
			Ever	NR	1.80 (1.07–3.01)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Opium use, histologically confirmed cases (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	224	1		
			Ever	85	1.43 (1.08–1.90)		
		Oesophagus (mainly SCC), incidence	Opium use, excluding first 2 yr of follow-up (HR):				
			Never	199	1		
			Ever	77	1.52 (1.13–2.04)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Khademi et al. (2012) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 234 928 person-years (through May 2011; median, 4.7 yr) Cohort	GCS: 50 045 participants; prospective population-based cohort of Golestan population aged 40–75 yr Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus, mortality Oesophagus, mortality	Opium use, men (HR) Never Ever Opium use, women (HR): Never Ever	 NR NR NR NR	 1 1.12 (0.62–2.04) 1 2.40 (1.13–5.10)	Age, ethnicity (Turkman/ non-Turkman), education (illiterate/up to 8 yr/high school/ university), marital status (married/ single/widow or widower/ divorced or other), residence (rural/ urban), cigarette smoking (ever/ never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders; blinded evaluation of outcome. *Limitations*: small number of deaths among participants who ingested opium (vs smoking); may also be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: 50 045 participants; prospective population-based cohort of Golestan population aged 40–75 yr Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus, mortality	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), cigarette smoking (ever/ never), alcohol consumption (ever/never), HBV infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders; blinded evaluation of outcome. *Limitations*: small number of deaths among participants who ingested opium (vs smoking); may be also some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			Never	NR	1		
			Ever	NR	1.55 (1.02–2.34)		
		Oesophagus, mortality	Opium use, excluding deaths in first 12 mo (HR):				
			Never	NR	1		
			Ever	NR	1.54 (0.99–2.38)		
		Oesophagus, mortality	Opium use, excluding participants who started using opium after disease diagnosis (HR):				
			Never	NR	1		
			Ever	NR	1.69 (1.11–2.56)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Shakeri et al. (2012) Golestan Province, Iran (Islamic Republic of) Hospital study (March 2002 to November 2003) Case–control	Cases: 130 pathology-proven cases identified at Atrak Clinic in Khatam Hospital, Gonbad City Controls: 260 hospital-based controls; inpatients (without diseases thought to be related to tobacco use, alcohol consumption, or diet) individually matched on age and sex Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex, cigarette smoking, nass, hookah, ethnicity (Turkman/ non-Turkman), education, place of residence (urban/ rural)	*Exposure assessment critique*: Well-defined and well-characterized opium exposure, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Other comments*: the standardized prevalence of opium consumption was 17%, 16%, and 23%, respectively, in the GCS, neighbourhood-based controls, and hospital-based controls in this study. *Strengths*: two methods of control selection; information on potential covariates; cancer cases confirmed by biopsy; high participation rates of the controls; steps taken to minimize interviewer bias. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.
			Never	85	1		
			Ever	45	1.09 (0.63–1.87)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never	85	1		
			≤ Median duration of use among controls	27	1.48 (0.78–2.81)		
			> Median duration of use among controls	18	0.73 (0.35–1.51)		
		Oesophagus (SCC), incidence	Age started opium use (OR):				
			Never	85	1		
			> Median age started among controls	26	1.07 (0.54–2.10)		
			≤ Median age started among controls	19	1.11 (0.55–2.27)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Shakeri et al. (2012) Golestan Province, Iran (Islamic Republic of) Neighbourhood study (December 2004 to June 2007) Case–control	Cases: 300 pathologically confirmed cases identified at Atrak Clinic in Khatam Hospital, Gonbad City Controls: 571 neighbourhood controls individually matched on place of residence, age, and sex Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex, cigarette smoking, nass, hookah, ethnicity (Turkman/ non-Turkman), education, place of residence (urban/ rural)	*Exposure assessment critique*: Opium exposure well defined and well characterized, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Other comments*: the standardized prevalence of opium consumption was 17%, 16%, and 23%, respectively, in the GCS, neighbourhood-based controls, and hospital-based controls in this study. *Strengths*: two methods of control selection; information on potential covariates; cancer cases confirmed by biopsy. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.
			Never	210	1		
			Ever	90	1.77 (1.17–2.68)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never	210	1		
			≤ Median duration of use among controls	34	1.44 (0.84–2.45)		
			> Median duration of use among controls	56	2.12 (1.28–3.50)		
		Oesophagus (SCC), incidence	Age started opium use (OR):				
			Never	210	1		
			> Median age started among controls	41	1.25 (0.71–2.18)		
			≤ Median age started among controls	49	2.32 (1.40–3.82)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Nasrollahzadeh et al. (2008) Golestan Province, Iran (Islamic Republic of) December 2003 to June 2007 Case–control	Cases: 300; as for Shakeri et al. (2012) (neighbourhood study) above Controls: 571; as for Shakeri et al. (2012) (neighbourhood study) above Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium and tobacco use (OR): Never opium – never tobacco Never opium – ever tobacco Ever opium – never tobacco Ever opium – ever tobacco	 166 43 30 60	 1 1.70 (1.05–2.73) 2.12 (1.21–3.74) 2.35 (1.50–3.67)	Age, sex, residence (urban/ rural), education, ethnicity (Turkman/non-Turkman), total intake of fruit and vegetables	*Exposure assessment critique*: Opium exposure well defined and well characterized, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Strengths*: information on potential covariates; cancer cases confirmed by biopsy. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Bakhshaee et al. (2017) Mashhad, Iran (Islamic Republic of) 2008–2010 Case–control	Cases: 95 biopsy-confirmed cases of oesophageal SCC from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences Controls: 28 hospital-based healthy controls from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences, with no evidence of head and neck or oesophageal malignancies, matched on age Exposure assessment method: questionnaire; interview collected data on opium use, defined as "snuffing"	Oesophagus (SCC), incidence	Opium dependency (OR): Never Ever	 NR NR	 1 1.44 (0.57–3.62)	Age	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Information on intensity, duration, and type of opium exposure not collected. Only "snuffing" (presumed to be smoking) use is described. Not clear how systematic the interview was. Limited details and exposure information. Unexposed referent group could include exposed. Exposure data collection after case identification. No exposure lagging. *Other comments*: cigarette smoking was inversely associated with risk of oesophageal cancer. *Strengths*: biopsy-confirmed cases. *Limitations*: controls were selected from the otolaryngology and radiation oncology department; only opium consumption by snuffing was assessed; limited information in the methods and results to allow critical review by the Working Group.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (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
Pournaghi et al. (2019) North Khorasan, Iran (Islamic Republic of) 2013–2015 Case–control	Cases: 96 pathologically confirmed cases from cancer registry Controls: 187 hospital-based controls matched on age and sex Exposure assessment method: questionnaire; structured interview of cases and controls	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Exposure data collection after case identification. Considers age at onset, duration, intensity, and exposure method. No exposure lagging. *Other comments*: prevalence of opium use was 45%. *Strengths*: pathologically confirmed cases. *Limitations*: high prevalence of drug use (45%) may indicate some selection bias; minimal adjustment for possible confounding.
			Never used	42	1		
			Current use	51	2.1 (1.2–3.5)		
			Previous use	3	0.6 (0.1–2.2)		
		Oesophagus (SCC), incidence	Consumption methods (OR):				
			Never used	42	1		
			Inhaler	42	2.3 (1.3–3.9)		
			Eating [ingestion]	12	1.2 (0.5–2.8)		
		Oesophagus (SCC), incidence	Age at onset of opium use (OR):				
			Never used	45	1		
			< 30 yr	9	1.3 (0.5–3.1)		
			30–50 yr	24	2.8 (1.4–5.6)		
			≥ 50 yr	18	2.5 (1.2–5.1)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never used	45	1		
			< 10 yr	27	2.2 (1.2–4.2)		
			10–20 yr	15	1.6 (0.8–3.5)		
			20–30 yr	6	7.8 (1.5–40.1)		
			≥ 30 yr	3	0.5 (0.1–2.03)		
		Oesophagus (SCC), incidence	Daily opium consumption (OR):				
			Never consumed	45	1		
			≤ 1 time per day	9	0.8 (0.3–2.01)		
			1–3 times per day	30	2.8 (1.5–5.2)		
			≥ 3 times per day	12	2.4 (1.03–5.7)		

–, risk estimate could not be calculated; CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; HBV, hepatitis B virus; HR, hazard ratio; mo, month; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

[a] This value was incorrectly reported in the original publication as 1.14, but was verified by the Secretariat with the authors (Sheikh et al., 2020).

Group noted that the strengths of the GCS include the large study size with minimal loss to follow-up; the collection of detailed information on exposure; the collection of data for multiple possible confounders, including multiple forms of tobacco use; and the use of a reliable and valid questionnaire (validated against the presence of opium metabolites in urine). A limitation of the study was that the definition of opium exposure allows some exposed individuals to be classified as never-users.]

Sheikh et al. (2020) investigated associations with regular opium use in 342 cases of oesophageal cancer, the majority of which (over 90%) were histologically confirmed as SCC. Overall, a hazard ratio (HR) of 1.38 (95% confidence interval, CI, 1.06–1.80) for ever-use of opium compared with never-use was observed for oesophageal cancer incidence, adjusting for a range of factors including cigarette smoking (status and pack-years) and regular alcohol use. Results were similar with further adjustment for chewing nass, using a water pipe, household fuel type, and diet, and similar, but less precise, when stratified by sex (HR for men, 1.31; 95% CI, 0.94–1.82; HR for women, 1.40; 95% CI, 0.87–2.23). There was also a positive trend with increasing quartiles of cumulative opium consumption by smoking (P = 0.0046; HR, 1.79; 95% CI, 1.12–2.86 in the highest consumption quartile) but not by ingestion (P = 0.527). Regarding opium type, the majority of users consumed raw opium (*teriak*), for which the hazard ratio was 1.43 (95% CI, 1.09–1.89) compared with never-users, whereas results for other opium types were based on smaller numbers of users. Results were also stronger for current (HR, 1.44; 95% CI, 1.09–1.90) than for former (HR, 1.05; 95% CI, 0.51–2.16) opium consumption (as measured at baseline). [The Working Group noted that cessation of opium use appears to reduce the risk of oesophageal cancer for former users compared with current users (as measured at baseline). No information on the length of cessation among former users at baseline was provided.] Among tobacco never-users, the adjusted hazard ratio for oesophageal cancer in opium users (compared with never-users) was higher than that for the overall study population, although the confidence intervals widened slightly (HR, 1.41; 95% CI, 1.02–1.96). The evidence for an interaction between opium use (ever or never) and either socioeconomic status (P for interaction, 0.236) or sex (P for interaction, 0.481) was not strong. Findings were similar, but somewhat stronger, upon the exclusion of cases without histological confirmation (HR, 1.43; 95% CI, 1.08–1.90) as well as exclusion of the first 2 years of follow-up (HR, 1.52; 95% CI, 1.13–2.04).

[The strengths of this study, beyond those already stated for the GCS, include the sensitivity analysis and the sex-specific analysis, given the lower prevalence of opium consumption among women than men.] Previous analyses of oesophageal cancer in the GCS have reported similar findings for both cancer incidence (Sheikh et al., 2019) and mortality (Malekzadeh et al., 2013), including among women (Khademi et al., 2012).

2.1.2 Case–control studies

Shakeri et al. (2012) reported the results of two related case–control studies conducted in Golestan Province, Iran; one included 130 cases of oesophageal SCC and 260 hospital-based controls (inpatients with diseases unrelated to tobacco, alcohol, or diet), and the other included 300 cases of oesophageal SCC and 571 neighbourhood-based controls. Case definition and selection were the same for both studies. The neighbourhood control study reported elevated adjusted odds ratios (ORs) for opium use compared with never-use (adjusted OR, 1.77; 95% CI, 1.17–2.68), as well as increasing effects with increasing duration of use and with decreasing age of start of use. However, the effect estimates for the hospital-based control study were not as large as the neighbourhood-based

study (adjusted OR, 1.09; 95% CI, 0.63–1.87), and did not show consistent increases with duration or earlier age at which consumption started. The prevalence of opium smoking was similar in cases and hospital-based controls (cases, 30–35%; hospital controls, 28%), and higher than in neighbourhood controls (18%). [The Working Group noted that the prevalence of opium consumption differed in the two control groups. The lower prevalence of opium consumption in the neighbourhood controls may be an indicator of under-reporting of opium use in this group; however, the prevalence was generally consistent with prevalence estimates from other sources in this region (Pourshams et al., 2005; Shakeri et al., 2013). The similarly elevated prevalence of consumption in both cases and hospital controls, compared with the neighbourhood controls, may have been the result of similar biases or artefacts of data collection operating in both these groups. For example, recent opium consumption as a method of pain relief for underlying health conditions could inflate the prevalence of opium consumption for cases and for hospital-based controls. In addition, recall bias could similarly affect both cases and hospital controls. Hospital controls were mainly admitted for elective surgery (73%) or trauma (21%), or by the internal medicine department (6%). These biases and artefacts would tend to bias the results from the study with hospital-based controls towards the null, and the results from the study with neighbourhood-based controls away from the null (reverse causation). Consequently, the neighbour-control results for the categories of longer duration of use (greater than the median) and younger age of start of use (less than or equal to the median) may be less likely to be biased due to the effects of reverse causation.] The study with neighbourhood controls reported an increase in risk of more than 2-fold for the categories of longer duration of use (greater than the median) and younger age of start of use (less than or equal to the median). [The Working Group noted that the median duration of use and median age started were not reported in the paper. A strength of this study was the adjustment for multiple possible confounders, including multiple forms of tobacco use.]

Two papers have presented additional analyses of the neighbourhood-based control case–control study described in Shakeri et al. (2012). Nasrollahzadeh et al. (2008) reported a 2-fold increase in risk among opium users who did not use tobacco. Abedi-Ardekani et al. (2011) reported a high ratio of *TP53* mutations among oesophageal SCC cases, with 84.2% of the mutations detected in exons 5–8, although the mutation pattern was not observed to differ with opium use.

Bakhshaee et al. (2017) reported an elevated age-adjusted odds ratio (OR, 1.44; 95% CI, 0.57–3.62) for the association between opium dependency and oesophageal cancer (SCC) in a study of 95 cases and 28 controls (as per the methodology description; however, the abstract indicated 98 cases and 27 controls) in Mashhad, Iran. Controls were described as healthy individuals selected from the otolaryngology and radiation oncology department of the same hospital as the cases. The study collected data via "comprehensive interview" but did not present the demographic characteristics of the participants, did not adequately assess opium exposure, and did not further adjust for potential confounders in the analysis. [The Working Group noted that the limited reporting of the methods and results hampered critical review. Moreover, the small sample size, the control selection, and the lack of adjustment in these results, particularly for tobacco use, may have contributed to biased estimates.]

Pournaghi et al. (2019) described a hospital-based case–control study of 96 cases and 187 controls from North Khorasan, Iran. They reported elevated age- and sex-adjusted odds ratios for association between oesophageal cancer SCC and opium consumption,

including for current use, smoking as the mode of consumption, later age at first use, and higher frequency of consumption. The results were not further adjusted for potential confounders, such as tobacco consumption. The prevalence of tobacco consumption was reported to be around 23% (and similar in cases and controls). [The Working Group noted that the lack of adjustment for potential confounding in these results, particularly for tobacco use, may have biased estimates away from the null.] Exposure assessment in this study was by structured interview. The study reported a high prevalence of opium use in the study population (overall, 45%; cases, 56%; controls, 41%). [The Working Group noted that limited details were provided in the paper to allow critical review of the assessment of exposure. Both cases and controls in a hospital-based setting may have recently consumed opium as a method of pain relief for underlying health conditions, and this may explain the high prevalence of opium use in this study.]

2.2 Cancer of the urinary bladder

See Table 2.2.

Results from a systematic review and meta-analysis (Afshari et al., 2017), one cohort study (Sheikh et al., 2020), and eight case–control studies (Sadeghi et al., 1979; Asgari et al., 2004; Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Aliramaji et al., 2015; Ghadimi et al., 2015; Lotfi et al., 2016) were evaluated to draw inferences on the association between opium exposure and risk of urinary bladder cancer. A total of eight studies were excluded on the basis of the study design (cross-sectional or case series) or a lack of information on the analysis, population characteristics, and/or exposure to opium (Behmard et al., 1981; Tootoonchi et al., 2000; Ghavam-Nasiri et al., 2002; Ketabchi et al., 2005; Mohseni et al., 2005; Nourbakhsh et al., 2006; Salehi et al., 2011; Karbakhsh et al., 2013).

2.2.1 Systematic reviews

Kamangar et al. described the characteristics and outcomes of seven primary studies on the association between opium exposure and bladder cancer published between 1979 and 2010 (Kamangar et al., 2014); however, an updated systematic review and meta-analysis that included these studies summarized the evidence and estimated a meta-risk using a fixed effects model (Afshari et al., 2017). A pooled odds ratio of 3.9 (95% CI, 3.1–5.1) was reported for opium use adjusted for other potential confounders including cigarette smoking, while the pooled unadjusted odds ratio was 3.40 (95% CI, 1.60–7.21) for 34 cases exposed only to opium (Afshari et al., 2017). [The Working Group noted that these odds ratios may not be meaningful as this result was based on five studies presenting methodological limitations and because of the heterogeneity in the definition of the comparison groups between studies. Control selection, adjustment for confounding, and a clear definition of exposure were among the limitations of several of these studies. Nevertheless, the Working Group noted that all study risk estimates pointed towards an increased risk of bladder cancer associated with opium exposure.]

2.2.2 Cohort study

Sheikh et al. recently published results for the incidence of urinary bladder cancer from the GCS; see the detailed description of the GCS in Section 2.1 (Sheikh et al., 2020). Of the 47 cases of bladder cancer, 43 were histologically confirmed. Hazard ratios were estimated by Cox regression analyses, with adjustment for a range of factors including cigarette smoking (status and pack-years). The fully adjusted hazard ratio was 2.86 (95% CI, 1.47–5.55) for ever-users compared with never-users, the hazard ratio was 3.36 (95% CI, 1.74–6.50) for current users (as measured at baseline), and there was a positive trend in

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder

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
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from both rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 47 bladder cancers (43 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Urinary bladder, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: selection of the population; detailed exposure assessment and validation of exposure with urine testing; the temporality of the effect; extensive statistical and sensitivity analysis conducted. *Limitations*: relatively small sample size; unclear whether opium exposure was collected during follow-up.
			Never	24	1		
			Ever	23	2.86 (1.47–5.55)		
		Urinary bladder, incidence	Opium use status (HR):				
			Never	24	1		
			Former	0	–		
			Current	23	3.36 (1.74–6.50)		
		Urinary bladder, incidence	Cumulative opium use (HR):				
			0 (never used)	24	1		
			≤ 5 nokhod-years	NR	3.24 (1.28–8.20)		
			5.1–21 nokhod-years	NR	0.55 (0.07–4.21)		
			21.1–60 nokhod-years	NR	3.31 (1.27–8.59)		
			> 60 nokhod-years	NR	4.28 (1.81–10.15)		
			Trend-test *P* value, 0.0009				

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Sheikh et al. (2020) (cont.)		Urinary bladder, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.57 (1.23–5.37)		
		Urinary bladder, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	4.10 (1.03–16.22)		
		Urinary bladder, incidence	Route of opium use (HR):				
			Never used opium	24	1		
			Only by smoking	13	2.56 (1.21–5.40)		
			Only by ingesting	9	3.79 (1.61–8.88)		
			Both routes	1	1.66 (0.21–13.02)		
		Urinary bladder, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	17	1		
			Used opium but not tobacco	9	3.74 (1.63–8.59)		
			Used tobacco but not opium	7	2.03 (0.78–5.27)		
			Used both opium and tobacco	14	4.21 (1.87–9.46)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Sadeghi et al. (1979) Shiraz, Fars Province, Iran (Islamic Republic of) 1969–1976 Case–control	Cases: 99 histologically confirmed cases with diagnosis of bladder carcinoma Controls: 99 controls individually matched on age (± 5 yr) and sex Exposure assessment method: opium exposure data were from patient records and reported as verified for controls but no details on how this was done	Urinary bladder, incidence	Opium and cigarette use, men and women combined (OR):			Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data collection after case identification. No analyses by intensity or duration of use, or type of opium. Exposure was likely by smoking and/or ingesting. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: opium and smoking combined estimates provided. *Limitations*: small sample size; exposure assessment from clinical records. *Other comments*: almost all opium users were also cigarette smokers, consequently the OR CI for opium use among non-cigarette smokers was quite wide; ORs presented here are relative to non-users of both opium and cigarettes.
			Never opium, never cigarette	24	1		
			Never opium, ever cigarette	30	[1.6 (0.8–3.1)]		
			Ever opium, never cigarette	2	[4.3 (0.4–49.2)]		
			Ever opium, ever cigarette	43	[13.1 (5.1–33.2)]		
		Urinary bladder, incidence	Opium and cigarette use, men only (OR):			Age	
			Never opium, never cigarette	17	1		
			Never opium, ever cigarette	27	[2.1 (1.0–4.4)]		
			Ever opium, never cigarette	1	[2.7 (0.2–45.7)]		
			Ever opium, ever cigarette	43	[19.4 (7.0–53.7)]		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Asgari et al. (2004) Tehran, Iran (Islamic Republic of) 1997–2000 Case–control	Cases: 52 hospital cases of men with pathological diagnosis of bladder cancer; undergone surgery Controls: 108 men in hospital with diagnosis of BPH; undergone surgery Exposure assessment method: data on duration of opium consumption was taken from patients' records	Urinary bladder, incidence	Opium use (OR):			Cigarette smoking	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data could have been before case identification. No data on intensity, type, or method of opium exposure. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: cigarette smoking-adjusted result reported in Kamangar et al. (2014). One of the first studies that reported an association between opium exposure and bladder cancer risk. *Limitations*: small sample size; poor and retrospective exposure assessment from patient's records; controls with BPH; minimally adjusted risk estimates.
			Never	39	1		
			Ever	13	2.6 (0.8–8.5)		
		Urinary bladder, incidence	Opium use, cigarette smokers (OR):			None	
			Never opium	24	[1]		
			Ever opium	12	[2.0 (0.6–6.6)]		
		Urinary bladder, incidence	Opium and cigarette use (OR):			None	
			Never opium – never cigarette	15	[1]		
			Never opium – ever cigarette	24	[6.6 (3.0–14.9)]		
			Ever opium – never cigarette	1	–		
			Ever opium – ever cigarette	12	[13.3 (4.1–43.2)]		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Hosseini et al. (2010) Tehran, Iran (Islamic Republic of) 2004–2008 Case–control	Cases: 179 consecutively recruited, histologically confirmed, incident cases of TCC of the bladder. Controls: 179 hospital-based controls recruited from those who were seeking health care and assumed to be cancer-free if urine cytology, cystoscopy, and bladder biopsy did not reveal evidence of bladder cancer; frequency-matched on sex, geographical origin, age (± 5 yr), ethnicity, and smoking history	Urinary bladder (TCC), incidence	Opiate use (OR):			Age, sex, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	*Exposure assessment critique*: Opiate exposure well defined and moderately characterized. Timing of opium use relative to outcome not considered. Exposure data collection after case identification. No data on intensity of opium exposure. Only raw opium and opiates discussed, heroin was included in many analyses. Method of exposure to opium categorized but includes injection, which is unlikely (except for heroin). Unexposed referent group could include exposed. No exposure lagging. *Other comments*: it is unclear whether the identical CIs for men and/or women are correct.
			Never	119	1		
			Ever	60	4.60 (3.53–6.28)		
		Urinary bladder (TCC), incidence	Type of opiate (OR):				
			Never used opiates	119	1		
			Codeine	8	2.12 (1.22–3.32)		
			Raw opium	37	4.16 (2.62–6.34)		
			Heroin	15	6.16 (4.24–8.22)		
		Urinary bladder (TCC), incidence	Route of administration (OR):				
			Never used opiates	119	1		
			Smoking	20	3.80 (2.74–5.48)		
			Snorting	13	3.86 (2.57–5.36)		
			Ingestion	7	4.10 (3.22–6.22)		
			Both smoking or snorting and ingestion	6	4.88 (3.54–6.76)		
			Injection	9	5.72 (3.44–7.24)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Hosseini et al. (2010) (cont.)	Exposure assessment method: questionnaire; retrospective data from an interview including smoking history; opiate exposure duration collected; opiate abuse and dependency categorized from DSM-IV and urine analysis	Urinary bladder (TCC), incidence	Opiate consumption, men (OR):			Age, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	*Strengths:* validated questionnaires with urine tests; risk models adjusted for potential confounders; stratified analysis by sex, age, tobacco-smoking status and pack-years, type of opium/opiates, and routes of administration. *Limitations:* controls may suffer from selection bias (86% men with BPH and 84% women with urinary symptoms); risk estimates based on small numbers in the control group; consumption of opiates (codeine, heroin) cannot be ruled out.
			Non-addicts	95	1		
			Addicts	48	5.10 (3.54–5.88)		
		Urinary bladder (TCC), incidence	Opiate consumption, women (OR):				
			Non-addicts	24	1		
			Addicts	12	4.10 (3.54–5.88)		
		Urinary bladder (TCC), incidence	Opiate consumption, age ≥ 60 yr (OR):			Sex, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	
			Non-addicts	97	1		
			Addicts	29	5.42 (4.12–7.28)		
		Urinary bladder (TCC), incidence	Opiate consumption, age ≤ 60 yr (OR):				
			Non-addicts	22	1		
			Addicts	31	3.8 (2.72–6.12)		
		Urinary bladder (TCC), incidence	Opiate consumption, < 28 pack-years of cigarette smoking (OR):			Age, sex, geographical origin, ethnicity, family history of cancer	
			Non-addicts	17	1		
			Addicts	21	1.8 (1.42–2.62)		
		Urinary bladder (TCC), incidence	Opiate consumption, ≥ 28 pack-years of cigarette smoking (OR):				
			Non-addicts	27	1		
			Addicts	34	6.16 (3.34–8.3)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Shakhssalim et al. (2010) Iran (Islamic Republic of) (Tehran, Khorasan, Khoozestan, Isfahan, and East Azarbayjan) 2006 Case–control	Cases: 692 pathologically confirmed, newly registered cases of TCC bladder cancer Controls: 692 population-based controls individually matched on age (± 5 yr), sex, and neighbourhood Exposure assessment method: questionnaire; data from questionnaire by interview; no evidence presented for its reliability or validity; 38% of cases and 23% of controls completed by proxy	Urinary bladder (TCC), incidence Urinary bladder (TCC), incidence Urinary bladder (TCC), incidence	Opium consumption (OR): Never Ever History of opium consumption (OR): Never Ever Current opium consumption (OR): No Yes	 NR NR 20 67 34 85	 1 2.57 (1.55–4.26) 1 3.50 (2.41–8.41) 1 2.88 (1.84–4.50)	Age, sex, neighbourhood, cigarette smoking Age, sex, neighbourhood	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. High proportion of missing exposure information. Exposure data collection after case identification. No information on intensity, method, or duration of use, or type of opium. Food and occupational exposures examined as co-exposures. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: the definitions and applications of the categories for "current opium consumption" and "history of opium consumption" were unclear. *Strengths*: large population-based case–control study. *Limitations*: unclear whether newly registered cases could include prevalent cases; selection bias towards less aggressive bladder cancer; large proportion of proxy respondents.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Akbari et al. (2015) Shiraz, Fars Province, Iran (Islamic Republic of) 2012–2013 Case–control	Cases: 198 incident cases identified from cancer registry or hospital records Controls: 396 sex- and age- (± 5 yr) matched neighbourhood controls Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection For cases, history of opium exposure reported to be taken before diagnosis to "minimize the impact of reverse causality". [However, this seems inconsistent with other descriptions of the exposure assessment in the paper.]	Urinary bladder, incidence	Opium use (OR):			Age, sex, neighbourhood, tobacco use (never/ever), alcohol use (never/ever), dietary variables (red meat, poultry, fish, hydrogenated oil, olive oil, butter intake, fat intake, fruits, nut consumption, and mouldy food)	*Exposure assessment critique*: Opium exposure well defined and well characterized. Systematic data collection after case identification. Opium use defined as ever used, cumulative opium dose known. Type of opium and exposure routes combined. A few heroin users included. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: population-based case–control study; relatively large sample size; detailed exposure assessment; minimized bias and variation due to the interviewer. *Limitations:* no combined opium + smoking risk estimate is provided; reverse causation cannot be ruled out.
			Never	155	1		
			Ever	43	3.9 (1.3–12.0)		
		Urinary bladder, incidence	Amount of daily opium use (OR):				
			Never	155	1		
			≤ Median amount in controls	17	4.4 (0.5–33.5)		
			> Median amount in controls	26	2.4 (0.6–9.4)		
		Urinary bladder, incidence	Duration of opium use (OR):				
			Never	155	1		
			≤ Median duration in controls	17	2.5 (0.5–11.3)		
			> Median duration in controls	26	6.0 (1.1–34.7)		
		Urinary bladder, incidence	Cumulative opium use (OR):				
			Never	155	1		
			≤ Median use in controls, nokhod-years	12	3.3 (0.5–23.1)		
			> Median use in controls, nokhod-years	31	4.9 (1.1–21.9)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Aliramaji et al. (2015) Babol, Iran (Islamic Republic of) 2001–2012 Case–control	Cases: 175 patients diagnosed with histologically confirmed bladder cancer who underwent surgery during 2001–2012 in Shahid Beheshti Hospital Controls: 175 controls selected among the patients who underwent ERCP for gallstones in the same hospital and had no tumours and genitourinary problems, and matched to cases by age and sex Exposure assessment method: questionnaire; details from patient records but also telephone calls; data collated with checklist	Urinary bladder, incidence Urinary bladder, incidence	Opium use (> 1 yr) (OR): Never Ever Opium and cigarette use (OR): Never opium – never cigarette Never opium – ever cigarette Ever opium – never cigarette Ever opium – ever cigarette	 117 58 67 50 14 44	 [1] [2.7 (1.6–4.6)] [1] [9.3 (4.5–19.0)] [4.1 (1.6–10.6)] [4.5 (2.5–8.2)]	Age, sex	*Exposure assessment critique*: Opium exposure defined but poorly characterized, and timing of opium use relative to outcome undefined. Opium exposure data could have been collected before case identification. No data on amount or type of opium, or method of exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: relatively large sample size. *Limitations*: poor assessment of opium exposure; risk estimates not provided; minimally adjusted estimates; potential selection bias among cases; relatively low sample size.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Ghadimi et al. (2015) Kurdistan Province, Iran (Islamic Republic of) around 2012–2014 Case–control	Cases: 152 patients with histologically confirmed bladder cancer in the cancer registry system in Kurdistan Province (in the west of the Islamic Republic of Iran) during the past 3 yr Controls: 152 hospital controls; patients referred to a specialized clinic in the same city and hospital, frequency-matched for age (± 5 yr), sex, and place of residency Exposure assessment method: retrospective data from a questionnaire that asked for history of smoking and drug use; 20 yr job history; job titles translated into ISCO codes	Urinary bladder, incidence	Opium use (OR): Never Ever	 136 16	 1 4.96 (1.07–22.92)	Age, sex, place of residency (urban/ rural), smoking status	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome unclear. Exposure data collection after case identification. Opium use undefined, all opium use via smoking. No data on duration, amount, or type of opium exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: relatively large sample size. *Limitations*: unclear from which specialist clinics the controls were recruited, with the potential for selection bias; the exposure assessment was not well described; lack of adjustment for other potential confounders.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (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
Lotfi et al. (2016) Yazd Province, Iran (Islamic Republic of) 2009–2013 Case–control	Cases: 200 pathologically confirmed cases of bladder cancer Controls: 200 population controls frequency-matched for age (± 2 yr), sex, and residence Exposure assessment method: researcher-designed questionnaire; no evidence presented for its reliability or validity; includes use of hookah but not clear if this is tobacco, opium, or both	Urinary bladder, incidence	Opium use (OR): Never Ever	 147 52	 1 3.01 (1.73–5.23)	Age, sex, residence	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data collection after case identification. No information on intensity or duration of use, type of opium, or method of exposure. No exposure lagging. *Strengths*: population-based; relatively large sample size. *Limitations*: no adjustment for tobacco consumption; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

–, risk estimate could not be calculated; BPH, benign prostatic hyperplasia; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ERCP, endoscopic retrograde cholangiopancreatography; GCSQ, Golestan Cohort Study Questionnaire; HR, hazard ratio; ISCO, International Standard Classification of Occupations; NR, not reported; OR, odds ratio; TCC, transitional cell carcinoma; vs, versus; yr, year.

risk of bladder cancer with cumulative exposure (P = 0.0009) with a hazard ratio of 4.28 (95% CI, 1.81–10.15) for the highest quartile of cumulative use (> 60 nokhod-years) compared with never-users. Risk estimates for ever-use of opium tended to be higher among women (HR, 4.10; 95% CI, 1.03–16.22) than men (HR, 2.57; 95% CI, 1.23–5.37), among those who ingested opium (HR, 3.79; 95% CI, 1.61–8.88), and among tobacco never-users (HR, 3.74; 95% CI, 1.63–8.59), although the test for interaction with tobacco was not significant. [The Working Group noted that despite the small number of cases observed in this cohort, there was a consistent positive association between each of the opium exposure-related variables and risk of bladder cancer, as well as a strong monotonic exposure–response relationship with respect to cumulative use of opium. The GCS represents an important improvement over previous case–control studies in terms of the selection of the population, exposure assessment and validation, rigorous study design, temporality of the effect, and the statistical and sensitivity analysis conducted, and the continuing surveillance for further cases in this cohort, which should strengthen the current body of evidence.]

2.2.3 Case–control studies

The eight case–control studies contributing evidence on opium exposure and risk of bladder cancer are described in chronological order below.

Sadeghi et al. (1979) conducted a hospital-based case–control study between 1969 and 1976 in Shiraz, southern Iran. The study included 122 patients with histologically confirmed bladder cancer (23 were excluded because of lack of tobacco information) and 99 age- and sex-matched controls. Opium exposure data were collected from patient records. [The Working Group noted that the very small number of cases and controls exposed to opium but not tobacco, missing data from patient records, and poor statistical analysis performed with inappropriate reference categories made this a less informative study.]

Asgari et al. (2004) conducted a study between 1997 and 2000 in Tehran, Iran. This study included 52 men consecutively diagnosed with pathologically confirmed bladder cancer (case group) and 108 patients with benign prostatic hyperplasia (BPH; control group) who had undergone surgery. [The Working Group noted that BPH has been suggested as a risk factor for bladder cancer. Therefore, the study may suffer from differential misclassification that could have an impact on the risk estimates in both directions.] Data on opium addiction were collected from patients' records. [The Working Group noted that the data on opium exposure were not comprehensive, potentially leading to exposure misclassification.] The unadjusted odds ratio for individuals exposed to both opium and tobacco was 6.2 (95% CI, 2.04–18.7). [The Working Group noted, however, that the results compared users of both cigarettes and opium with a combined group consisting of users of neither, users of just opium, and users of just cigarettes. Using data reported in the paper, compared with those who used neither opium nor cigarettes, the Working Group calculated that the unadjusted odds ratio for cigarette smoking alone was 6.6 (95% CI, 3.0–14.9) and that the odds ratio for both opium use and cigarette smoking was 13.3 (95% CI, 4.1–43.2); however, an odds ratio for opium use alone could not be determined because practically all opium users were also cigarette smokers.] Kamangar et al. (2014) reported an odds ratio for opium use, adjusted only for cigarette smoking, of 2.6 (95% CI, 0.8–8.5) based on data provided in Asgari et al. (2004). [The Working Group noted that although this was one of the first case–control studies published on the risk of bladder cancer associated with opium exposure, the small sample size, poor characterization of exposure to

opium, and poorly conducted statistical analyses made it less informative.]

Hosseini et al. (2010) carried out a hospital-based case–control study between 2004 and 2008 in Tehran, Iran, including 179 consecutive newly diagnosed patients with histologically confirmed transitional cell carcinoma of the bladder and 179 cancer-free controls, matched to cases by age, sex, geographical origin, ethnicity, and smoking status. Controls were recruited from patients under investigation for BPH (86% in men) or urinary symptoms (84% in women). Multivariable logistic regression analysis including smoking history indicated that opiate use was associated with an increased risk of bladder cancer (OR, 4.60; 95% CI, 3.53–6.28). [The Working Group noted that BPH has been suggested as a risk factor for bladder cancer, hence the inclusion of such patients in the control group could result in an underestimation of the risk. However, while urinary symptoms in women may relate to urinary tract infections, also suggested to be a potential risk factor for bladder cancer, it has been suggested that the risk of bladder cancer is inversed when such infections are treated. This could result in overestimation of the risk of bladder cancer associated with opium use.] Participants were also assessed for dependence on and abuse of 13 substance types using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Over 60% of those diagnosed as "addicts" were using raw opium, with the remainder using heroin (25%) or codeine (13%). The adjusted odds ratio for raw opium use was 4.16 (95% CI, 2.62–6.34). Results for routes of administration were similarly elevated. [The Working Group noted, however, that the different opiate types (opium, codeine, and heroin) were combined for these analyses and, as such, may be less informative for the evaluation of opium as an independent agent.] Stratified analyses showed that odds ratios for opiate use were slightly higher among men, older (aged > 60 years) participants, and heavy smokers, and were also higher for muscle-invasive bladder cancer and high-grade tumours. [However, again the Working Group noted that the different opiate types were combined for all these stratified analyses and, as such, may be less informative for the evaluation of opium.]

Shakhssalim et al. (2010) conducted a population-based case–control study in 2006 in several provinces of Iran. The study included 692 patients with histologically confirmed transitional cell carcinoma of the bladder and 692 healthy controls who were neighbours of cases, individually matched on sex and age. Cases were identified from the Iranian cancer registry and were alive at study entry [The Working Group noted that by including only patients who were alive, the study may suffer from survival bias. No information on patient survival at entry was provided.] The participation rate was 80%. Opium exposure data were collected during face-to-face interviews using a structured questionnaire. A tobacco smoking-adjusted odds ratio of 2.57 (95% CI, 1.55–4.26) for opium consumption was reported, in addition to non-adjusted odds ratios of 2.88 (95% CI, 1.84–4.50) for current opium consumption and 3.50 (95% CI, 2.41–8.41) for history of opium consumption. [The Working Group noted that the results were difficult to interpret because of the high percentage of cases (> 80%) with missing information on opium exposure compared with 4% of controls. Also, a large proportion of information was provided by proxy responders, and it is unclear whether the variable "history of opium consumption" refers to former users or ever-users.]

Akbari et al. (2015) carried out a population-based case–control study between 2012 and 2013 in Shiraz, southern Iran. The study included 198 patients with bladder cancer, identified mainly on the basis of the results of pathology assessment, and 396 healthy controls matched for age, sex, and residence setting. Opium exposure assessment was done through the structured and validated GCSQ. For analysis, exposure

was characterized in detail including intensity (nokhods per day), duration, cumulative exposure, route of exposure, and type of opium. [The Working Group noted that while the authors stated that the history of opium consumption before cancer diagnosis was obtained to minimize the chances of reverse causation, the lack of a well-defined cut-off period may still have hampered this objective being achieved because opium use to relieve cancer pain could not be excluded.] The study estimated a multivariable-adjusted (including tobacco) odds ratio in opium ever-users of 3.9 (95% CI, 1.3–12.0) for bladder cancer. An exposure–response relationship was reported with an odds ratio of 4.9 (95% CI, 1.1–21.9) for the highest (above the median) consumption category compared with non-use. The duration of consumption also showed an exposure–response relationship with an odds ratio of 6.0 (95% CI, 1.1–34.7) for the longest duration of consumption (above the median). [The Working Group noted that the medians for duration and consumption were not reported in the paper.]

Aliramaji et al. (2015) conducted a hospital-based case–control study between 2001 and 2012 in Babol, northern Iran. The study included 236 patients with histologically confirmed bladder cancer (transitional cell carcinoma, 96%) who underwent surgery; 61 cases (26%) were excluded due to incomplete data. [The Working Group noted that further information on the characteristics of the excluded cases without bladder cancer morphology was not provided.] Controls (n = 175) were sex- and age-matched participants selected from patients with gallbladder stones who sought treatment with endoscopic retrograde cholangiopancreatography in the same hospital. Opium exposure data were collected from the patients' files and telephone calls. [The Working Group noted that opium exposure was poorly defined and its assessment not comprehensive, and that timing of opium use relative to outcome occurrence was not considered. Furthermore, the timing of exposure data in relation to case identification was unclear. No data were included on the intensity, type, or method of opium exposure.] Opium exposure (consumption for > 1 year) was more prevalent among cases (33%) than controls (15%). Using data reported in the paper, compared with those who used neither opium nor cigarettes, the odds ratio for opium use alone was [4.1 (95% CI, 1.6–10.6)], the odds ratio for cigarette smoking alone was [9.3 (95% CI, 4.5–19.0)], and the odds ratio for both opium use and cigarette smoking was [4.5 (95% CI, 2.5–8.2)]. Duration of opium use was positively associated (P = 0.0001) with risk of bladder cancer. [The Working Group noted that this risk was calculated using the numbers displayed in Fig. 1 of the published study and that, on the basis of the previously mentioned limitations, this study was less informative for the evaluation.]

Ghadimi et al. (2015) conducted a hospital-based case–control study in Kurdistan Province, Iran, during 3 years. [The Working Group noted that the exact years of the study were not mentioned in the paper but inferred that the study was conducted in about 2012–2014.] The study included 152 patients with histologically confirmed bladder cancer and 152 hospital-based, cancer-free controls who were frequency-matched to cases on the basis of age, sex, and place of residency. [The Working Group noted that the lack of information on the disease categories relating to the controls did not allow assessment of the appropriateness of this group, leading to possible exposure misclassification. Selection of hospital controls is always a limitation in studies of this kind, especially if some of the conditions leading to hospitalization are indeed related to opium use and/or tobacco use, and this would bias results towards the null.] Opium exposure status was assessed retrospectively using a structured questionnaire. [The Working Group noted that opium exposure was poorly defined and characterized in this study,

and that no information had been collected regarding the duration of exposure or the amount or type of opium consumed; therefore, non-differential misclassification of exposure could result. Information on route of exposure was collected, with all participants reported to consume opium by smoking.] A tobacco smoking-adjusted logistic regression model estimated an odds ratio of 4.96 (95% CI, 1.07–22.92) for the association between opium exposure and bladder cancer. [The Working Group noted the nearly 5-times increased risk for opium exposure and bladder cancer; however, due to the large confidence interval resulting from the small numbers of exposed cases and controls, it was deemed less informative for the evaluation.]

Lotfi et al. (2016) conducted a population-based case–control study between 2009 and 2013 in Yazd Province, Iran. The study included 200 patients with pathologically confirmed bladder cancer and 200 healthy controls, matched on age and sex, who were neighbours of patients. Opium exposure data were collected during interviews using a structured questionnaire. The odds ratio for opium history (3.01; 95% CI, 1.73–5.23) was obtained using logistic regression analysis but was not adjusted for cigarette smoking. [The Working Group noted that because the results were not adjusted for tobacco smoking, residual confounding may be present, which would partly explain the reported increased risk of bladder cancer. Therefore, the results were less informative for the evaluation.]

2.3 Cancers of the respiratory tract

See Table 2.3.

2.3.1 Cancer of the larynx

A cohort study (Sheikh et al., 2020) and six case–control studies (Khoo, 1981; Mousavi et al., 2003; Bakhshaee et al., 2017; Berjis et al., 2018; Alizadeh et al., 2020; Mohebbi et al., 2020) have investigated the association between opium use and incidence of laryngeal cancer. In addition, the cohort study also investigated laryngeal cancer mortality (Rahmati et al., 2017). [The Working Group considered that the cross-sectional study by Dabirmoghaddam et al. (2016) was uninformative for the evaluation and it was not considered further.]

(a) Cohort study

Sheikh et al. (2020) investigated the incidence of cancer of the larynx in the GCS, the methods of which have been described previously. There were 38 cases of laryngeal cancer, of which almost 80% were histologically confirmed. Adjusting for a range of factors including cigarette smoking (status and pack-years), the study reported a hazard ratio of 2.53 (95% CI, 1.21–5.29) in opium ever-users compared with never-users for cancer of the larynx, with a positive exposure–response trend (P = 0.0004) for increasing quartiles of consumption (HR, 3.34; 95% CI, 1.33–8.34; in the highest consumption quartile). Sex-stratified analysis yielded evidence of increased risk associated with ever-consumption of opium in men (HR, 2.24; 95% CI, 1.03–4.86) while only 5 cases of cancer of the larynx were reported in women (HR, 6.09; 95% CI, 0.67–54.82). The majority of opium users smoked opium (HR, 2.54; 95% CI, 1.14–5.68; for ever-smoking of opium) and consumed raw opium (*teriak*) (HR, 2.38; 95% CI, 1.10–5.12; for ever-consumption of *teriak*), and strong positive associations were observed. However, elevated hazard ratios were also observed for ingesting opium (all forms combined) as well as consuming refined opium. There was also some evidence for an interaction between opium consumption and tobacco use, although the multiplicative interaction term was not significant and results were based on small numbers (n = 38) of cases of laryngeal cancer. Risks for laryngeal cancer were found to be consistently elevated when excluding the first 2 years of follow-up and in the

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory 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
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from both rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 38 laryngeal (30 histologically confirmed) and 116 lung (76 histologically confirmed) cancers Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Larynx, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration of exposure, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: respiratory tract (154 cases) included lung cancer (116 cases) and laryngeal cancer (38 cases). *Strengths*: prospective design; large sample size, extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and deaths that occurred during the first 2 yr of follow-up.
			Never	15	1		
			Ever	23	2.53 (1.21–5.29)		
		Larynx, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.24 (1.03–4.86)		
		Larynx, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	6.09 (0.67–54.82)		
		Larynx, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.11 (0.24–5.01)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.55 (0.87–7.42)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Larynx, incidence (cont.)	3rd quartile (21.1–60 nokhod-years)	NR	2.98 (1.08–8.22)		*Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			4th quartile (> 60 nokhod-years)	NR	3.34 (1.33–8.34)		
			Trend-test *P* value, 0.0004				
		Larynx, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	6	1		
			Used opium but not tobacco	4	4.85 (1.33–17.62)		
			Used tobacco but not opium	9	8.65 (2.86–27.84)		
			Used both opium and tobacco	19	17.75 (6.06–51.94)		
		Larynx, incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			Only by smoking	14	2.54 (1.14–5.68)		
			Only by ingesting	7	2.48 (0.93–6.62)		
			Both routes	2	2.61 (0.55–12.41)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Larynx, incidence	Opium type (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			Raw opium (*teriak*)	18	2.38 (1.10–5.12)		
			Refined opium (*shireh*)	3	3.40 (0.92–12.55)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	0	–		
			Combination of the above	2	3.63 (0.77–17.15)		
		Larynx, incidence	Opium use, excluding the first 2 yr of follow-up (HR):				
			Never	15	1		
			Ever	22	2.38 (1.12–5.03)		
		Lung, incidence	Opium use (HR):				
			Never	59	1		
			Ever	57	2.21 (1.44–3.39)		
		Lung, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.37 (1.45–3.72)		
		Lung, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.60 (0.48–5.38)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Lung, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	59	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.15 (0.49–2.73)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.34 (1.23–4.43)		
			3rd quartile (21.1–60 nokhod-years)	NR	2.04 (1.05–3.95)		
			4th quartile (> 60 nokhod-years)	NR	3.19 (1.85–5.50)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	41	1		
			Used opium but not tobacco	8	1.50 (0.69–3.25)		
			Used tobacco but not opium	18	2.56 (1.38–4.76)		
			Used both opium and tobacco	49	7.34 (4.43–12.13)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Lung, incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	59	1		
			Only by smoking	30	1.90 (1.17–3.10)		
			Only by ingesting	20	2.66 (1.51–4.68)		
			Both routes	7	3.27 (1.40–4.64)		
		Lung, incidence	Opium type (HR):				
			Never used opium	59	1		
			Raw opium (*teriak*)	48	2.19 (1.41–3.4)		
			Refined opium (*shireh*)	3	1.25 (0.38–4.12)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	1	109.28 (13.98–853.93)		
			Combination of the above	5	3.05 (1.16–7.99)		
		Lung, incidence	Opium use, excluding the first 2 yr of follow-up (HR):				
			Never	52	1		
			Ever	44	1.96 (1.22–3.14)		
		Respiratory tract, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	74	1		
			Ever	80	2.28 (1.58–3.30)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Respiratory tract, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.30 (1.54–3.44)		
		Respiratory tract, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	2.08 (0.74–5.83)		
		Respiratory tract, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	74	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.14 (0.54–2.40)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.38 (1.37–4.11)		
			3rd quartile (21.1–60 nokhod-years)	NR	2.26 (1.30–3.92)		
			4th quartile (> 60 nokhod-years)	NR	3.22 (2.02–5.14)		
			Trend-test *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Sheikh et al. (2020) (cont.)		Respiratory tract, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	47	1		
			Used opium but not tobacco	12	1.94 (1.02–3.71)		
			Used tobacco but not opium	27	3.35 (1.96–5.72)		
			Used both opium and tobacco	68	8.71 (5.56–13.66)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Rahmati et al. (2017) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, through June 2015 Cohort	GCS: a sample of 50 045 healthy men and women from Golestan Province of Iran aged 40–75 yr; urban dwellers were selected randomly from five areas of Gonbad City by systematic clustering, while all eligible residents of villages in the study catchment area were invited to participate Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Larynx, mortality Larynx, mortality Lung, mortality Lung, mortality Respiratory tract, mortality (all were cancers of lung or larynx)	Opium use (HR): Never Ever Opium use > 10 yr (HR): Never used opium Ever Opium use (HR): Never Ever Opium use > 10 yr (HR): Never used opium Ever Opium use (HR): Never Former Current	 NR NR NR NR NR NR NR NR 42 5 38	 1 3.46 (0.99–12.07) 1 4.16 (1.10–15.74) 1 1.73 (0.99–3.03) 1 2.42 (1.32–4.46) 1 1.95 (0.73–5.16) 2.11 (1.25–3.55)	Age, sex, residence (urban/rural), education, marital status, drinking alcohol, and cumulative use of any type of tobacco (pack-years for cigarette and amount × duration of use for hookah and nass)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: respiratory tract (85 deaths) included lung cancer (70 deaths) and laryngeal cancer (15 deaths). *Strengths*: prospective design, large sample size, extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding deaths that occurred during the first 2 yr of follow-up and excluding subjects who had used opium for < 10 yr.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Rahmati et al. (2017) (cont.)		Respiratory tract, mortality (all were cancers of lung or larynx)	Duration of opium use (HR):				*Limitations*: small number of deaths; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			Never	42	1		
			Former	5	2.01 (0.75–5.31)		
			1st quintile (≤ 3 yr)	3	1.11 (0.34–3.66)		
			2nd quintile (4–7 yr)	2	0.73 (0.17–3.08)		
			3rd quintile (8–12 yr)	5	1.77 (0.67–4.66)		
			4th quintile (13–20 yr)	10	2.58 (1.22–5.44)		
			5th quintile (> 20 yr)	18	3.01 (1.55–5.81)		
			Trend-test *P* value, < 0.001				
		Respiratory tract, mortality (all were cancers of lung or larynx)	Cumulative opium use (HR):				
			Never	42	1		
			Former	5	1.99 (0.75–5.27)		
			1st quintile (≤ 1148 nokhod-days)	2	0.73 (0.17–3.09)		
			2nd quintile 1149–4383 nokhod-days)	5	1.64 (0.63–4.28)		
			3rd quintile (4384–12 054 nokhod-days)	6	1.92 (0.78–4.68)		
			4th quintile (12 055–30 681 nokhod-days)	9	2.38 (1.09–5.18)		
			5th quintile (> 30 682 nokhod-days)	16	2.95 (1.48–5.88)		
			Trend-test *P* value, < 0.001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Rahmati et al. (2017) (cont.)		Respiratory tract, mortality (all were cancers of lung or larynx)	Type of opium product used (HR):				
			Never used opium	42	1		
			Teriak only	37	2.01 (1.19–3.35)		
			Shireh only	2	1.06 (0.25–4.53)		
			Combinations	4	3.06 (1.02–9.18)		
		Respiratory tract, mortality (all were cancers of lung or larynx)	Route of opium use (HR):				
			Never used opium	42	1		
			Smoking	21	1.69 (0.94–3.03)		
			Ingestion	17	2.29 (1.21–4.36)		
			Both	5	2.99 (1.11–8.06)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
MacLennan et al. (1977) Singapore 1972–1973 Case–control	Cases: 233 patients (147 men; 86 women) with provisional hospital diagnosis of lung cancer Controls: 300 (134 men; 166 women); hospital controls from the same wards, matched on sex, age (5 yr), and dialect; patients with smoking-related diagnosis were excluded (chronic bronchitis, emphysema, myocardial infarction, oral cancer, pharyngeal cancer, laryngeal cancer, and cancers of oesophagus, pancreas, and bladder)	Lung, incidence	Opium smoking, men (OR): Never smoked Ever smoked	 84 63	 1 [2.39 (1.43–4.00)]	Age, dialect	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. The consistency of exposure ascertainment was assessed to some degree by comparing how questions were asked in cases and controls. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: too few opium users who were women to calculate OR.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopa-thology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLennan et al. (1977) (cont.)	Exposure assessment method: questionnaire; opium only investigated as "ever smoked" in interviews with no information on how systematic these were; no information on any metrics of exposure.						*Limitations*: provisional diagnosis of lung cancer includes any type of cancer (including adenocarcinoma and SCC); there is concern about risks of different types of lung cancers and some cases could have had tuberculosis; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Khoo (1981) China, Hong Kong Special Administrative Region 1970–1977 Case–control	Cases: 123 patients with SCC of the larynx, who were referred to the radiotherapy division in Queen Mary Hospital for primary radiotherapy from January 1970 to December 1977 Controls: NR; those with other cancers not associated with smoking or drinking alcohol, matched for sex and age Exposure assessment method: questionnaire; unclear how information was obtained; no definition of opium exposure, opium and/or heroin addiction used	Larynx (SCC), incidence	Opium and/or heroin addiction, non-drinking cigarette smokers (OR): Never addicted to opium Ever addicted to opium	 42 27	 1 9.3 (2.1–42.3)	Sex, age	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. Exposure assessment unclear. Heroin addiction included as exposed. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: the OR was not calculated by the study's authors but by Kamangar et al. (2014) for their systematic review of epidemiological studies associating opium use with cancer. *Limitations*: no definition of "other cancers", which form the "control" group.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Mousavi et al. (2003) Kerman Province, Iran (Islamic Republic of) 1996–2002 Case–control	Cases: 98 pathologically confirmed laryngeal SCCs, referred by a Kerman University of Medical Sciences-affiliated hospital in Kerman Province in the south of the Islamic Republic of Iran Controls: sex- and age-matched patients (312 patients in all) who were admitted to the otolaryngology department in the same period; patients with other cancers of the head and neck were excluded because of the possible effect of opium	Larynx (SCC), incidence	Opium consumption for ≥ 5 yr (OR): Never Ever	 23 75	 1 10.74 (5.76–20.02)	Age, sex, cigarette smoking status (ever/ never)	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Not a comprehensive approach to exposure assessment (no intensity, duration, cumulative exposure, temporality, or type of exposure). Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: pathologically confirmed cases; large number of exposed cases.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Mousavi et al. (2003) (cont.)	Exposure assessment method: questionnaire; exposure: opium-dependent based on DSM-IV opium dependency and opium consumption for ≥ 5 yr; types of consumption and route of ingestion not recorded						*Limitations*: selection bias possible with controls selected from an otolaryngology department; these patients may be less likely to use opium and cigarettes than the general population; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Masjedi et al. (2013) Tehran, Iran (Islamic Republic of) 2002–2005 Case–control	Cases: 242 histologically and cytologically confirmed cases of primary lung cancer Controls: 484 (242 hospital controls and 242 visiting healthy controls) matched on age (± 3 yr), sex, and place of residence Exposure assessment method: questionnaire; opium addiction defined as consumption of opium at least once per day for minimum of 6 mo; study considered smoked and ingested opium via assessment of ever vs never use, frequency of use based on ≤ or > median per day, duration of use, cumulative use, age at start of use, and method of exposure	Lung, incidence	Opium smoking, men (OR): Never Ever	 145 33	 1 3.1 (1.2–8.1)	Age, residence, ethnicity (Fars/Azeri/Kurd/Lur/other), education (ordinal: nil, < 5 yr, 5–8 yr, 8–12 yr, > 12 yr), cigarette smoking pack-years	*Exposure assessment critique*: Opium exposure well defined and well characterized. Table 3 mentions smoked "opiate"; not clear if this instead means opium (therefore, not clear whether opiates also included in the exposure here). Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: too few opium users who were women to calculate OR; the authors reported that a dose–response association was present, but the data provided in the tables of the article did not show such a pattern. *Strengths*: histologically and cytologically confirmed primary lung cancer; high participation rate (91%); both population and hospital controls; different metrics of exposure were investigated.
		Lung, incidence	Opium smoking, men (OR): Never Ever	 145 33	 1 7.5 (3.4–16.7)	Age, residence, ethnicity (Fars/Azeri/Kurd/Lur/other), education (ordinal: nil, < 5 yr, 5–8 yr, 8–12 yr, > 12 yr)	
		Lung, incidence	Frequency of opium smoking, men (OR): Never ≤ Median among controls (twice per day) > Median among controls Trend-test *P* value, < 0.0001	 145 30 3	 1 7.7 (3.4–17.4) 5.3 (0.8–36.8)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Masjedi et al. (2013) (cont.)		Lung. incidence	Cumulative opium smoking, men (OR):				*Limitations*: only one set of analyses were adjusted for cigarette smoking.
			Never	145	1		
			≤ Median among controls (36.5 nokhod-years)	18	9.6 (3.5–26.8)		
			> Median among controls	15	6.9 (2.3–20.4)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Opium ingestion, men (OR):				
			Never	142	1		
			Ever	36	2.2 (1.3–3.8)		
		Lung, incidence	Frequency of opium ingestion, men (OR):				
			Never used	142	1		
			≤ Median (once per day)	13	1.5 (0.7–3.4)		
			> Median	14	17.5 (3.4–89.8)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Cumulative opium ingestion, men (OR):				
			Never used	142	1		
			≤ Median among controls (23 nokhod-years)	13	3.8 (1.5–9.9)		
			> Median among controls	14	2.5 (1.01–3.2)		
			Trend-test *P* value, 0.003				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Masjedi et al. (2013) (cont.)		Lung, incidence	Age started opium use, men (OR):				
			Never	142	1		
			≤ Median among controls (35 yr)	19	2.9 (1.3–6.5)		
			> Median among controls	16	2.4 (1.1–5.1)		
			Trend-test *P* value, 0.003				
		Lung, incidence	Route of opium use, men (OR):				
			Never used	127	1		
			Ingested only	18	1.4 (0.7–2.7)		
			Smoked only	15	5.4 (2.1–14)		
			Both	18	13.7 (4.2–44)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Bakhshaee et al. (2017) Mashhad, Iran (Islamic Republic of) 2008–2010 Case–control	Cases: 58 cases of laryngeal cancer from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences Controls: 27 healthy hospital-based controls from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences, with no evidence of head and neck or oesophageal malignancies, matched for age Exposure assessment method: questionnaire; interview collected data on opium use, defined as "snuffing"	Larynx, incidence	Opium dependency (OR): Never Ever	 NR NR	 1 6.06 (1.10–33.23)	Smoking, age, sex	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Intensity, duration, and type of opium exposure not collected. Only "snuffing" (presumed to be smoking) use is described. Not clear how systematic the interview was. Limited details, limited exposure information. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments:* the number of controls in abstract was 27 but in methods was 28. *Strengths*: pathologically confirmed cases.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopa-thology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bakhshaee et al. (2017) (cont.)							*Limitations*: matching was only on age (without defined difference number) and not on sex; small number of controls and unclear how they were selected; controls described as "healthy" but were selected from otolaryngology and radiation oncology departments; only opium consumption by snuffing was assessed; unclear whether primary exposure was opium use or opium dependency.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Berjis et al. (2018) Isfahan, Iran (Islamic Republic of) 2015 Case–control	Cases: 180 biopsy-confirmed SCCs of the larynx Controls: 180; people aged > 40 yr referred to hospital clinics Exposure assessment method: questionnaire; no information on how opium "drug addicted" was defined; three sources of data collection but not clear how systematic	Larynx (SCC), incidence	Drug (opium) addiction (OR): Never Ever	 79 101	 1 18.6 (7.9–43.6)	Tobacco	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. No evidence of questionnaire validation. No information on the data collection instrument. Information regarding the intensity and duration of opium consumption not collected. No dose–response assessment. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: large number of exposed cases; cases were pathologically confirmed. *Limitations*: details on the selection method, including the clinics from which controls were selected, were unclear, with potential for selection bias; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Alizadeh et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 (and earlier) Case–control	Cases: 140 patients with head and neck cancers (nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, or salivary gland) with pathological information in the cancer registry of Kerman University of Medical Sciences Controls: 280 neighbourhood-based controls; individually matched on age (± 5 yr), sex, and neighbourhood (nearest and first neighbours to the right of the case's home who met the inclusion criteria)	Larynx, incidence	Opium use (OR):			Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), education (illiterate, elementary/ middle school, high school/high school diploma, or above), cigarette smoking, alcohol drinking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Comprehensive exposure assessment (intensity, duration, cumulative exposure, type, and mode). Temporality not specified; opium use in the 2 yr before cancer diagnosis excluded to minimize reverse causation. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. Only raw opium and opium sap used. *Strengths*: cases confirmed pathologically; used population-based neighbour controls; showed a dose–response relationship with opium use.
			Never	23	1		
			Ever	88	11.98 (5.05–28.39)		
		Larynx, incidence	Amount of daily opium use (OR):				
			Never used	23	1		
			≤ Median (among controls)	41	11.17 (4.33–28.83)		
			> Median (among controls)	47	12.82 (4.96–33.11)		
		Larynx, incidence	Duration of opium use (OR):				
			Never used	23	1		
			≤ Median (among controls)	57	7.05 (3.17–15.67)		
			> Median (among controls)	31	13.68 (5.12–36.56)		
		Larynx, incidence	Cumulative use of opium (OR):				
			Never used	23	1		
			≤ Median (among controls)	44	9.46 (3.97–22.52)		
			> Median (among controls)	44	11.17 (4.44–28.09)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Alizadeh et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; trained interviewers; conducted at participants homes; comfortable and friendly environment; used median use in controls to define non-use, and low and high use						*Limitations*: retrospective study (sampling began by enrolling all diagnosed cases from 2017 and then enrolling cases from previous years); possible recall bias, most of the cases (60%) but fewer of the controls (30%) were illiterate or had only elementary education; the frequency of non-response was 19.5%; timing of opium use relative to outcome unclear and uncertainty about reverse causation; small sample size.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Mohebbi et al. (2020) Iran (Islamic Republic of) April 2016 to April 2019 Case–control	Cases: 663 (327 larynx) incident cases of head and neck SCC referred to cancer care centres in 10 provinces (IROPICAN study) Controls: 3065; ≥ 4 controls per case, frequency-matched on age, sex, and place of residence, selected from hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or persons who visited the hospital for any reason other than receiving treatment concurrently	Larynx (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome was considered. Multiple exposure metrics (regular/non-regular use, average intensity as daily amount of use, duration in years, type of opium used, and route of use). Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging.
			Non-user	96	1		
			Regular user	231	6.55 (4.69–9.13)		
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≤ 11 yr)	35	1		
			2nd tertile (12–23 yr)	80	1.91 (1.10–3.31)		
			3rd tertile (≥ 24 yr)	116	2.71 (1.56–4.68)		
			Trend-test *P* value, < 0.0001				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≤ 3.6 gram-years)	26	1		
			2nd tertile (3.7–24.4 gram-years)	77	2.32 (1.28–4.20)		
			3rd tertile (≥ 24.5 gram-years)	128	2.29 (1.26–4.16)		
			Trend-test *P* value, 0.01				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Mohebbi et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Larynx (SCC), incidence	Frequency-years of opium use (OR):				*Strengths*: all cases confirmed pathologically (SCC); a multicentre study with large numbers of cases and controls; 4 controls for each case, frequency-matched on age, sex, and place of residence; opium use disregarded for those who started using opium in the 3 yr before cancer diagnosis to reduce reverse causation; evaluated dose–response relationship between opium use and larynx cancer; use of hospital visitor controls; to minimize interviewer bias, a comprehensive protocol of interviewer training, data collection, and monthly review of the protocols was used; confounders were strictly controlled by limiting the analyses of head and neck cancers to never tobacco smokers. *Limitations*: potential information bias; centre heterogeneity.
			1st tertile (≤ 8 frequency-years)	14	1		
			2nd tertile (8.1–22 frequency-years)	43	3.38 (1.63–6.99)		
			3rd tertile (≥ 23 frequency-years)	174	9.05 (4.62–17.71)		
			Trend-test *P* value, < 0.0001				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	44	1		
			2nd tertile (0.5–2 g/day)	83	1.27 (0.74–2.16)		
			3rd tertile (≥ 2 g/day)	104	0.92 (0.53–1.60)		
			Trend-test *P* value, 0.62				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Type of opium used (OR):				
			Non-user	96	1		
			Crude opium (*teriak*)	182	5.77 (4.09–8.15)		
			Opium juice (*shireh*)	49	12.69 (7.25–22.22)		
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Route of opium use (OR):				
			Non-user	96	1		
			Only smoking	125	4.28 (2.98–6.14)		
			Only oral ingestion	25	17.17 (8.44–34.91)		
			Both routes	81	25.11 (14.55–43.33)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Naghibzadeh-Tahami et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 Case–control	Cases: 140 patients with pathologically confirmed lung cancer in the Kerman University of Medical Sciences cancer registry Controls: 280; 2 healthy controls per case, individually matched on age (± 5 yr), sex, and neighbourhood Exposure assessment method: questionnaire; used the GCSQ, systematic retrospective data collection; validated questionnaire assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure	Lung, incidence	Opium use (OR): Never Ever	 57 83	 1 5.95 (1.87–18.92)	Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), cigarette smoking (non-user/low user/high user), alcohol (non-user/low user/high user), education (illiterate, elementary/middle school, high school/high school diploma, or above)	*Exposure assessment critique*: Opium exposure not well defined but well characterized. Timing of opium use relative to outcome was considered. Risks by ever-/never-use, average intensity as daily amount of use, and duration in years were considered. Risks by type of opium used and by route of using opium were not considered. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging *Other comments*: interaction *P* values for cigarette smoking (ever-use) with opium (and derivatives) were 0.38 and 0.14 for ever-use and cumulative dose, respectively.
		Lung, incidence	Opium use, never cigarette smokers (OR): Never Ever	 30 29	 1 6.50 (2.89–14.64)	Age, sex, neighbourhood	
		Lung, incidence	Amount of daily opium use (OR): Never used ≤ Median among controls (4.5 g/day) > Median among controls (4.5 g/day)	 57 36 47	 1 3.81 (1.13–12.77) 9.36 (2.05–42.72)	Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), cigarette smoking (non-user/low user/high user), alcohol (non-user/low user/high user), education (illiterate, elementary/middle school, high school/high school diploma, or above)	

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (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
Naghibzadeh-Tahami et al. (2020) (cont.)		Lung, incidence	Duration of opium use (OR):				*Strengths*: cases confirmed pathologically; use of population-based neighbourhood controls; evaluated exposure–response association between opium use and lung cancer; disregarded opium use in those who started in the 2 yr before diagnosis to address reverse causation. *Limitations*: pathological subtypes of the cases were not clear (the risk factors of adenocarcinoma, SCC, and metastatic form may be different); possible recall bias, most of the cases but about 1/4 of the controls were illiterate or had just elementary education; the frequency of non-response was 19.5%; timing of opium use relative to outcome unclear and uncertainty about reverse causation; imprecise estimates due to small sample size.
			Never used	57	1		
			≤ Median among controls (20 yr)	41	3.47 (1.13–10.62)		
			> Median among controls (20 yr)	42	5.50 (1.32–22.91)		
		Lung, incidence	Cumulative opium use (OR):				
			Never used	57	1		
			≤ Median among controls (87.5 gram-years)	46	3.95 (1.29–12.12)		
			> Median among controls (87.5 gram-years)	37	4.79 (0.88–26.08)		
		Lung, incidence	Age at start of opium use (OR):				
			Never used	57	1		
			> Median among controls (41 yr)	22	4.71 (1.38–16.08)		
			≤ Median among controls (41 yr)	61	8.64 (1.90–39.18)		

–, risk estimate could not be calculated; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; HR, hazard ratio; IROPICAN, Iranian Study of Opium and Cancer; mo, month; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

subgroup of tobacco never-users (HR, 4.85; 95% CI, 1.33–17.62; 4 exposed cases). However, many of these analyses were based on small numbers of exposed cases and the estimates were imprecise.

Analyses of laryngeal cancer mortality in the GCS have reported similar findings (Rahmati et al., 2017). Opium use for at least 6 months was associated with higher risk of laryngeal cancer mortality overall (HR, 3.46; 95% CI, 0.99–12.07; based on 15 laryngeal cancer deaths), compared with never-use, and in sensitivity analyses that excluded users with less than 10 years of use (HR, 4.16; 95% CI, 1.10–15.74 based on 13 laryngeal cancer deaths) (Rahmati et al., 2017). [The Working Group noted that limitations of the study included the small numbers of deaths, and possibly also some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.]

(b) Case–control studies

Khoo (1981) conducted a hospital-based case–control study in Hong Kong Special Administrative Region, China. The cases were 123 patients with SCC of the larynx, who were referred to the radiotherapy division in Queen Mary Hospital for primary radiotherapy from January 1970 to December 1977. Controls were patients with other cancers (diagnosed in the same department, but not associated with smoking or drinking alcohol), matched on sex and age. The odds ratio of 9.3 (95% CI, 2.1–42.3) for opium and/or heroin addiction among smokers was not calculated by these authors but by Kamangar et al. (2014) in their systematic review of epidemiological studies associating opium use with cancer. [The Working Group noted several limitations of this study. Opium exposure in this study was poorly defined, its assessment was not comprehensive, and opium users included an unknown proportion of heroin users. In addition, information on recent versus distant use of opium was not collected and there was the potential for reverse causation in patients who began using opium to control pain associated with cancer. Furthermore, there was potential for control selection bias, given that the "other cancers" experienced by the controls were undefined and may have been associated with opium exposure, which would have biased results towards the null.]

In a study by Mousavi et al. (2003), 98 pathologically confirmed cases of laryngeal SCC, referred by a Kerman University of Medical Sciences-affiliated hospital in Kerman Province, southern Iran, were compared with 312 patient controls (sex- and age-matched) who were admitted to the otolaryngology department during the same period as the cases. [The Working Group noted that selection bias was possible since these controls would likely have already been experiencing functional disease to warrant admittance to the otolaryngology department and, as a result, may have been less likely to use opium and cigarettes than the general population, possibly resulting in a bias away from the null. However, bias towards the null may also have resulted if controls were protopathic opium users or if opium use induced other otolaryngological disease.] Opium dependency, as determined by the DSM-IV, Text Revision, was used as the opium exposure metric. A multivariable-adjusted odds ratio (including ever-smoking of tobacco) was calculated for ever having consumed opium for at least 5 years compared with never having done so (OR, 10.74; 95% CI, 5.76–20.02). [The Working Group considered that opium exposure was well-defined but that its assessment was not comprehensive. Information on recent versus distant use of opium was not collected, although the exposure criteria included using opium regularly for at least 5 years. The Working Group further noted that the exposure assessment approach was not comprehensive (e.g. no information on intensity, duration, cumulative exposure, temporality, type of opium, or route of exposure) and that the reference group could have included patients who used opium

for less than 5 years, possibly resulting in bias towards the null. The Working Group also noted difficulty in interpreting the odds ratio reported given a possible reporting error in the original manuscript that suggested an apparently high prevalence of opium consumption.]

In a case–control study conducted by Bakhshaee et al. (2017) in Mashhad, Iran, between 2008 and 2010, 58 cases of laryngeal cancer (pathology not mentioned) were compared with 27 or 28 controls. [The Working Group noted that the number of controls reported was different in the abstract compared with in the methods.] Matching was on age (without a defined difference number) but not on sex. [The Working Group noted that controls were described as "healthy" but were selected from otolaryngology and radiation oncology departments, which may have introduced selection bias.] Exposure information was collected by interview, with the metric being opium use (described as snuffing or inhalation) at least once per day for a minimum of 1 year. [The Working Group considered opium snuffing or inhalation, as mentioned in this paper, to be equivalent to opium smoking.] The tobacco smoking-adjusted odds ratio for opium consumption was 6.06 (95% CI, 1.10–33.23). [The Working Group noted that opium exposure was well-defined but that the assessment was not comprehensive. Timing of opium use relative to outcome was unclear, as was how systematic the interviews were.]

Berjis et al. (2018) compared 180 biopsy-confirmed cases of SCC of the larynx with 180 controls (people aged > 40 years referred to hospital clinics) in Isfahan, Iran, in 2015. Details regarding the selection method, including of the clinics from which controls were selected, how "drug addicted" was defined, and how data were collected were not provided. Information on recent versus distant use of opium was not collected. A highly elevated (yet imprecise) tobacco smoking-adjusted odds ratio of 18.6 (95% CI, 7.9–43.6) was calculated for drug (opium) addiction. [The Working Group noted that given the lack of information on study design, the potentials for selection, misclassification, and information bias were difficult to evaluate. There was potential for selection bias because the controls were selected from individuals who had been referred to the hospital and had undergone indirect laryngoscopy examination. The reason for referral may also have been related to opium use. The lack of a clear definition of "drug addicted" and the collection of non-systematic data across multiple sources (patient records, telephone interviews with patients, or telephone interview with family members), without a clear description of the collection parameters, may have contributed to misclassification and information bias. In addition, there was potential for bias if cases or controls began using opium due to disease symptoms. Other limitations included the fact that information on the intensity and duration of opium consumption was not collected, and that exposure–response associations were not provided.]

Alizadeh et al. (2020) conducted a case–control study in Kerman, Iran, in 2014–2017, that enrolled 140 patients with cancers of the head and neck (including 111 cases of cancer of the larynx) and included 280 healthy controls (matched for age, sex, and place of residence) (see also Section 2.5). Information about use of opium and its derivatives was collected using the validated GCSQ. Conditional logistic regression was used to investigate the relationships between variables. The use of opioids at least 2 years before cancer diagnosis, adjusted for a range of potential confounders including tobacco, was associated with an increased risk of cancer of the larynx (OR, 11.98; 95% CI, 5.05–28.39). The amount of daily opium use, duration of use, and cumulative use showed consistent evidence for increasing odds with increasing exposure (below- and above-median exposure in controls compared with never-users) for cancer of the larynx. [The Working Group considered the well-defined

opium exposure, pathologically confirmed cases, use of population-based neighbour controls, and evaluation of an exposure–response relationship with opium use to be strengths of the study. Limitations included the retrospective study design, potential recall bias, non-response frequency of 19.5%, uncertainty about reverse causation, and the small sample size.]

Mohebbi et al. (2020) conducted a multicentre case–control study within the IROPICAN study. They recruited 327 cases of cancer of the larynx and 3065 frequency-matched controls between 2016 and 2019. Regular opium use was associated with an increased risk of cancer of the larynx, with an odds ratio of 6.55 (95% CI, 4.69–9.13), adjusted for potential confounders including multiple forms of tobacco use. There were also strong positive trends observed with increasing tertiles of frequency, duration, and cumulative opium use. While associations between opium use and cancer of the larynx were not reported for tobacco never-smokers, the observed associations for cancers of the head and neck, nearly half of which were cancers of the larynx, were also strongly positive among tobacco never-smokers (including cigarette and water-pipe smoking). Risk estimates tended to be higher among those participants who ingested opium (HR, 17.17; 95% CI, 8.44–34.91) and those who consumed opium juice (*shireh*) (HR, 12.69; 95% CI, 7.25–22.22). However, positive hazard ratios were also observed for smoking opium as well as consuming raw opium (*teriak*). [Strengths of the study included all cases having been confirmed pathologically (as SCC), the large-scale multicentre design, opium use having been disregarded in those who started using opium 3 years before cancer diagnosis, and analysis among tobacco never-smokers. Limitations included information bias and centre heterogeneity.]

2.3.2 Cancer of the lung

One cohort study (Sheikh et al., 2020) and three case–control studies (MacLennan et al., 1977; Masjedi et al., 2013; Naghibzadeh-Tahami et al., 2020) investigated associations between opium use and lung cancer incidence. In addition, the cohort study also investigated lung cancer mortality (Khademi et al., 2012; Rahmati et al., 2017).

(a) Cohort study

Sheikh et al. (2020) investigated incidence of lung cancer in the GCS, the methods of which have been described previously (Sections 1.6 and 2.1.1). Of the 116 cases of lung cancer, 76 (65%) were histologically confirmed. Adjusting for a range of factors including cigarette smoking (status and pack-years), the study reported that ever-users of opium had an increased risk of lung cancer (HR, 2.21; 95% CI, 1.44–3.39) with an exposure–response trend ($P < 0.0001$) for increasing quartiles of cumulative consumption (HR, 3.19; 95% CI, 1.85–5.50; in the highest quartile). In sex-stratified analysis, results were stronger in men (HR, 2.37; 95% CI, 1.45–3.72) than in women (HR, 1.60; 95% CI, 0.48–5.38). Risks for lung cancer were found to be elevated in the subgroup of tobacco never-users; however, there was only a small number of exposed cases and the estimate was imprecise (HR, 1.50; 95% CI, 0.69–3.25; 8 exposed cases). The majority of opium users smoked opium (HR, 1.90; 95% CI, 1.17–3.10) and consumed raw opium (*teriak*) (HR, 2.19; 95% CI, 1.41–3.40), and strong positive associations were observed. There was also a strong positive association with ingestion of opium (HR, 2.66; 95% CI: 1.51–4.68). There was also some evidence for an association between opium and tobacco use, although the association was imprecise because of the small number of lung cancer cases. Most of the subgroup and sensitivity analyses for this site also reported elevated lung cancer risk; however, many of

these analyses were based on small numbers of exposed cases and the estimates were imprecise.

A mortality study within the GCS also reported that ever-consumption of opium (at least once a day for at least 6 months) (adjusted HR, 1.73; 95% CI, 0.99–3.03 on the basis of 70 lung cancer deaths) and long-term opium consumption (≥ 10 years) (adjusted HR, 2.42; 95% CI, 1.32–4.46 on the basis of 65 lung cancer deaths) were associated with lung cancer mortality (Rahmati et al., 2017). [The Working Group noted that a limitation of the study was that there may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.]

(b) Case–control studies

MacLennan et al. (1977) conducted the first case–control study that evaluated the association between opium use and lung cancer in Singapore (1972–1973). Initial selection of cases and controls for data collection was on the basis of a provisional diagnosis of lung cancer for cases and, for controls, non-smoking-related causes (as defined by the United States Public Health Service in 1964). Before analysis, all diagnoses were reviewed and several participants were reassigned, including 13 controls who, upon review, were found to have lung cancer. Only half of the cases were histologically confirmed, and the types of lung cancer (i.e. adenocarcinoma or SCC) could not be specified. The final analysis compared 233 cases (147 men, 86 women) with 300 hospital controls (134 men, 166 women) from the same wards (patients with smoking-related diagnoses were excluded: chronic bronchitis, emphysema, myocardial infarction, oral cancer, pharyngeal cancer, laryngeal cancer, and cancers of the oesophagus, pancreas, and urinary bladder), matched on sex, age (± 5 years), and dialect (MacLennan et al., 1977). Opium use was defined as "ever smoked". Information on recent versus long-ago use of opium was not collected. [The Working Group noted the potential for reverse causation in patients who began using opium to control pain associated with cancer, and also noted concern that any opium-related risks may differ for different subtypes of lung cancer.] Minimal results were reported, and no 95% confidence intervals were presented. An unadjusted odds ratio was calculated in men of 2.39 [95% CI, 1.43–4.00]. [The Working Group noted that the authors calculated the odds ratio but reported it as relative risk.]

Masjedi et al. (2013) conducted a case–control study in Tehran, Iran, in 2002–2005. Masjedi et al. (2013) is a more recent update of the study by Hosseini et al. (2009), so only the former study is discussed here. Masjedi et al. (2013) compared 242 histologically and cytologically confirmed primary lung cancers with 484 controls (hospital controls, excluding those with neoplasms and respiratory disease, 242; visiting healthy controls, 242), matched on age, sex, and place of residence. Opium addiction was defined as consumption of opium at least once per day for a minimum of 6 months. A detailed structured questionnaire, administered by a physician, was used to collect information on tobacco and opium use, including age use started and stopped, duration and frequency of use, and types of products used. Information was available on smoking, alcohol use, and other risk factors, but analyses were, in general, only adjusted for education and ethnicity. The odds ratio for opium smoking among men was reduced from 7.5 (95% CI, 3.4–16.7) to 3.1 (95% CI, 1.2–8.1) when the model was additionally adjusted for cigarette smoking (pack-years) (33 exposed cases). The study also presented results for mode of opium ingestion, duration and frequency of use, and types of products, including exposure–response trends, but these results were not adjusted for tobacco use. [The Working Group noted the potential for confounding by tobacco in studies of lung cancer and also that the data provided in the tables of the article did not always show a pattern to support a strong positive exposure–response trend.]

Naghibzadeh-Tahami et al. (2020) conducted a case–control study in Kerman, Iran, in 2014–2017. They enrolled 140 patients with lung cancer and 280 healthy controls matched on age, sex, and place of residence. Data were collected on four categories of opiates – raw opium (*teriak*), sap (*shireh*), burned opium (*sukhteh*), and heroin – using a structured questionnaire; however, no participants reported use of heroin or burned opium. The relation between the use of opium and lung cancer was evaluated using conditional logistic regression adjusted for a range of factors including tobacco smoking. Opium ever-use was associated with an increased risk of lung cancer (adjusted OR, 5.95; 95% CI, 1.87–18.92). Participants were divided into low- and high-use groups based on the median of opium use in the control group. A positive exposure–response relation was observed between the amount of opium consumed per day and lung cancer, and the relation was stronger for the high-use group (for low-use group: adjusted OR, 3.81; 95% CI, 1.13–12.77; and for high-use group: OR, 9.36; 95% CI, 2.05–42.72). The odds ratio for the association between opium consumption and lung cancer among non-smokers of tobacco was 6.50 (95% CI, 2.89–14.64). Interaction *P* values for cigarette smoking (ever-use) with opium were 0.38 and 0.14 for ever-use and cumulative exposure, respectively. [The Working Group noted that strengths of the study included well-defined opium exposure, use of pathologically confirmed cases, and the use of population-based neighbour controls. Limitations included the retrospective study design, lack of clarity regarding the pathological subtypes of cases (the risk factors for adenocarcinoma could be different from those for SCC, as well as from those for metastatic cancers), potential recall bias, non-response, and the small sample size.]

2.3.3 Combined cancers of the respiratory tract

Sheikh et al. (2020) also investigated all respiratory cancers combined in the GCS. The study reported a fully adjusted hazard ratio in opium ever-users of 2.28 (95% CI, 1.58–3.30) for all respiratory cancers combined, with similar results when men and women were analysed separately. There was a positive exposure–response trend ($P < 0.0001$) for increasing quartiles of consumption (in the highest consumption quartile: HR, 3.22; 95% CI, 2.02–5.14). Risks for respiratory cancers combined were not as strong when limited to the subgroup of tobacco never-users (HR, 1.94; 95% CI, 1.02–3.71; 12 exposed cases). Analysis of mortality from respiratory cancers combined in the GCS revealed that current opium consumption, longer-term opium use, and higher cumulative consumption were all associated with an increased risk of death from respiratory cancers of 2–3-fold (Rahmati et al., 2017). [The Working Group noted that deaths from lung and laryngeal cancers made up all the cases included in these analyses, and that those sites were reported separately (and are included in the relevant sections above).]

2.4 Cancer and preneoplastic lesions of the stomach

See Table 2.4.

Two cohort studies and two case–control studies investigated the association of opium use with cancer of the stomach, in some cases including gastric cardia and preneoplastic lesions of the stomach. There was also a case series by Islami et al. (2004), which reported opium use data for 82 cases of gastric cancer (43% used opium) and 260 patients with no lesions that were visible endoscopically (27% used opium). [The Working Group considered the study to be uninformative because it was analysed as a case

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach

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
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 308 stomach cancers (243 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Stomach, incidence	Opium use (HR): Never Ever	 218 90	 1 1.36 (1.03–1.79)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and deaths that occurred during the first 2 yr of follow-up. *Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
		Stomach, incidence	Opium use, men (HR): Never Ever	 NR NR	 1 1.43 (1.05–1.93)	Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	
		Stomach, incidence	Opium use, women (HR): Never Ever	 NR NR	 1 1.08 (0.51–2.24)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Sheikh et al. (2020) (cont.)		Stomach (cardia subtype), incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	
			Never	133	1		
			Ever	48	1.18 (0.81–1.70)		
		Stomach (noncardia subtype), incidence	Opium use (HR):				
			Never	85	1		
			Ever	42	1.69 (1.11–2.56)		
		Stomach, incidence	Cumulative opium use (HR):				
			Never used opium	218	1		
			≤ 5 nokhod-years	NR	1.33 (0.83–2.13)		
			5.1–21 nokhod-years	NR	1.57 (1.01–2.43)		
			21.1–60 nokhod-years	NR	1.19 (0.73–1.94)		
			> 60 nokhod-years	NR	1.37 (0.88–2.11)		
			Trend-test *P* value, 0.067				
		Stomach/gastric cancer, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	188	1		
			Used opium but not tobacco	37	1.22 (0.85–1.75)		
			Used tobacco but not opium	30	0.79 (0.53–1.18)		
			Used both opium and tobacco	53	1.33 (0.96–1.86)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: 50 045 participants in a population-based cohort of individuals aged 40–75 yr at enrolment; cohort participants were primary rural individuals; 58% women; 123 stomach cancer deaths Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Stomach, mortality	Opium use (HR): Never Ever	 NR NR	 1 1.19 (0.78–1.83)	Age, sex, ethnicity (Turkman/non-Turkman), place of residence (urban/rural), cigarette smoking (ever/never), alcohol consumption (ever/never), and HBV infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Risk analysed by opium type and method of exposure. Also combined in analyses to ever/never opium exposure and cumulative nokhod-days. Few heroin users. Considers current and former exposure, duration of exposure, and time since last exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective; large sample size; minimal loss to follow-up; adjustment for major confounders; exposure measurement validated; reverse causation sensitivity analysis. *Limitations*: reverse causation not entirely ruled out; potential for outcome misclassification for deaths with verbal autopsy only.

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Sadjadi et al. (2014) Ardabil Province, Iran (Islamic Republic of) Enrolment, NR/ follow-up, 9036 person-years (median, 10 yr) Cohort	928; healthy individuals aged ≥ 40 yr and infected with *Helicobacter pylori* Exposure assessment method: data collected using a questionnaire described as validated, but no details of questions or validation provided; very low prevalence of opium use	Stomach, incidence	Opium use (HR): Never Ever	 32 4	 1 4.6 (1.6–13.3)	Age	*Exposure assessment critique*: Well-defined but poorly characterized (single-metric) exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; low loss to follow-up; adjustment for major confounders; availability of biopsy data and reporting associations with precancerous lesions; outcome ascertainment using histology in > 90% of cases. *Limitations*: small sample size; no information on dose–response relationship; no sensitivity analyses reported.
		Stomach, incidence	Opium use (HR): Never Ever	 32 4	 1 3.24 (1.37–7.66)	Age, sex, cigarette smoking, hookah smoking, alcohol use, fruit/vegetable intake < 400 g/day, salt intake > 6 g/day, family history of gastric cancer	
		Stomach (baseline precancerous lesion: antral intestinal metaplasia), incidence	Opium use (OR): Never Ever	 NR NR	 1 3.29 (1.2–9.1)	Age, cigarette smoking, hookah smoking, fruit/ vegetable intake < 400 g/day, salt intake > 6 g/day	
		Stomach (baseline precancerous lesion: gastric body intestinal metaplasia), incidence	Opium use (OR): Never Ever	 NR NR	 1 7.34 (2.5–21.5)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Shakeri et al. (2013) Golestan Province, Iran (Islamic Republic of) 2004–2011 Case–control	Cases: 309 cases of gastric cancer (adenocarcinoma) including 118 noncardia, 161 cardia, and 30 of mixed or unspecified site were enrolled from patients referred to Atrak Clinic, the only gastroenterology specialty clinic in the area Controls: 613 controls were selected from the GCS, a population-based cohort in the area; controls were individually matched on age, sex, and neighbourhood	Stomach (adenocarcinoma), incidence	Opium use (OR):			Age, sex, neighbourhood, ethnicity, education, wealth score, total daily fruit intake, total daily intake of vegetables, use of hookah, nass, and cigarettes, and *Helicobacter pylori* infection	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Opium exposure intensity, duration, cumulative use, and temporality determined. Data on type or method of consumption were not considered. Sensitivity analyses excluding exposure 1 yr before diagnosis to minimize reverse causation. Unexposed referent group could include exposed. No exposure lagging.
			Never	200	1		
			Ever	109	3.1 (1.9–5.2)		
		Stomach (adenocarcinoma), incidence	Cumulative opium use (OR):				
			Never used opium	200	1		
			≤ Median among controls (29 nokhod-years)	87	2.5 (1.4–4.3)		
			> Median among controls	22	4.5 (2.3–8.5)		
		Stomach (adenocarcinoma), incidence	Opium use, excluding cases who started within 1 yr before diagnosis (OR):				
			Never	NR	1		
			Ever	NR	2.9 (1.7–4.8)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Shakeri et al. (2013) (cont.)	Exposure assessment method: GCSQ; reasonably detailed exposure history, although type of opium exposure and method of exposure was not defined; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Stomach (adenocarcinoma: cardia subtype), incidence	Opium use (OR): Never Ever	 110 51	 1 2.8 (1.4–5.7)	Age, sex, neighbourhood, ethnicity, education, wealth score, total daily fruit intake, total daily intake of vegetables, use of hookah, nass, and cigarettes, and *Helicobacter pylori* infection	*Other comments*: neither the interviewers nor the participants had a preconceived notion that opium was a risk factor for gastric cancer, which reduced the possibility of reporting bias. *Strengths*: histological diagnosis of all cases; classification of most cases as noncardia or cardia subsites; use of population-based controls previously shown to be appropriate controls for cases; use of reliable and validated questionnaires with detailed questions about opium use. *Limitations*: slight potential for reporting bias and reverse causation.
		Stomach (adenocarcinoma: noncardia subtype), incidence	Opium use (OR): Never Ever	 72 46	 1 3.9 (1.6–9.4)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Naghibzadeh Tahami et al. (2014) Kerman Province, Iran (Islamic Republic of) 2010–2012 Case–control	Cases: 142 cases cancer of the upper GI tract (oral cavity, oesophagus, liver, pancreas, and stomach) were identified using a local cancer registry (89 stomach cancer cases) Controls: 284 neighbours of the cases, matched on sex and age (± 5 yr) (178 matched controls for stomach cancer cases); The closest neighbour to the right was selected	Stomach, incidence Stomach, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Never ≤ Median among controls, nokhod-years > Median among controls, nokhod-years	 55 34 55 8 26	 1 3.0 (1.6–5.6) 1 7.3 (1.2–43.0) 9.2 (2.5–33.7)	Age, sex, residence (urban/rural), dietary factors (meat, fruit, vegetables, and hydrogenated fats), smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Opium use defined. Intensity, duration, cumulative use, and type of use included. No information on mode of exposure. Systematic data collection after case identification. Raw and prepared opium only, no heroin or dross users. Unexposed referent group could include exposed. No exposure lagging.

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (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
Naghibzadeh Tahami et al. (2014) (cont.)	Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection; one interviewer (main researcher) performed most interviews; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)						*Strengths*: used structured questionnaire with detailed data on opium use and potential confounders; used trained interviewers; adjusted for potential confounders; conducted the study in an area where opium use is common and relatively free of stigma; a system for selecting controls. *Limitations*: limited sample size; small potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls.

CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; GI, gastrointestinal; HBV, hepatitis B virus; HR, hazard ratio; NR, not reported; OR, odds ratio; vs, versus; yr, year.

series and only percentages were shown, without adjustment for potential confounders.]

Sheikh and colleagues investigated stomach cancer incidence (308 cases; 79% histologically confirmed) in the GCS; see the detailed description of the GCS in Section 2.1 (Sheikh et al., 2020). After adjusting for potential confounders, including cigarette smoking (status and pack-years), opium use was associated with increased incidence of cancer of the stomach (HR, 1.36; 95% CI, 1.03–1.79), particularly for men (HR, 1.43; 95% CI, 1.05–1.93; 225 cases) and the noncardia subtype (HR, 1.69; 95% CI, 1.11–2.56; 127 cases). Stomach cancer incidence generally increased with increasing amounts of opium used; however, the increase was not monotonic (*P* for trend, 0.067).

Two earlier analyses of the GCS investigated the association of mortality from cancer of the stomach with opium use (Khademi et al., 2012; Malekzadeh et al., 2013). Because the study by Sheikh et al. (2020) had a longer follow-up period and included a larger number of cases, these two studies are not discussed in detail here; however, the results of Malekzadeh et al. (2013) (as the more recent of the two analyses) are included in Table 2.4.

In a population-based cohort study (Sadjadi et al., 2014) in Ardabil Province, Iran, 928 healthy, *Helicobacter pylori*-infected individuals were randomly selected. During nearly 10 years of follow-up, 36 new cases of gastric cancer were identified. Opium use was associated with an increased risk of gastric cancer, with an age-adjusted hazard ratio of 4.6 (95% CI, 1.6–13.3) and a multivariable-adjusted hazard ratio of 3.24 (95% CI, 1.37–7.66). Furthermore, opium use was strongly associated with increased risk of precursor lesions for gastric cancer at baseline, including antral (OR, 3.29; 95% CI, 1.2–9.1) and gastric body (OR, 7.34; 95% CI, 2.5–21.5) intestinal metaplasia.

In a case–control study (Shakeri et al., 2013), 309 cases of gastric adenocarcinoma (noncardia, 118; cardia, 161; and mixed or unspecified adenocarcinomas, 30) and 613 matched controls were enrolled. Cases were enrolled from December 2004 to December 2011 at Atrak Clinic, a gastroenterology specialty clinic in Gonbad City, the largest city in Golestan Province, Iran. For each case, up to 2 age-, sex-, and neighbourhood-matched controls were selected from 50 045 healthy participants, aged 40–75 years, who were enrolled in the GCS. Detailed information on long-term use of opium was obtained using the structured, validated GCSQ. After adjustment for multiple potential confounders including tobacco, opium use was associated with an increased risk of gastric adenocarcinoma with an adjusted odds ratio of 3.1 (95% CI, 1.9–5.2), and this increased risk was apparent for both anatomical subsites (cardia and noncardia). When cases who started using opium 1 year or less before diagnosis were excluded from the analysis, the results did not change materially, reducing the possibility of protopathic bias and reverse causality. There was an exposure–response effect, and individuals with the highest cumulative opium use had the strongest association (OR, 4.5; 95% CI, 2.3–8.5).

Another case–control study (Naghibzadeh Tahami et al., 2014) enrolled 89 cases of gastric cancer and 178 controls from Kerman Province, Iran. The cases were identified using a cancer registry. For each case, 2 neighbourhood controls were selected, matched to cases on sex, age, and place of residence. Data were collected on the amount of daily use and duration of use, from which cumulative use was calculated. All interviews were conducted by the primary investigator. After adjusting for potential confounders (including smoking), ever-use of opium was associated with an increased risk of gastric cancer, with an odds ratio of 3.0 (95% CI, 1.6–5.6). There was some evidence of an exposure–response association, and those who had cumulative use above the median had an odds ratio of 9.2 (95% CI, 2.5–33.7). [The Working Group noted that it

was unclear why the odds ratios for these two groups, stratified on exposure below and above the median, were both higher than the summary odds ratio for all opium users combined.]

2.5 Other cancers

See Table 2.5.

2.5.1 Cancer of the pancreas

Two epidemiological studies, a cohort study and a case–control study, investigated the association between opium use and incidence of pancreatic cancer.

The cohort study (Sheikh et al., 2020) investigated the association between opium use and incidence of pancreatic cancer in the GCS, updating an earlier analysis by Moossavi et al. (2018). During a median of 10 years of follow-up, 1833 individuals were diagnosed with cancer, including 78 with pancreatic cancer (65 diagnoses were histologically confirmed). Adjusting for a range of factors including cigarette smoking (status and pack-years), only high-exposure (> 60 nokhod-years) opium users had an increased risk of pancreatic cancer (HR, 2.66; 95% CI, 1.23–5.74; *P* for trend, 0.028). Risk of pancreatic cancer was not increased for ever-use of opium overall (HR, 1.54; 95% CI, 0.87–2.72), in sex-stratified results, or in the subgroup of tobacco never-users (HR, 1.40; 95% CI, 0.65–3.00).

The case–control study (Shakeri et al., 2016) recruited 357 cases of pancreatic cancer (316 histologically confirmed) and 328 controls from among patients who were referred to four endoscopic ultrasound centres in Tehran, Iran, from 2011 to 2015. Opium consumption was ascertained using the structured GCSQ (see Section 1.6, and Table S1.6.2D, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). The unadjusted odds ratio was 2.77 (95% CI, 1.64–4.69). After adjusting for potential confounders, including tobacco use, opium consumption was associated with an increased risk of cancer of the pancreas, with an odds ratio of 1.91 (95% CI, 1.06–3.43). Reclassification of individuals who started using opium 1 year before diagnosis as non-users did not materially change the results. There was no exposure–response association with either duration of opium use or cumulative opium use.

2.5.2 Cancers of the colon and rectum

One cohort study investigated the association between opium use and cancer of the colon, and two case–control studies investigated the association between opium use and cancers of the colon and rectum.

Sheikh and colleagues investigated the incidence of colon cancer (95 cases; 80% histologically confirmed) in the GCS cited earlier (Sheikh et al., 2020). Ever-use of opium was not associated with overall incidence of colon cancer (adjusted HR, 0.90; 95% CI, 0.48–1.67) or cumulative opium use (*P* for trend, 0.379), nor for men or women separately.

In a population-based case–control study conducted in the city of Kerman in Iran (Naghibzadeh-Tahami et al., 2016), 175 patients with cancer of the colon or rectum (diagnosed between January 2012 and December 2014) and 350 healthy controls were interviewed from September to November 2014. [The Working Group noted that it was not specified when the cases diagnosed in December 2014 were interviewed.] The cases were identified using a cancer registry. For each case, 2 controls were selected and matched to cases on the basis of sex, age, and place of residence. The use of opium was assessed using the structured and validated GCSQ. Opium use was associated with an increased risk of colorectal cancer, with an adjusted odds ratio of 4.5 (95% CI, 2.4–8.7). An exposure–response relation was observed between cumulative use of opium and incidence of colorectal cancer, where the odds ratios were 3.7 (95% CI, 1.6–8.6) and

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations

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
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 78 pancreatic, 95 colon, 914 GI, 80 brain, and 73 liver cancers (65, 76, 761, 52, and 51 histologically confirmed, respectively) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Pancreas, incidence	Opium use (HR): Never Ever	 56 22	 1 1.54 (0.87–2.72)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration of exposure, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and cases that occurred during the first 2 yr of follow-up.
		Pancreas, incidence	Opium use, men (HR): Never Ever	 NR NR	 1 1.85 (0.91–3.72)	Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
		Pancreas, incidence	Opium use, women (HR): Never Ever	 NR NR	 1 1.19 (0.42–3.33)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Sheikh et al. (2020) (cont.)		Pancreas, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy, for cases identified after death.
			Never used opium	56	1		
			1st quartile (≤ 5 nokhod-years)	NR	0.91 (0.28–2.97)		
			2nd quartile (5.1–21 nokhod-years)	NR	1.50 (0.58–3.90)		
			3rd quartile (21.1–60 nokhod-years)	NR	1.19 (0.41–3.43)		
			4th quartile (> 60 nokhod-years)	NR	2.66 (1.23–5.74)		
			Trend-test *P* value, 0.028				
		Pancreas, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	48	1		
			Used opium but not tobacco	8	1.40 (0.65–3.00)		
			Used tobacco but not opium	8	1.44 (0.63–3.30)		
			Used both opium and tobacco	14	2.52 (1.25–5.07)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Sheikh et al. (2020) (cont.)		Colon, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	80	1		
			Ever	15	0.90 (0.48–1.67)		
		Colon, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	0.75 (0.36–1.56)		
		Colon, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.30 (0.43–3.88)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Sheikh et al. (2020) (cont.)		Colon, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	80	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.58 (0.71–3.51)		
			2nd quartile (5.1–21 nokhod-years)	NR	0.49 (0.11–2.06)		
			3rd quartile (21.1–60 nokhod-years)	NR	0.74 (0.22–2.44)		
			4th quartile (> 60 nokhod-years)	NR	0.66 (0.19–2.25)		
			Trend-test *P* value, 0.379				
		GI cancers (oesophagus, stomach, pancreas, liver, colon, and rectum) combined, incidence	Opium use (HR):				
			Never	672	1		
			Ever	242	1.31 (1.11–1.55)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Sheikh et al. (2020) (cont.)		GI cancers combined, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	1.34 (1.10–1.62)		
		GI cancers combined, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.18 (0.83–1.66)		
		GI cancers combined, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	580	1		
			Used opium but not tobacco	105	1.27 (1.03–1.57)		
			Used tobacco but not opium	92	1.02 (0.80–1.29)		
			Used both opium and tobacco	137	1.46 (1.18–1.79)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Sheikh et al. (2020) (cont.)		Brain, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	63	1		
			Ever	17	1.13 (0.61–2.09)		
		Brain, incidence	Route of opium use (HR):				
			Never used opium	63	1		
			Only smoking	7	0.71 (0.31–1.64)		
			Only ingesting	9	2.15 (1.00–4.63)		
			Both	1	1.05 (0.14–7.90)		
		Liver, incidence	Opium use (HR):				
			Never	53	1		
			Ever	20	1.22 (0.68–2.18)		
		Liver and bile ducts, incidence	Route of opium use (HR):				
			Never used opium	53	1		
			Only smoking	8	0.78 (0.35–1.71)		
			Only ingesting	12	2.46 (1.23–4.95)		
			Both	0	–		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2012/ follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: a population-based cohort of 50 045 individuals (women, 58%) aged 40–75 yr at enrolment; cohort participants were primarily from rural areas Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Combined cancers of pancreas, colon, and rectum, mortality	Opium use (HR): Never Ever	 NR NR	 1 1.39 (0.90–2.16)	Age, sex, ethnicity (Turkman/non-Turkman), place of residence (urban or rural), cigarette smoking (ever or never), alcohol consumption (ever or never), and hepatitis B virus (HBV) infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Risk analysed by opium type and method of exposure. Also combined in analyses of ever/ never opium exposure and cumulative nokhod-days. Few heroin users. Cancer risk analysed by current and former exposure, duration of exposure, and time since last exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; large sample size; minimal loss to follow-up; adjusted for major confounders; validation of exposure measurement; sensitivity analysis for reverse causation. *Limitations*: reverse causation cannot be entirely ruled out; potential for outcome misclassification for deaths that only had verbal autopsy.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Naghibzadeh Tahami et al. (2014) Kerman Province, Iran (Islamic Republic of) 2010–2012 Case–control	Cases: 142 cases of cancer of the upper GI tract (oral cavity, oesophagus, liver, pancreas, and stomach) were identified using a local cancer registry Controls: 284 neighbours of the cases, matched on sex and age (± 5 yr); the closest neighbours to the right were selected Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; one interviewer (main researcher) performed most interviews; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Other upper GI tract (oral cavity, oesophagus, liver, and pancreas), incidence	Opium use (OR): Never Ever	 33 20	 1 9.3 (1.6–53.9)	Age, sex, residence (urban/rural), dietary factors (meat, fruit, vegetables, and hydrogenated fats), smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Opium use defined. Intensity, duration, cumulative use, and type of use included. No information on mode of exposure. Systematic data collection after case identification. Raw and prepared opium only, no heroin or dross users. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: used structured questionnaire with detailed data on opium use and potential confounders; used trained interviewers; adjusted for potential confounders; conducted the study in an area where opium use is common and relatively free of stigma; a system for selecting controls. *Limitations*: limited sample size; small potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls; exposure–response not considered for this end-point.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Naghibzadeh-Tahami et al. (2016) Kerman, Iran (Islamic Republic of) 2012–2014 Case–control	Cases: 175 cases of cancer of the colon or rectum selected using a local cancer registry Controls: 350 neighbours of the cases, matched on sex and age (± 5 yr); the closest neighbour to the right was selected Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Colon and rectum, incidence	Opium use (OR):			Age, sex, residence, consumption of various dietary items (total daily fruit and vegetables, red meat, and hydrogenated fats), cigarette smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome considered. Study considered ever vs never opium use, amount of daily opium use (based on median), duration of use, and cumulative use. History of opium use before diagnosis considered to neutralize the effect of reverse causation. Exposure assessed after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: reasonable sample size; structured questionnaire with detailed data on opium use and potential confounders; trained interviewers; adjusted for potential confounders; study conducted in area where opium use is common and relatively free of stigma; system for selecting controls.
			Never	130	1		
			Ever	45	4.5 (2.4–8.7)		
		Colon and rectum, incidence	Cumulative opium use (OR):				
			Never	130	1		
			≤ Median among controls (nokhod-years)	21	3.7 (1.6–8.6)		
			> Median among controls (nokhod-years)	24	8.0 (2.9–21.7)		
		Colon, incidence	Opium use (OR):				
			Never	103	1		
			Ever	39	5.7 (2.7–11.9)		
		Colon, incidence	Cumulative opium use (OR):				
			Never	103	1		
			≤ Median among controls (nokhod-years)	16	3.9 (1.5–9.9)		
			> Median among controls (nokhod-years)	21	9.4 (3.3–27.0)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Naghibzadeh-Tahami et al. (2016) (cont.)							*Limitations*: some potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls.
Shakeri et al. (2016) Tehran, Iran (Islamic Republic of) 2011–2015 Case–control	Cases: 357 cases with histopathologically or clinically confirmed pancreatic carcinoma selected from patients referred for endoscopic ultrasonography to 4 endoscopic ultrasound centres in Tehran Controls: 328 controls without pancreatic adenocarcinoma selected from patients referred for ultrasonography to the same 4 endoscopic ultrasound centres Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Pancreas, incidence	Opium use (OR):			None	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Comprehensive exposure assessment, just before case/control identification. Exposure included combined smoked and ingested opium, ever vs never, frequency of use based on ≤ or > the median per day, duration of use, cumulative use, and age at start of use. To address reverse causation, opium use was excluded 1, 2, and 3 yr before diagnosis. Study mentions "injected" use so could therefore incorporate heroin use, but no details are given. Unexposed referent group could include exposed. No exposure lagging.
			Never	300	1		
			Ever	57	2.77 (1.64–4.69)		
		Pancreas, incidence	Opium use (OR):			Age, sex, residence (urban/rural), alcohol use, ever-use of any type of tobacco	
			Never	300	1		
			Ever	57	1.91 (1.06–3.43)		
		Pancreas, incidence	Opium use (OR):				
			Never-use or use only within 1 yr of diagnosis	302	1		
			Ever	55	1.82 (1.01–3.29)		
		Pancreas, incidence	Duration of opium use (OR):				
			Never	305	1		
			≤ Median among controls (20 yr)	22	1.61 (0.72–3.52)		
			> Median among controls	30	1.79 (0.81–3.97)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Shakeri et al. (2016) (cont.)	Questionnaires administered by general practitioners when cases, controls, and interviewers were blinded to disease status (i.e. before ultrasound); route and type of opium consumed assessed but results are not included	Pancreas, incidence	Cumulative opium use (OR):			Age, sex, residence (urban/rural), alcohol use, ever-use of any type of tobacco	*Strengths*: relatively large sample size; detailed questions on opium use and potential confounders; uniform data collection; cases and controls selected from the same clinics; patients were questioned about opium use before diagnosis; strict case and control selection criteria. *Limitations*: potential for selection bias and information bias.
			Never	305	1		
			≤ Median among controls (34 nokhod-years)	26	1.85 (0.85–4.01)		
			> Median among controls	26	1.52 (0.67–3.43)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Iankarani et al. (2017) Fars Province, Iran (Islamic Republic of) 2014–2015 Case–control	Cases: 160 cases identified from the cancer registry centre of Shiraz University of Medical Sciences Controls: 320 controls selected from cases' neighbours, matched on age (± 5 yr) and sex Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection Trained interviewers; median opium use in controls considered cut-off point for low vs high use (likely reflective of background population)	Colon and rectum, incidence Colon and rectum, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Never used opium ≤ Median use among controls > Median use among controls	 128 32 128 16 16	 1 4.48 (2.27–8.82) 1 3.82 (1.58–9.18) 4.63 (1.78–12.05)	Age, sex, neighbourhood, special dietary factors (meat, fruit, vegetables, and hydrogenated fats), plus other main exposures (smoking)	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Comprehensive exposure assessment (intensity, duration, cumulative exposure, temporality, type, and mode). Exposure assessed after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: adequately large sample size; matched and/or adjusted for important potential confounders; used a structured questionnaire with detailed data on opium exposure; provided dose–response data. *Limitations*: potential for interviewer and reporting bias; potential for reverse causation.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Tahergorabi et al. (2018) Birjand, Iran (Islamic Republic of) 2016–2017 Case–control	Cases: 68 patients referred to a hospital for colonoscopy with pathologically confirmed GI cancer (oesophagus, stomach, colon, or rectum) Controls: 100 healthy individuals referred to 3 health clinics in the same city, matched on age and sex Exposure assessment method: structured questionnaire with no further details; exposure defined only as "opium addict" with no additional information	GI cancers (oesophagus, stomach, colon, or rectum) combined, incidence	Opium use (OR): Never Ever	 48 20	 1 4.3 (1.6–11.5)	Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. No cumulative exposure or information on duration. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. *Limitations*: lack of detailed data on opium exposure; adjustment methods and covariates included in the model are unclear; potential for reverse causation; potential interviewer bias; potential under-reporting by cases.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Alizadeh et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 (and earlier) Case–control	Cases: 140 patients with head and neck cancers (nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, or salivary gland) with pathological information in the cancer registry of Kerman University of Medical Sciences Controls: 280 neighbourhood-based controls individually matched on age (± 5 yr), sex, and neighbourhood (nearest and first neighbours on the right side of the case's home who met the inclusion criteria)	Head and neck, incidence	Opium use (OR):			Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), education (illiterate, elementary/middle school, high school/high school diploma, or above), cigarette smoking, alcohol drinking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Comprehensive exposure assessment (intensity, duration, cumulative exposure, type, and mode). Temporality not specified; opium use in the 2 yr before cancer diagnosis excluded to minimize reverse causation. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. Only raw opium and opium sap used.
			Never	42	1		
			Ever	98	8.13 (4.08–16.21)		
		Head and neck, incidence	Amount of daily opium use (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	45	7.19 (3.32–15.60)		
			> Median (among controls)	53	9.22 (4.19–20.28)		
		Head and neck, incidence	Duration of opium use (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	58	5.65 (2.90–10.98)		
			> Median (among controls)	40	13.16 (5.32–32.53)		
		Head and neck, incidence	Cumulative use of opium (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	48	6.52 (3.18–13.36)		
			> Median (among controls)	50	8.91 (4.03–19.65)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Alizadeh et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; trained interviewers; conducted at participants' homes; comfortable and friendly environment; used median use in controls to define non-use, and low and high use						*Strengths*: adequately large sample size; matched and/ or adjusted for important potential confounders; used a structured questionnaire with detailed data on opium exposure; provided dose–response data; disregarded opium use in those who started using opium in the 2 yr before diagnosis to address reverse causation. *Limitations*: potential for interviewer bias; potential under-reporting by controls.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) Iran (Islamic Republic of) April 2016 to April 2019 Case–control	Cases: 663 incident cases of head and neck SCC referred to cancer care centres in 10 provinces (IROPICAN study) Controls: 3065; ≥ 4 controls per case, frequency-matched on age, sex, and place of residence, selected from hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or persons who visited the hospital for any reason other than receiving treatment concurrently Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Head and neck (SCC), incidence	Regular opium use (OR): Non-user Regular user Centre-heterogeneity *P* value, < 0.0001	 368 295	 1 3.76 (2.96–4.79)	Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome was considered. Multiple exposure metrics (regular/non-regular use, average intensity as daily amount of use, duration in years, type of opium used, and route of use). Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: large sample size; detailed data on opium exposure assessment; assessment of dose–response relationship; adjustment for important confounders, using the most reliable control group; sensitivity analysis for differential response between cases and controls; disregarded opium use in those who started using opium in the 3 yr before diagnosis to address reverse causation.
		Head and neck (SCC), incidence	Regular opium use, never-smokers of tobacco (OR): Non-user of opium Regular user Centre-heterogeneity *P* value, < 0.0001	 207 39	 1 5.17 (3.26–8.21)	Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
		Head and neck (SCC), incidence	Duration of opium use (OR): 1st tertile (≤ 11 yr) 2nd tertile (12–23 yr) 3rd tertile (≥ 24 yr) Trend-test *P* value, < 0.0001 Centre-heterogeneity *P* value, < 0.0001	 51 101 143	 1 1.68 (1.04–2.72) 2.52 (1.55–4.11)	Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Duration of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	*Limitations*: retrospective design; potential for under-reporting by controls.
			1st tertile (≤ 11 yr)	15	1		
			2nd tertile (12–23 yr)	11	2.11 (0.68–6.49)		
			3rd tertile (≥ 24 yr)	13	2.70 (0.95–7.65)		
			Trend-test *P* value, 0.05				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Cumulative opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 3.6 gram-years)	38	1		
			2nd tertile (3.7–24.5 gram-years)	104	2.27 (1.36–3.78)		
			3rd tertile (≥ 24.5 gram-years)	153	2.06 (1.22–3.47)		
			Trend-test *P* value, 0.022				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Cumulative opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 3.6 gram-years)	11	1		
			2nd tertile (3.7–24.4 gram-years)	17	2.08 (0.77–5.59)		
			3rd tertile (≥ 24.5 gram-years)	11	2.42 (0.80–7.35)		
			Trend-test *P* value, 0.10 Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 8)	30	1		
			2nd tertile (8.1–22)	52	1.70 (0.97–2.99)		
			3rd tertile (≥ 23)	213	5.09 (3.05–8.47)		
			Trend-test *P* value, < 0.0001 Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Frequency-years of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 8)	8	1		
			2nd tertile (8.1–22)	11	1.91 (0.61–6.02)		
			3rd tertile (≥ 23)	20	6.27 (2.03–19.39)		
			Trend-test *P* value, 0.001 Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Average intensity of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 0.4 g/day)	62	1		
			2nd tertile (0.5–2 g/day)	110	1.33 (0.83–2.13)		
			3rd tertile (≥ 2 g/day)	123	0.88 (0.53–1.44)		
			Trend-test *P* value, 0.46				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Average intensity of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 0.4 g/day)	17	1		
			2nd tertile (0.5–2 g/day)	9	0.57 (0.16–2.01)		
			3rd tertile (≥ 2 g/day)	13	1.71 (0.50–5.80)		
			Trend-test *P* value, 0.26				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Type of opium used (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	368	1		
			Crude opium (*teriak*)	238	3.40 (2.64–4.37)		
			Opium juice (*shireh*)	57	7.17 (4.44–11.58)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Type of opium used, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			Non-user	207	1		
			Crude opium (*teriak*)	35	5.11 (3.16–8.26)		
			Opium juice (*shireh*)	4	5.79 (1.71–19.57)		
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Route of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	368	1		
			Only smoking	168	2.66 (2.03–3.47)		
			Only ingestion	35	8.33 (4.67–14.85)		
			Both routes	92	12.96 (8.14–20.62)		
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Route of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			Non-user	207	1		
			Only smoking	20	3.39 (1.93–5.95)		
			Only ingestion	6	6.45 (2.21–18.82)		
			Both routes	13	24.78 (9.18–66.89)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Lip and oral cavity (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	221	1		
			Regular user	33	1.53 (0.97–2.41)		
			Centre-heterogeneity *P* value, 0.28				
		Lip and oral cavity (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≤ 11 yr)	8	1		
			2nd tertile (12–23 yr)	11	1.01 (0.37–2.76)		
			3rd tertile (≥ 24 yr)	14	2.09 (0.75–5.80)		
			Trend-test *P* value, 0.15				
			Centre-heterogeneity *P* value, 0.43				
		Lip and oral cavity (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≤ 3.6 gram-years)	7	1		
			2nd tertile (3.7–24.4 gram-years)	13	1.52 (0.56–4.13)		
			3rd tertile (≥ 24.5 gram-years)	13	1.24 (0.44–3.43)		
			Trend-test *P* value, 0.73				
			Centre-heterogeneity *P* value, 0.46				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Lip and oral cavity (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 8)	11	1		
			2nd tertile (8.1–22)	5	0.41 (0.13–1.27)		
			3rd tertile (≥ 23)	17	1.24 (0.52–2.95)		
			Trend-test *P* value, 0.53				
			Centre-heterogeneity *P* value, 0.19				
		Lip and oral cavity (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	7	1		
			2nd tertile (0.5–2 g/day)	15	2.28 (0.869–6.03)		
			3rd tertile (≥ 2 g/day)	11	1.12 (0.39–3.19)		
			Trend-test *P* value, 0.96				
			Centre-heterogeneity *P* value, 0.52				
		Lip and oral cavity (SCC), incidence	Type of opium used (OR):				
			Non-user	221	1		
			Crude opium (*teriak*)	28	1.41 (0.87–2.27)		
			Opium juice (*shireh*)	5	2.90 (1.05–7.97)		
			Centre-heterogeneity *P* value, 0.37				
		Lip and oral cavity (SCC), incidence	Route of opium use (OR):				
			Non-user	221	1		
			Only smoking	20	1.09 (0.64–1.86)		
			Only oral ingestion	6	4.25 (1.45–11.69)		
			Both routes	7	5.10 (2.41–12.89)		
			Centre-heterogeneity *P* value, 0.17				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Pharynx (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	37	1		
			Regular user	17	2.90 (1.40–6.02)		
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≥ 11 yr)	5	1		
			2nd tertile (12–23 yr)	5	0.93 (0.23–3.75)		
			3rd tertile (≥ 24 yr)	7	1.9 (0.4–8.6)		
			Trend-test *P* value, 0.40				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≥ 3.6 gram-years)	4	1		
			2nd tertile (3.7–24.4 gram-years)	6	1.35 (0.31–5.83)		
			3rd tertile (≥ 24.5 gram-years)	7	1.07 (0.22–5.08)		
			Trend-test *P* value, 0.95				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Pharynx (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≥ 8)	3	1		
			2nd tertile (8.1–22)	3	0.99 (0.17–5.54)		
			3rd tertile (≥ 23)	11	3.24 (0.76–13.71)		
			Trend-test *P* value, 0.07				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≥ 0.4 g/day)	5	1		
			2nd tertile (0.5–2 g/day)	8	1.63 (0.48–6.51)		
			3rd tertile (≥ 2 g/day)	4	0.41 (0.07–2.26)		
			Trend-test *P* value, 0.26				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Type of opium used (OR):				
			Non-user	37	1		
			Crude opium (*teriak*)	15	2.81 (1.32–5.97)		
			Opium juice (*shireh*)	2	3.77 (0.80–17.68)		
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx	Route of opium use (OR):				
			Non-user	37	1		
			Only smoking	15	3.04 (1.43–6.47)		
			Only oral ingestion	1	2.67 (0.33–21.57)		
			Both routes	1	1.74 (0.21–14.26)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	14	1		
			Regular user	14	5.95 (2.41–14.71)		
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≥ 11 yr)	3	1		
			2nd tertile (12–23 yr)	5	1.89 (0.35–10.05)		
			3rd tertile (≥ 24 yr)	6	2.96 (0.55–15.91)		
			Trend-test *P* value, 0.20				
			Centre-heterogeneity *P* value, NR				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≥ 3.6 gram-years)	1	1		
			2nd tertile (3.7–24.4 gram-years)	8	9.79 (1.06–89.78)		
			3rd tertile (≥ 24.5 gram-years)	5	6.71 (0.65–68.99)		
			Trend-test *P* value, 0.13				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Mohebbi et al. (2020) (cont.)		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≥ 8)	2	1		
			2nd tertile (8.1–22)	1	0.31 (0.02–4.06)		
			3rd tertile (≥ 23)	11	5.53 (1.03–29.66)		
			Trend-test *P* value, 0.02				
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	6	1		
			2nd tertile (0.5–2 g/day)	4	0.80 (0.19–3.34)		
			3rd tertile (≥ 2 g/day)	4	0.82 (0.19–3.42)		
			Trend-test *P* value, 0.77				
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Type of opium used (OR):				
			Non-user	14	1		
			Crude opium (*teriak*)	13	6.04 (2.43–15.05)		
			Opium juice (*shireh*)	1	4.83 (0.55–41.97)		
			Centre-heterogeneity *P* value, 0.002				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Route of opium use (OR):				
			Non-user	14	1		
			Only smoking	8	3.97 (1.44–10.99)		
			Only oral ingestion	3	17.92 (4.32–74.26)		
			Both routes	3	11.96 (2.83–50.52)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (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
Vazirinejad et al. (2020) Rafsanjan, Iran (Islamic Republic of) 2016–2018 Case–control	Cases: 95 patients with cancer of the GI tract (oesophagus, stomach, pancreas, and colon or rectum) aged ≥ 18 yr referred to the oncology department of Ali ibn Abi Talib Hospital in Rafsanjan Controls: 190 relatives and neighbourhood controls individually matched on age (± 2 yr), sex, place of residence (urban/ rural), and smoking status Exposure assessment method: questionnaire; retrospective interview using checklist including intensity, duration of exposure, cumulative exposure, and type and method of exposure	GI cancers (oesophagus, stomach, pancreas, colon, and rectum) combined, incidence GI cancers combined, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Per 1 mesghal/ year increase	 70 25 25	 1 5.95 (2.37–14.99) 1.04 (1.02–1.06)	Age, sex, residence, smoking status, education, diet, family history of cancer	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to the outcome was considered; did not record opium use in the 1 year before cancer diagnosis, to minimize reverse causation. Exposure data collection after case identification. No exposure lagging. Use of one trained interviewer minimized interpersonal variability and, potentially, interviewer bias. *Strengths*: adequately large sample size; matched and/ or adjusted for important confounders; excluded exposure to opium in the 1 yr before case diagnosis; detailed exposure data; reported dose–response relationship with cumulative opium exposure. *Limitations*: potential interviewer bias; potential under-reporting by controls.

–, risk estimate could not be calculated; CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; GI, gastrointestinal; HBV, hepatitis B virus; HR, hazard ratio; IROPICAN, Iranian study of Opium and Cancer; NOS, not otherwise specified; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

8.0 (95% CI, 2.9–21.7) for lower and higher than median use, respectively. Similar results were obtained when cancer of the colon alone was the outcome.

The second case–control study was similar to the one reported above, except that it was conducted in Fars Province, Iran (Iankarani et al., 2017). In this study, 160 new cases of cancer of the colon or rectum and 320 age-, sex-, and place of residence-matched healthy neighbourhood controls (2 controls to each case) were selected. The cases were identified using the cancer registry centre of Shiraz University. Opium use was assessed using the structured and validated GCSQ. The use of opium was associated with an increased risk of colorectal cancer. The multivariable-adjusted odds ratio was 4.48 (95% CI, 2.27–8.82) for the association of opium use with cancer of the colon or rectum. Furthermore, there was some evidence of an exposure–response association, with odds ratios of 3.82 (95% CI, 1.58–9.18) and 4.63 (95% CI, 1.78–12.05) for cumulative opium use below and above the median, respectively, compared with never-use.

2.5.3 Cancers of the head and neck, excluding the larynx

The carcinogenic potential of opium use regarding carcinoma of the tongue was first proposed by Lyons & Yazdi (1969). Since then, a large case series (Fahmy et al., 1983), an ecological study (Rashidian et al., 2016), and four case–control studies (Saedi et al., 2012; Razmpa et al., 2014; Alizadeh et al., 2020; Mohebbi et al., 2020) have been published on this topic. The case series (Fahmy et al., 1983) and the ecological study (Rashidian et al., 2016) were considered uninformative by the Working Group. The case–control study by Saedi et al. (2012) reported data for 557 cases of oral cancer referred to two tertiary hospitals in Tehran, Iran. Of these cases, 9% had a history of opium abuse; however, the study did not report the results of opium use in the 300 controls, so the study was not considered informative. Another case–control study by Razmpa et al. (2014), which included 80 cases of oral cancer and 80 controls, was also considered uninformative because of methodological issues and potential problems with statistical analysis. In particular, the crude odds ratios could not be confirmed; the magnitudes of adjusted odds ratios were not presented; and although the reported *P* value for opium was below 0.05, the value of the corresponding *t*-statistic did not reach 1.96. The study by Alizadeh et al. (2020) did not report results for individual subsites (other than the larynx) and their results for "other head and neck cancers combined" are included in Section 2.5.4 below.

A large-scale case–control study by Mohebbi et al. (2020) compared opium use of 663 cases with SCC of the head and neck (lip and oral cavity, 254 cases; pharynx, 54 cases; larynx, 327 cases; and other subsites, 28 cases) with 3065 controls. The cases were selected from 10 centres in various cities in Iran. For each case, at least 4 frequency-matched controls (matched on age, sex, and place of residence) were selected. Potential controls were hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or who visited the hospital for reasons other than receiving treatment. Pilot studies showed that this control group was more appropriate for opium use studies than other control groups (e.g. hospital or clinic patients, or neighbourhood controls). Detailed data were available on the history of opium use (e.g. frequency, duration, amount used each time, type of opium used, etc.) and for a range of potential confounders (including tobacco use). To alleviate concerns regarding protopathic bias and reverse causality, opium use was disregarded in those who started using opium up to 3 years before diagnosis. Results for cancer of the larynx are presented in Section 2.3; results for other cancers are discussed here. After adjusting

for potential confounders, including pack-years of cigarette smoking, head-years of water-pipe smoking, and regular alcohol drinking, there was an increased risk of all head and neck SCCs (OR, 3.76; 95% CI, 2.96–4.79), and cancers of the pharynx (OR, 2.90; 95% CI, 1.40–6.02), lip and oral cavity (OR, 1.53; 95% CI, 0.97–2.41), and other subsites (OR, 5.95; 95% CI, 2.41–14.71). On the basis of frequency-years of opium use, there was a clear exposure–response relation for all cancers of the head and neck combined, cancer of the pharynx, and cancers of other subsites. [The Working Group noted that this measure seemed to be the most appropriate measure of cumulative use.] The point estimate for the association of opium use with all head and neck cancers was larger among never-smokers, with an odds ratio of 5.17 (95% CI, 3.26–8.21), ruling out confounding by smoking. Associations were seen both for those who smoked and for those who ingested opium, but the strongest association was seen for those who used opium by both ingestion and smoking. After adjusting for the sensitivity of responses in cases (0.77) and controls (0.68), obtained from previous studies, the odds ratios were attenuated but the association remained strong. A positive association was observed for those participants who used crude opium (*teriak*) (OR, 2.81; 95% CI, 1.32–5.97) and cancer of the pharynx.

2.5.4 Other cancer sites or cancer combinations

Data for other cancers, as well as for other cancer combinations, were sparse.

(a) Cohort studies

Sheikh and colleagues investigated the incidence of all cancers of the gastrointestinal (GI) tract combined (914 cases; 83% histologically confirmed), cancer of the brain (80 cases; 65% histologically confirmed), and cancer of the liver (73 cases; 70% histologically confirmed) in the GCS cited earlier (Sheikh et al., 2020). Compared with never-use of opium, there was no association between ever-use of opium and incidence of cancer of the brain or liver; however, incidence was increased among opium users who only ingested opium compared with never-users for both of these sites. After adjustment for multiple potential confounders, opium users also had increased risk of incidence of all GI cancers combined (HR, 1.31; 95% CI, 1.11–1.55). Results were similar for men (HR, 1.34; 95% CI, 1.10–1.62), but not as strong for women (HR, 1.18; 95% CI, 0.83–1.66). Compared with non-users of both tobacco and opium, opium use was associated with increased incidence of all GI cancers combined both for non-tobacco users (HR, 1.27; 95% CI, 1.03–1.57) and for tobacco users (HR, 1.46; 95% CI, 1.18–1.79). Malekzadeh et al. (2013) found that the mortality of "cancers of pancreas, colon, and rectum combined in this same cohort was slightly elevated in opium users", with a hazard ratio of 1.39 (95% CI, 0.90–2.16), but did not report results for each individual cancer.

Sheikh et al. (2020) also investigated the association between opium use and all cancers combined. In total, 1833 of the study participants were diagnosed with cancer. After adjusting for multiple potential confounders, opium use was associated with an increased risk of developing all cancers combined, with a hazard ratio of 1.40 (95% CI, 1.24–1.58). The association for all cancers remained positive in a group of tobacco never-users, with a hazard ratio of 1.32 (95% CI, 1.13–1.55). There was a clear exposure–response association ($P < 0.0001$), and for the highest quartile of use the hazard ratio was 1.70 (95% CI, 1.42–2.04). Likewise, there was an increased risk of all cancers combined for those who smoked and those who ingested opium.

Two other reports presented data for all cancers combined. Nalini et al. (2020) used data from the GCS, which were the same as those used by Sheikh et al. (2020). [Given that the

paper by Sheikh and colleagues was focused on cancer outcomes and provided a substantially more detailed analysis, the Working Group considered that the data presented by Nalini et al. did not add any further information.] Another cohort study (Firouzabadi et al., 2020) reported very few (only 8) cases of cancers among opium users and the data were not adjusted for important confounders. [The Working Group considered this study uninformative because of these limitations.]

(b) Case–control studies

The case–control study by Naghibzadeh Tahami et al. (2014) (previously described for gastric cancer) reported data for a total of 53 cases of cancer of other upper GI sites (oral cavity, oesophagus, liver, and pancreas), but did not report the results for each cancer because of the small sample size. After adjusting for potential confounders, ever-use of opium was associated with increased risk of other upper GI cancers, with an odds ratio of 9.3 (95% CI, 1.6–53.9). Results for an exposure–response association were not reported. A study by Tahergorabi et al. (2018) used data from 68 patients with histologically confirmed GI cancer (cancers of the oesophagus, stomach, colon, and rectum) and 100 controls. The controls were patients referred to three centres in the same city as the cases (Birjand, Iran), matched on age and sex. It was reported that 29.4% of the cases and 8.8% of the controls used opium, leading to an odds ratio of 4.3 (95% CI, 1.6–11.5) that was not adjusted for smoking or other potential confounders.

Vazirinejad et al. (2020) investigated the incidence of GI cancers combined (cancers of the oesophagus, stomach, pancreas, colon, and rectum) in the city of Rafsanjan, Kerman Province, Iran (cases, 95; controls, 190). Cases were selected by convenience sampling and had received a pathologically confirmed diagnosis in the previous 2 years. [The Working Group noted the potential for selection bias in the use of convenience sampling of controls.] Cases were excluded if the patient consumed alcohol, nass, or other opioid drugs. Cases were individually matched to 1 family and 1 neighbourhood control on age (± 2 years), sex, residence (urban or rural), and smoking status (26% of cases and controls smoked cigarettes). After adjustment for several potential confounders, ever-use of opium was associated with an increased risk of GI cancer (OR, 5.95; 95% CI, 2.37–14.99; on the basis of 25 exposed cases). The average daily intake of opium in this study, 0.54 among cases and 0.07 among controls, was measured in *mesghals*, which is reported to be equal to 4.55 g (see Section 1.6.1). [The Working Group noted the use of the *mesghal* is unique to this study, and other studies have reported opium consumption in the much smaller unit of the *nokhod*.] Cumulative opium use was associated with an odds ratio of 1.04 (95% CI, 1.02–1.06) for an increase of 1 mesghal per year.

Alizadeh et al. (2020) conducted a case–control study of incident cancers of the head and neck (including tumours of the nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, and salivary gland) (see also Section 2.3). Cases were identified from a cancer registry both prospectively and retrospectively, and each case was matched on age (± 5 years) and sex to 2 neighbourhood controls. Information on opium consumption was collected using the validated GCSQ. Only opium use that occurred at least 2 years before cancer diagnosis was considered. Ever-use of opium was associated with increased risk of all cancers of the head and neck combined (OR, 8.13; 95% CI, 4.08–16.21) in multivariable-adjusted analyses (including adjustment for alcohol and tobacco use). Increased exposure, as measured by increased daily opium use, duration of use, and cumulative use, was associated with increased risk (below and above median exposure in controls compared with never-users) for all cancers of the head and neck combined.

2.6 Evidence synthesis for cancer in humans

This section provides a synthesis of studies of opium consumption in humans in relation to cancer of various sites. A detailed definition of opium, as the agent of investigation in the present monograph, has been provided in Section 1.1. It is important to note that the body of evidence regarding the carcinogenicity of opium and cancer in humans is derived from studies of populations exposed to the minimally processed latex of the poppy plant (*Papaver somniferum*). Processing may have included air drying, heat drying, or boiling, and included dross and (minimally) processed opium. Opium products, as consumed by the people in these epidemiological studies, comprise a complex chemical mixture that includes alkaloids (e.g. morphine and thebaine), non-alkaloids (e.g. sugars, fats, meconic acid, and water), and adulterants or contaminants (e.g. lead and chromium). Opium consumption by participants in the available studies was of raw or crude opium (*teriak*), opium dross (*sukhteh*), or refined or sap opium (*shireh*). All these forms of opium may be commonly ingested or smoked. No studies of cancer in humans were found that investigated users of opium tinctures that are produced legally and used for medicinal purposes.

Three prospective cohort studies and a large number of retrospective case–control studies investigated the association between opium use and different cancers. Cancers that were studied more extensively were those of the oesophagus, urinary bladder, larynx, lung, pancreas, stomach, colon and rectum, and oral cavity and pharynx; less evidence was available for other cancer types. With a few exceptions, the majority of the studies were conducted in Iran, where opium use is common, and a reasonably strong epidemiological research infrastructure allows for the study of the association between opium use and cancer. While the studies were conducted in a limited geographical area, the results can probably be generalized to other populations. The studies were conducted in various provinces of Iran (Table 2.6; Fig. 2.1), with substantial diversity in dietary and cultural habits, as well as different prevalence rates and average amounts of opium consumption. Their findings are unlikely to be attributable to an unnoticed fixed and strong confounding structure limited to Iran, because the reported associations between opium use and some cancers were stronger than for most other major cancer risk factors (e.g. cigarette smoking).

2.6.1 Studies evaluated

In assessing the carcinogenicity of opium use, substantial weight was given to the results from the GCS, a prospective study of over 50 000 individuals with median follow-up of 10 years (Sheikh et al., 2020). The GCS collected detailed and validated data on opium use, adjusted the results for a large number of potential confounders, and applied multiple methods to minimize the possibility of reverse causation. Although the GCS results offered high-quality data, sample sizes were only sufficiently large for a limited number of cancer sites (e.g. cancers of the oesophagus and stomach). Another limitation of the GCS was that the median amount of opium use was quite low (0.6 g/day according to Khademi et al., 2012); therefore, the results may have underestimated the associations for other populations that may consume higher amounts of opium. Another cohort in Ardabil Province offered data only for gastric cancer and had a small sample size (Sadjadi et al., 2014). The results of the third cohort study were not informative because the study had a short follow-up period and only 8 individuals had developed cancer (Firouzabadi et al., 2020). These three cohort studies used similar questionnaires.

Case–control studies were at greater risk of selection, information, and protopathic bias (more details in Annex 2 and

Table 2.6 Geographical distribution of key epidemiological studies of cancer and opium consumption in the Islamic Republic of Iran, by province

Province	Number of studies[a]	References
Kerman	7	IROPICAN (Mohebbi et al., 2020); Mousavi et al. (2003), Naghibzadeh-Tahami et al. (2014, 2016, 2020), Alizadeh et al. (2020), Vazirinejad et al. (2020)
Tehran	7	IROPICAN (Mohebbi et al., 2020); Asgari et al. (2004), Hosseini et al. (2010), Shakhssalim et al. (2010), Masjedi et al. (2013), Razmpa et al. (2014), Shakeri et al. (2016)
Golestan	5	GCS (Khademi et al., 2012, Malekzadeh et al., 2013, Rahmati et al., 2017, Sheikh et al., 2020); IROPICAN (Mohebbi et al., 2020); Nasrollahzadeh et al. (2008); Shakeri et al., (2012, 2013)
Khorasan-Rasavi	5	IROPICAN (Mohebbi et al., 2020); Shakhssalim et al. (2010), Bakhshaee et al. (2017), Tahergorabi et al. (2018), Pournaghi et al. (2019)
Fars	4	IROPICAN (Mohebbi et al., 2020); Sadeghi et al. (1979), Akbari et al. (2015), Iankarani et al. (2017)
Esfahan	2	Shakhssalim et al. (2010), Berjis et al. (2018)
Mazandaran	2	IROPICAN (Mohebbi et al., 2020); Aliramaji et al. (2015)
Ardabil	1	Sadjadi et al. (2014)
Boushehr	1	IROPICAN (Mohebbi et al., 2020)
East Azarbaijan	1	Shakhssalim et al. (2010)
Hormozgan	1	IROPICAN (Mohebbi et al., 2020)
Kermanshah	1	IROPICAN (Mohebbi et al., 2020)
Khouzestan	1	Shakhssalim et al. (2010)
Kordestan	1	Ghadimi et al. (2015)
Sistan and Baluchestan	1	IROPICAN (Mohebbi et al., 2020)
Yazd	1	Lotfi et al. (2016)

GCS, Golestan Cohort Study; IROPICAN, Iranian Study of Opium and Cancer.
[a] The GCS has multiple references.

Sections 2.6.3 and 2.6.4), but generally had larger numbers of cases and were mainly conducted in areas where average opium consumption was higher, for example, in Kerman Province, Iran. The degree to which each study was informative varied substantially. Some case–control studies, such as the IROPICAN study (Mohebbi et al., 2020), had a clear definition of exposure, were adjusted for multiple confounders, presented exposure–response analyses, provided results in tobacco never-smokers, and incorporated exposure only up to a certain period before diagnosis, avoiding reverse causality; however, other case–control studies were less informative due to a lack of information in one or more of the areas discussed above. While the IROPICAN study and some other case–control studies (e.g. Naghibzadeh-Tahami et al., 2020) were focused on opium consumption as a potential carcinogen, many of the other case–control studies were designed to study a host of risk factors and provided relatively little information on opium use.

Case series, cross-sectional studies, and ecological studies were considered, but ultimately excluded from this review because they were uninformative for the assessment of the association between opium consumption and cancer. In some earlier GCS publications, cancer mortality, rather than incidence, was the outcome; however, these publications were superseded by the paper by Sheikh et al. (2020), which presented data on

Fig. 2.1 Map of the Islamic Republic of Iran

cancer incidence. The results of the latter study were qualitatively and quantitatively similar to those of the earlier publications.

2.6.2 Exposure assessment and misclassification of exposure

The GCS collected detailed data on lifetime opium consumption at baseline, which included duration of use, ages of initiation and quitting, frequency and amount of use, and route of consumption (Section 2.1). It has been shown (Abnet et al., 2004) that the participants in the GCS provided data that were reliable and highly correlated with results from testing for metabolites of opium in the urine, and therefore that the quality of exposure assessment was high; however, there may have been a small amount of bias towards the null, because infrequent opium users (use for < 6 months) were included in the referent group of "never" opium users. The Working Group considered that the accuracy of the GCS exposure data may be close to that of studies of cigarette smoking, in which misclassification is low enough for the effect of the exposure to be studied. While some level of non-differential misclassification may still exist, which may bias the results towards the null, the positive and statistically significant associations between opium use and cancer identified by this study partially alleviate this concern.

Several of the case–control studies, such as the IROPICAN study (Mohebbi et al., 2020) and some other studies from Kerman Province (e.g. Naghibzadeh Tahami et al., 2014, 2020), also collected detailed exposure data. Some case–control studies may have suffered from differential exposure misclassification, particularly if they chose to use neighbourhood controls. Neighbourhood controls may under-report their amount of use and current use status, particularly if they were interviewed in their homes, where they may potentially have been heard by family members and friends. Such under-reporting in controls may bias the results away from the null. To avoid this problem, studies such as IROPICAN (Mohebbi et al., 2020) used healthy hospital visitors who were not family members of cancer cases and conducted sensitivity analyses for the differential sensitivities of responses between cases and controls.

Some case–control studies were even more limited, reporting the results of opium use in a dichotomous fashion and providing very little information on how opium use was assessed. For example, a case–control study by Pournaghi et al. (2019) offered almost no detail regarding exposure assessment beyond the statement that "data were collected through structured interviews".

2.6.3 Confounding and selection bias

There are at least four major confounding factors in assessing the causality of association between opium consumption and various cancers: sex, age, tobacco use, and socioeconomic status. Opium use in Iran, where the majority of the data came from, is much more common among men, older individuals, people with lower socioeconomic status, and those who use tobacco. All of these attributes are also associated with increased risk of several cancers. Many studies either adjusted for or matched on sex, age, and neighbourhood (a proxy for socioeconomic status). Likewise, many studies adjusted for tobacco smoking or stratified the results by smoking status.

The results from the GCS were meticulously adjusted for sex, age, tobacco use, and socioeconomic status. For reasons that are unclear, the association between tobacco use and oesophageal SCC and lung cancer in Iran and in some other Asian countries (Tran et al., 2005; Kamangar et al., 2007; Nasrollahzadeh et al., 2008; Zheng et al., 2014; Naghibzadeh-Tahami et al., 2020) is not as strong as that seen in countries in North America and Europe (e.g. Freedman et al., 2007, 2008). In fact, the association between opium

use and overall mortality and some tobacco-associated cancers (e.g. cancers of the larynx, pharynx and oral cavity, oesophagus, stomach, and urinary bladder) was stronger than the association between tobacco use and these outcomes; hence, any residual confounding after careful adjustment for tobacco use should have been minimal. Furthermore, the GCS and several other studies showed strong associations between certain cancers and opium use among never-smokers, which should considerably alleviate any concerns about residual confounding from tobacco use. While confounding by other exposures cannot be completely refuted, adjustments for other exposures have not been shown to materially affect relative risk estimates for opium. The GCS, due to its prospective nature and high participation rate, is not subject to selection bias.

Case–control studies varied in their adjustment for confounders. However, most had adjusted for age, sex, study location (if conducted in multiple cities), and tobacco use. Selection bias remains a concern. Case–control studies that used hospitalized patients as their sources of controls may have provided biased estimates, because opium use may be associated with various non-malignant diseases, such as chronic obstructive pulmonary disease and liver cirrhosis, leading to estimates of measures of association that would be likely to be biased towards the null. On the other hand, neighbourhood controls who were opium users may have been less likely to participate in such studies, leading to estimates of measures of association that were biased away from the null. It has been suggested that the best controls may be individuals who visit the hospital where the cases are treated, but who are neither sick nor family members of cases (Rashidian et al., 2017). Recall bias is unlikely to be a problem, because nearly all participants remembered their long-term use of opium, regardless of their case status.

2.6.4 Protopathic bias and reverse causation

The association between opium consumption and cancer may be subject to protopathic bias and reverse causation. Extensive treatment of this is provided in Annex 2. Reverse causation did not affect the GCS or the Ardabil cohort study, because the participants did not have cancer at baseline. Protopathic bias may be eliminated easily for cancers with relatively short survival periods, such as oesophageal or pancreatic cancer, by excluding cases that were diagnosed within the first year (or the first few years) of the cohort study. In these cohort studies, the exclusion of the early period of follow-up had little effect on risk estimates. Likewise, these biases may be addressed in case–control studies by excluding exposure that occurred one or several years before case enrolment. By contrast, it may be more difficult to address protopathic bias for cancers that have longer survival periods, particularly if those cancers have long-standing symptoms before diagnosis that may be alleviated by opium use (e.g. by opium's antitussive effect).

2.6.5 Cancer of the oesophagus

The results of the GCS (Sheikh et al., 2020) included an increased risk of cancer of the oesophagus in opium ever-users, with an adjusted hazard ratio of 1.38 (95% CI, 1.06–1.80). The point estimates remained similar or became even stronger among tobacco never-users (HR, 1.41; 95% CI, 1.02–1.96), and after excluding cases that were diagnosed within the first 2 years of follow-up (HR, 1.52; 95% CI, 1.13–2.04), making residual confounding and reverse causation unlikely explanations for the findings. There was a positive exposure–response relation (*P* for trend, 0.0099), with the highest quartile (> 60 nokhod-years) showing a hazard ratio of 1.60 (95% CI, 1.06–2.42). The association was stronger for those who smoked opium

than for those who ingested it. While there were at least three non-overlapping case–control studies (Shakeri et al., 2012; Bakhshaee et al., 2017; Pournaghi et al., 2019), only one (Shakeri et al., 2012) had investigated sizable numbers of cases and controls and had adequately adjusted for potential confounders. This study, which was conducted in Golestan Province (the same location as the GCS), found different results depending on which control group was considered. Compared with a neighbourhood control group, the cases were more likely to be opium ever-users (adjusted OR, 1.77; 95% CI, 1.17–2.68), whereas there was almost no increased probability of opium use compared with hospital-based controls (adjusted OR, 1.09; 95% CI, 0.63–1.87). While it is difficult to determine which control group (if either) was most appropriate, it appears that the reported prevalence of opium use in the neighbourhood controls (18%) was closer to that of the validated reports from the general population.

The Working Group concluded that a positive association between opium consumption and cancer of the oesophagus is credible; however, chance, bias, and confounding cannot be ruled out with reasonable confidence. The association observed in the GCS was not very strong, which makes it possible that it arose due to residual confounding. The results of the case–control study were subject to interpretation based on the appropriateness of the control group. These findings were applicable primarily to oesophageal SCC, which constituted the majority of the cases of oesophageal cancer in both the case–control and cohort studies.

2.6.6 Cancer of the urinary bladder

The GCS found an adjusted hazard ratio of 2.86 (95% CI, 1.47–5.55) for opium ever-users compared with never-users (Sheikh et al., 2020). There was a positive exposure–response relation (P = 0.0009), with an adjusted hazard ratio of 4.28 (95% CI, 1.81–10.15) for the highest quartile of cumulative use (> 60 nokhod-years). The point estimate for the association was stronger among tobacco never-users (HR, 3.74; 95% CI, 1.63–8.59).

Nearly all eight case–control studies, involving a total of almost 1750 cases of bladder cancer combined, found higher odds of opium use among cases than in controls (Sadeghi et al., 1979; Asgari et al., 2004; Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Aliramaji et al., 2015; Ghadimi et al., 2015; Lotfi et al., 2016). The adjusted odds ratios, when calculated, typically ranged from 2 to 5. These numbers are consistent with a summary pooled point estimate odds ratio of 3.40 calculated in a meta-analysis (Afshari et al., 2017) and those from the GCS (HR, 2.86) (see above). Control selection, adjustment for confounding, and a clear definition of exposure were among the limitations of several of these studies. However, studies that collected detailed data on exposure and adjusted for multiple confounders (e.g. Hosseini et al., 2010; Akbari et al., 2015) found strong associations between opium use and urinary bladder cancer. It is notable that the results of all studies, regardless of design, point in the same direction.

While many occupational exposures have been identified as risk factors for bladder cancer (Cogliano et al., 2011), occupation is unlikely to have been a major confounder for the association of opium use with bladder cancer in Iran. In the GCS, approximately 80% of the study population came from villages, where most of participants were farmers and did not have substantial exposure to occupational risk factors for bladder cancer. Likewise, in the earlier studies in Fars Province, where a very high male to female ratio (9 : 1) was found, there were no factories in the research area at the time. Thus far, no clear pattern of association has been shown between opium use and occupational exposures. As such, the Working Group did not consider occupational

exposure to be an important confounder in associations between opium consumption and bladder cancer in Iran.

The Working Group concluded that despite a modest number of cases in the GCS, a positive association was observed. Collectively, the most informative studies rule out chance, bias, confounding, and reverse causation with reasonable confidence. This inference is based on the observation of very strong associations, positive exposure–response associations, consistency across studies, the availability of studies with large sample sizes, and various efforts to rule out bias and confounding in a key study (the GCS).

2.6.7 Cancer of the larynx

The association between opium consumption and cancer of the larynx was extensively studied in a cohort study (the GCS) and in six case–control studies that included nearly 900 cases combined.

The GCS reported a fully adjusted hazard ratio of 2.53 (95% CI, 1.21–5.29) and a positive exposure–response trend (P = 0.0004), with an adjusted hazard ratio of 3.34 (95% CI, 1.33–8.34) in the highest cumulative consumption quartile (> 60 nokhod-years) (Sheikh et al., 2020). While the numbers were small, the point estimates were higher among women and those who had never smoked cigarettes.

All six case–control studies showed substantially increased opium use among patients with laryngeal cancer compared with controls, with odds ratios ranging from 2 to 16 (Khoo, 1981; Mousavi et al., 2003; Bakhshaee et al., 2017; Berjis et al., 2018; Alizadeh et al., 2020; Mohebbi et al., 2020). Four of these studies had serious methodological limitations, including lack of adjustment for important confounders, potential selection bias, and lack of analyses for reverse causation. However, two of these studies adjusted for many confounders and analysed the data in various ways (Alizadeh et al., 2020; Mohebbi et al., 2020), and found strong associations between opium use and laryngeal cancer. Alizadeh et al. (2020) found that the prevalence of opium use was 79% among the cases of cancer of the larynx, substantially higher than the prevalence of 29% among the controls, and the adjusted odds ratio was 11.98 (95% CI, 5.05–28.39). Likewise, 71% of the 327 cases of cancer of the larynx enrolled in the IROPICAN study (Mohebbi et al., 2020) were opium users, compared with only 13% of the controls, yielding an adjusted odds ratio of 6.55 (95% CI, 4.69–9.13). Furthermore, the IROPICAN study results showed a clear positive exposure–response relation with duration of opium use, with an odds ratio of 2.7 in the third tertile of use compared with the first tertile (P for trend, < 0.0001). The associations are unlikely to be attributable to recall bias because most people (cases and controls alike) recollect opium use. The study by Mohebbi et al. (2020) classified participants as non-users if they started using opium 3 years or less before diagnosis, ruling out reverse causation and protopathic bias. They also conducted a sensitivity analysis by calculating the odds ratio (95% CI) considering the sensitivity of self-report among cases and controls, and the results remained strongly positive.

The Working Group concluded that a positive association had been established between opium consumption and cancer of the larynx. Collectively, the most informative studies permitted chance, bias, confounding, and reverse causation to be ruled out with reasonable confidence. This inference was based on the observation of very strong associations, positive exposure–response trends, consistency across studies, availability of studies with large sample sizes, and various efforts to rule out bias and confounding in at least two key studies: the GCS and the IROPICAN study.

2.6.8 Cancer of the lung

Data on the association between opium consumption and cancer of the lung were limited to one cohort study (the GCS) and three case–control studies. The cohort study by Sheikh et al. (2020) found an adjusted hazard ratio of 2.21 (95% CI, 1.44–3.39) with a positive exposure–response trend ($P < 0.0001$) for increasing quartiles of consumption (HR, 3.19; 95% CI, 1.85–5.50 in the highest consumption quartile, i.e. > 60 nokhod-years). These results were carefully adjusted for cigarette smoking; however, assessment of cigarette never-smokers was difficult, because only 8 study participants with lung cancer had used opium but never smoked cigarettes. This may represent a limitation on the interpretation of the data due to the very strong associations between opium use and both smoking and lung cancer.

One of the case–control studies was conducted in the 1970s, when statistical adjustment methods were not as readily available (MacLennan et al., 1977). While the odds ratio for opium use was above unity, the limited adjustment for confounding makes interpretation difficult. A second case–control study enrolled 242 histologically and cytologically confirmed cases of primary cancer of the lung with 484 controls (hospital controls, 242; visiting healthy controls, 242) – matched on age, sex, and place of residence – and reported an increase in the risk of lung cancer among opium users after adjusting for pack-years of cigarette smoking, with an odds ratio of 3.1 (95% CI, 1.2–8.1) (Masjedi et al., 2013). The magnitude of this association was similar to that identified in the GCS and the other case–control study; however, no obvious exposure–response pattern was observed. A third case–control study enrolled 140 patients with cancer of the lung and 280 healthy controls matched on age, sex, and place of residence, and reported an adjusted odds ratio of 5.95 (95% CI, 1.87–18.92) (Naghibzadeh-Tahami et al., 2020). There was a positive exposure–response association, with an odds ratio of 9.36 (95% CI, 2.05–42.72) for high-level users. While this study had many strengths, it was difficult to rule out the possibility of under-reporting of opium use by the neighbourhood-based controls.

Despite the limitations observed in these three studies, the Working Group concluded that a positive association had been observed between opium consumption and cancer of the lung. Given the totality of evidence and the strong association observed in the GCS, the Working Group concluded that chance, bias, and confounding were unlikely to explain these findings.

2.6.9 Cancer of the stomach

The association between opium consumption and cancer of the stomach was well studied in two cohort studies (the GCS and Ardabil cohort study) with a combined total of nearly 380 cases, and in two case–control studies with nearly 400 cases combined. All studies showed increased risk of gastric cancer. In one study, opium consumers were observed to be at increased risk of precursor lesions for gastric cancer, alleviating concerns about reverse causation.

The GCS results showed an association between opium use and the risk of gastric cancer, with a fully adjusted hazard ratio of 1.36 (95%, CI, 1.03–1.79), particularly for the noncardia subtype (HR, 1.69; 95% CI, 1.11–2.56; 127 cases) (Sheikh et al., 2020); however, the strength of the evidence for an exposure–response trend was marginal ($P = 0.067$). In the Ardabil cohort study, opium use was associated with an increased risk of cancer of the stomach, with a multivariable-adjusted hazard ratio of 3.24 (95% CI, 1.37–7.66). Opium use in this cohort was also associated with a substantially increased risk of baseline antral and body intestinal metaplasia,

which are precursor lesions for gastric cancer (Sadjadi et al., 2014).

Both case–control studies showed an increased risk of gastric cancer of nearly 3-fold in multivariable-adjusted analyses, with odds ratios of 3.1 (95% CI, 1.9–5.2) and 3.0 (95% CI, 1.6–5.6) for studies conducted by Shakeri et al. (2013) and Naghibzadeh Tahami et al. (2014), respectively. The study by Shakeri et al. (2013) had a reasonably large sample size (n = 309 cases), used the GCSQ, adjusted for the most important potential confounders, performed a sensitivity analysis to rule out reverse causation, and found some evidence of a positive exposure–response association, such that individuals with the highest cumulative opium use had the strongest association (OR, 4.5; 95% CI, 2.3–8.5). The study by Naghibzadeh Tahami et al. also adjusted for multiple confounders and found some evidence of a positive exposure–response relation, showing an odds ratio of 9.2 (95% CI; 2.5–33.7) for those whose cumulative opium use was greater than the median. One of these studies (Shakeri et al., 2013) recruited controls from the GCS, and the other (Naghibzadeh Tahami et al., 2014) from the neighbourhoods of the participants, leaving some potential for under-reporting by the controls.

The Working Group's assessment was that the body of evidence indicated that a positive association was credible. However, chance, confounding, and bias could not be ruled out with reasonable confidence because of the lack of a positive exposure–response in the GCS, lack of adjustment for important risk factors of gastric cancer (most importantly, *H. pylori* and dietary intake) in some studies, and the possibility of under-reporting in controls in case–control studies.

2.6.10 Cancer of the pancreas

In the GCS, there was no evidence of a clear association between ever-use of opium and increased risk of cancer of the pancreas (adjusted HR, 1.54; 95% CI, 0.87–2.72) (Sheikh et al., 2020). However, there was an increased risk among those who were using opium at very high cumulative rates (> 60 nokhod-years), with an adjusted hazard ratio of 2.66 (95% CI, 1.23–5.74) and a trend P value of 0.028.

The case–control study by Shakeri et al. (2016) found an odds ratio of 1.91 (95%, CI, 1.06–3.43). This study had a reasonably large sample size (n = 357 cases), used detailed data similar to those collected in the GCS, adjusted for nearly all of the important confounders, and conducted a sensitivity analysis to rule out reverse causation. The controls were from the same clinic from which the cases were recruited, therefore reducing the possibility of biased reports; however, bias from data collection on the part of the interviewers cannot be entirely ruled out. Furthermore, there was no exposure–response association with either duration of opium use or cumulative opium use.

Although a positive association between opium consumption and cancer of the pancreas was seen in two studies, the Working Group concluded that chance, bias, and confounding cannot be ruled out, partly because the number of studies was small. Although the only case–control study showed some evidence for an association, the cohort study only showed an association with very high exposures.

2.6.11 Cancers of the colon and rectum

The association between opium consumption and cancers of the colon and rectum was studied in a cohort study and two case–control studies. The GCS, with 95 cases of colon cancer, found no positive association between opium use and risk of colon cancer (HR, 0.90; 95% CI, 0.48–1.67),

nor did it find an association with cumulative opium use. However, two case–control studies with similar designs, one conducted in Kerman Province (Naghibzadeh-Tahami et al., 2016) and the other in Fars Province (Iankarani et al., 2017), Iran, both found strong positive associations, with adjusted ORs of 4.5 (95% CI, 2.4–8.7) and 4.48 (95% CI, 2.27–8.82), respectively. Both studies found some evidence of exposure–response associations and both used neighbourhood controls.

The Working Group concluded that bias cannot be ruled out for the association between opium use and cancer of the colon and rectum. While two case–control studies (which were similar in design and were conducted by the same group of investigators) found a strong association with some evidence of an exposure–response relation, the cohort study did not find evidence of a positive association, despite reasonable numbers of cases. Because of conflicting evidence, the Working Group concluded that a positive association had not been observed in the overall body of evidence.

2.6.12 Cancers of the oral cavity, pharynx, and other sites in the head and neck

Although there were six studies of opium consumption and cancers of the oral cavity and pharynx (one case series, one ecological study, and four case–control studies), only one case–control (Mohebbi et al., 2020) study was informative. This study included 254 cancers of the lip and oral cavity, 54 cancers of the pharynx, 28 cases of other subsites, and thousands of controls. Opium consumers were at substantially increased risk of cancers of the pharynx (OR, 2.90; 95% CI, 1.40–6.02) and other subsites of the oral cavity (OR, 5.95; 95% CI, 2.41–14.71) compared with controls. The results were properly adjusted for all important confounders, and showed an exposure–response pattern that remained in tobacco never-smokers, and in sensitivity analysis adjusting for the sensitivity of response among combined cases of head and neck cancer and controls. Furthermore, the study disregarded all opium use that was initiated 3 years or less before case diagnosis.

The Working Group concluded that a positive association between opium consumption and cancer of the pharynx was credible; however, chance, bias, and confounding could not be excluded with reasonable confidence because there was only one well-conducted study.

For all other cancer sites there were too few studies, and the available studies were not considered suitably informative.

2.6.13 Results by route and type of opium consumed

Opium products are typically smoked or ingested. Where results showed an overall positive association between opium use and cancer risk, and were then stratified by route of exposure, increased risk of cancer was seen for both smoking and ingestion. Those who used opium via both routes typically had the highest relative risk compared with never-users. For example, in the GCS, increased risk and a positive exposure–response association ($P < 0.0001$) were seen for all cancers combined (Sheikh et al., 2020). In this study, for all cancers combined and the highest quartile of cumulative opium use (> 60 nokhod-years), the hazard ratios were 1.49 (95% CI, 1.14–1.95), 1.64 (95% CI, 1.33–2.02), and 1.70 (95% CI, 1.42–2.04) for ingestion, smoking, and any route, respectively. In the GCS, the results varied by cancer type. For example, smoking opium was more strongly associated with oesophageal cancer than was ingesting opium. Conversely, ingesting opium was more strongly associated with liver cancer than was smoking opium. However, because of the modest numbers of each cancer, the confidence intervals were wide and overlapping. In a case–control study, Masjedi et al. (2013) found that opium

smoking was a much stronger risk factor for lung cancer than opium ingestion. By contrast, in the IROPICAN case–control study (Mohebbi et al., 2020), ingesting opium was a stronger risk factor for all head and neck cancers combined, as well as for cancers of the lip and oral cavity (excluding the pharynx) and laryngeal cancers, than was smoking opium. Several other examples are summarized in a review article (Kamangar et al., 2014). In summary, the current evidence points to both smoking and ingesting opium as being carcinogenic.

Opium products studied in this monograph included raw opium (*teriak*), opium dross (*sukhteh*), and refined opium (*shireh*). A subset of studies examined risks according to the type of opium used. In these studies, where a positive association was found overall, all opium types were typically associated with an increased risk of cancer. In the GCS (Sheikh et al., 2020), 86% of the participants used raw opium only, 9% used refined opium only, and 5% used opium dross, heroin, or a combination of the above; therefore, it was difficult to adequately study each type of opium used. However, in the GCS, consumption of raw opium, refined opium, and a combination of all forms were positively associated with increased risk of all cancers combined, with hazard ratios of 1.40 (95% CI, 1.23–1.58), 1.18 (95% CI, 0.84–1.66), and 1.67 (95% CI, 1.14–2.44), respectively. In the IROPICAN case–control study (Mohebbi et al., 2020), consumption of raw and refined opium were each associated with increased risk of all head and neck cancers combined, with odds ratios of 3.40 (95% CI, 2.64–4.37) and 7.17 (95% CI, 4.44–11.58), respectively. When stratified by cancer type, refined opium was more strongly associated than raw opium with an increased risk of cancers of the lip and oral cavity, pharynx, and larynx. In summary, the current evidence suggests that all commonly consumed types of opium are associated with higher risk of cancer.

2.6.14 Results stratified by sex and other attributes of the study participants

Where data were provided, positive associations between opium consumption and cancer risk were seen for both men and women. For example, in the GCS (Sheikh et al., 2020), the adjusted hazard ratios for the association between opium use and all cancers combined were 1.43 (95% CI, 1.24–1.65) and 1.26 (95% CI, 1.00–1.59) for men and women, respectively. Increased risks of cancers of the oesophagus, urinary bladder, and lung were observed for both men and women who consumed opium compared with those who did not (Table 2.1, Table 2.2, and Table 2.3).

Similarly, when stratified by tobacco smoking or socioeconomic status, opium consumption was associated with increased risk of cancer in nearly all subgroups (Sheikh et al., 2020).

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3. CANCER IN EXPERIMENTAL ANIMALS

3.1 Mouse

See Table 3.1.

3.1.1 Subcutaneous injection

Three groups of 27–35 female CBA mice (age, 20–24 weeks) were exposed by weekly subcutaneous injection to olive oil only (vehicle control group, *n* =27) or *sukhteh* [opium dross] (collected in the Islamic Republic of Iran) at a total dose of 33 mg for 27 weeks, or to opium pyrolysates (pyrolysis of crude opium from India was carried out in the laboratory) at a total dose of 40 mg for 35 weeks. Moribund mice were killed and complete autopsies performed on all mice (Friesen et al., 1985). [The Working Group noted that reporting for this study was limited. The study duration was not reported, but the Working Group inferred that it was "for life", as with the experiment in hamsters reported in the same article. Similarly, survival was not reported, but reduced survival related to toxicity was implied.] The only results reported were "interim results" at 12 months. No tumours were reported in the control group, two mammary carcinomas were reported in mice treated with *sukhteh*, and one unspecified tumour was reported in mice treated with opium pyrolysates. [The Working Group noted that the denominators (effective number of mice) for the interim results were not provided and also that the study was limited by the low number of mice, possible decreased survival, lack of survival and body-weight data, unknown adequacy of the *sukhteh* and opium pyrolysate doses, and limited reporting.]

3.1.2 Skin application

Two groups of 30 female Swiss mice [assumed age, 52 days] were given *sukhteh* [opium dross] or opium pyrolysates at a total dose of 14.4 mg or 28.8 mg in acetone [presumed], respectively, by dorsal skin application three times per week for 50 weeks (Friesen et al., 1985). After 50 weeks, no tumours were found in mice treated with *sukhteh* or opium pyrolysates. [The Working Group noted that the study was limited by the low number of mice, short study duration, lack of an unexposed or vehicle control group, unknown adequacy of the doses of *sukhteh* and opium pyrolysates, lack of survival and body-weight data, and limited reporting.]

3.1.3 Initiation–promotion

In an initiation–promotion study, three groups of 30 female Swiss mice (age, 52 weeks) were given two doses of 1200 μg of *sukhteh* [opium dross], 200 μg of opium pyrolysates (in 0.05 mL of acetone), or 1000 μg of opium pyrolysates (in 0.05 mL of acetone), with an interval of 2 days, by dorsal skin application. Starting 10 days after initiation, these mice were given

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium

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, CBA (F) 20–24 wk NR [assumed for life] Friesen et al. (1985)	Subcutaneous injection *Sukhteh* [opium dross], NR Olive oil, 0.1 mL Injections given 1×/wk for 27 wk (vehicle control); injections given 1×/wk for 27 wk, totalling 33 mg 27, 27–35 NR	Control, no tumours reported *Sukhteh*, 2 mammary carcinomas (interim results at 12 mo; denominators [effective number of mice] NR)	NA NR	Duration of experiment not explicitly reported, but "for life", as with the study in hamsters in the same article (Friesen et al., 1985), can be inferred. Survival data not reported, but reduced survival possible from reference to toxicity with respect to number of surviving mice. Principal limitations: low number of mice; survival and body-weight data not reported; extent of possible decreased survival unknown; unknown adequacy of the dose; limited reporting.
Full carcinogenicity Mouse, CBA (F) 20–24 wk NR [assumed for life] Friesen et al. (1985)	Subcutaneous injection OP, NR Olive oil, 0.1 mL Injections given 1×/wk for 27 wk (vehicle control); injections given 1×/wk for 35 wk, totalling 40 mg 27, 27–35 NR	Control, no tumours reported OP, 1 unspecified tumour (interim results at 12 mo; denominators [effective number of mice] NR)	NA NR	Duration of experiment not explicitly reported, but "for life", as with the study in hamsters in the same article (Friesen et al., 1985), can be inferred. Survival data not reported, but reduced survival inferred from reference to toxicity with respect to number of surviving mice. Principal limitations: low number of mice; survival and body-weight data not reported; extent of possible decreased survival unknown; unknown adequacy of the dose; limited reporting.

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium (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 (F) NR [assumed to be 52 d] 50 wk Friesen et al. (1985)	Dorsal skin application *Sukhteh* [opium dross], NR Acetone [presumed], 0.05 mL 3×/wk for total of 14.4 mg; no unexposed or vehicle controls reported 30 NR	No tumours induced	NA	Principal limitations: lack of control group; low number of mice; survival and body-weight data not reported; only a 1-yr study; unknown adequacy of dose level; limited reporting (some details inferred from initiation–promotion study described below).
Full carcinogenicity Mouse, Swiss (F) NR [assumed to be 52 d] 50 wk Friesen et al. (1985)	Dorsal skin application OP, NR Acetone [presumed], 0.05 mL 3×/wk for total of 28.8 mg; no unexposed or vehicle controls reported 30 NR	No tumours induced	NA	Principal limitations: lack of control group; low number of mice; survival and body-weight data not reported; only a 1-yr study; unknown adequacy of dose level; limited reporting (some details inferred from initiation–promotion study described below).
Initiation–promotion Mouse, Swiss (F) 52 d 51 wk Friesen et al. (1985)	Dorsal skin application *Sukhteh* [opium dross], NR Acetone, 0.05 mL 0 (control) or 2 doses of 1200 µg (2 d apart), followed by application of 1 µg TPA 1×/wk for 50 wk, starting 10 d after initiation 30 (TPA only), 30 NR	Skin papilloma 1/30, 1/30	[NS]	Principal limitations: low number of mice; survival not reported; only a 1-yr study; unknown adequacy of dose. Positive results (skin papilloma, 23/30) with positive control of initiation with 50 µg DMBA.

Table 3.1 Carcinogenicity studies in experimental animals exposed to opium (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**
Initiation–promotion Mouse, Swiss (F) 52 d 51 wk Friesen et al. (1985)	Dorsal skin application OP, NR Acetone, 0.05 mL 0 (control), 2 doses of 200 µg or 2 doses of 1000 µg (2 d apart), followed by application of 1 µg TPA 1×/wk for 50 wk, starting 10 d after initiation 30 (TPA control), 30, 30 NR	Skin papilloma 1/30, 1/30, 1/30	[NS]	Principal limitations: low number of mice; survival not reported; only a 1-yr study; unknown adequacy of dose. Positive results (skin papilloma, 23/30) with positive control of initiation with 50 µg DMBA.
Full carcinogenicity Hamster, Syrian golden (F) 8 wk Lifetime Friesen et al. (1985)	Intratracheal instillation *Sukhteh* [opium dross], NR Tricaprylin, 0.2 mL 0 (vehicle), 0.880 mg, 1×/wk 10, 10 NR	Vehicle, malignant tumours, 0/10 *Sukhteh*, malignant lymphoma, 2/10; adrenal haemangioendothelioma, 1/10	NA [NS]	No significant decrease in survival. Principal limitations: low number of mice; survival and body-weight data not reported; short lifetimes (average survival of controls, 69 wk); unknown adequacy of dose.
Full carcinogenicity Hamster, Syrian golden (F) 8 wk Lifetime Friesen et al. (1985)	Intratracheal instillation OP, NR Tricaprylin, 0.2 mL 0 (vehicle), 1.659 mg, 1×/wk 10, 10 NR	Vehicle, malignant tumours, 0/10 OP, malignant tumours, 0/10	NA	No significant decrease in survival. Principal limitations: low number of mice; survival and body-weight data not reported; short lifetimes (average survival of controls, 69 wk); unknown adequacy of dose.

d, day; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; mo, month; NA, not applicable; NR, not reported; NS, not statistically significant; OP, opium pyrolysates; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week; yr, year.

12-*O*-tetradecanoylphorbol-13-acetate (TPA) at a dose of 1 µg by dorsal skin application once per week for 50 weeks. A control group of 30 mice was exposed to TPA only (Friesen et al., 1985). Histopathological examination was performed on gross skin tumours. After the 50 weeks of treatment with TPA, no increase in the incidence of skin papilloma was observed in the groups treated with *sukhteh* or opium pyrolysates compared with the controls. [The Working Group noted that the study was limited by the low number of mice, lack of survival data, and unknown adequacy of the *sukhteh* and opium pyrolysate doses.]

3.2 Rat

Initiation–promotion

In an initiation–promotion study, two groups of 15 male Wistar albino rats were given opium by oral administration [presumably by gavage] at a dose of 0 mg/kg body weight (bw) per day (purified water) for 20 (n = 5) or 40 (n = 5) weeks, or 300 mg/kg bw per day [presumably in purified water] for 5 days per week for 16 weeks followed by phenobarbital at a dose of 50 mg/kg bw per day for 5 days per week until the end of the experiment at 20 (n = 5) or 40 (n = 5) weeks (Alzaidi et al., 2018). [It was explicitly stated that a positive control group (diethylnitrosamine-treated) was treated by gavage, and the Working Group inferred the same route of administration for the other groups.] Histopathological examination was performed only on the liver, small intestine, and colon. No carcinogenic changes were found in opium-treated or control rats. [The Working Group noted that the study was limited by the low number of rats, short study duration, unknown adequacy of the opium dose, histopathology limited to the liver, small intestine, and colon, lack of a phenobarbital-only control, and unclear and incomplete reporting (e.g. lack of survival data). This study was deemed to be inadequate for informing the evaluation due to the low number of rats and other limitations, and it was not tabulated or considered further.]

3.3 Hamster

See Table 3.1.

Intratracheal instillation

Three groups of 10 female Syrian golden hamsters (age, 8 weeks) were given vehicle only (0.2 mL of tricaprylin), 0.88 mg of *sukhteh* [opium dross], or 1.659 mg of opium pyrolysates by intratracheal instillation, once per week for life. Moribund hamsters were killed and complete autopsies performed on all hamsters (Friesen et al., 1985). There was no significant decrease in average survival between hamsters treated with opium pyrolysates or *sukhteh* when compared with the vehicle control group. No malignant tumours were found in the control group or in hamsters treated with opium pyrolysates. Two malignant lymphomas and one adrenal haemangioendothelioma were reported in hamsters treated with *sukhteh*. [The Working Group noted that the study was limited by the low number of hamsters, lack of survival and body-weight data, short lifetimes, and unknown adequacy of the *sukhteh* and opium pyrolysate doses.]

3.4 Evidence synthesis for cancer in experimental animals

Opium, *sukhteh*, and opium pyrolysates were tested for carcinogenicity in mice, rats, and hamsters. The three studies available in mice (a study in female CBA mice treated by subcutaneous injection, a study in female Swiss mice treated by skin application, and an initiation–promotion study in female Swiss mice (Friesen et al., 1985) and the available study in Syrian golden hamsters (an intratracheal installation

study; Friesen et al., 1985) had various limitations, including low numbers of animals, lack of survival and body-weight data, unknown adequacy of the treatment doses, and limited reporting. The available study in rats, an initiation–promotion study (Alzaidi et al., 2018), was considered uninformative due to the low number of rats, and other limitations.

References

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Friesen M, O'Neill IK, Malaveille C, Garren L, Hautefeuille A, Cabral JR, et al. (1985). Characterization and identification of 6 mutagens in opium pyrolysates implicated in oesophageal cancer in Iran. *Mutat Res.* 150(1–2):177–91. doi:10.1016/0027-5107(85)90114-9 PMID:4000158

4. MECHANISTIC EVIDENCE

4.1 Absorption, distribution, metabolism, and excretion

This section describes the available evidence on the absorption, distribution, metabolism, and excretion of opium alkaloids after the consumption of opium by humans and experimental animals.

The biomedical effects of opium originate from the properties of either the major components of opium or their metabolic products. In the case of opium smokers, the products of pyrolysis should also be considered, although the structures of the products involved have not been clearly determined.

Direct studies characterizing rates of absorption after oral or inhalation exposure are sparse; however, evidence for absorption in humans and experimental animals is provided by the studies on intoxication and studies characterizing excretion described in Sections 4.1.1 and 4.1.2. Distribution of opium alkaloids to various tissues – and excretion including via the urine, gastrointestinal tract, and hair – has similarly been demonstrated both in humans and in rodents, as described below.

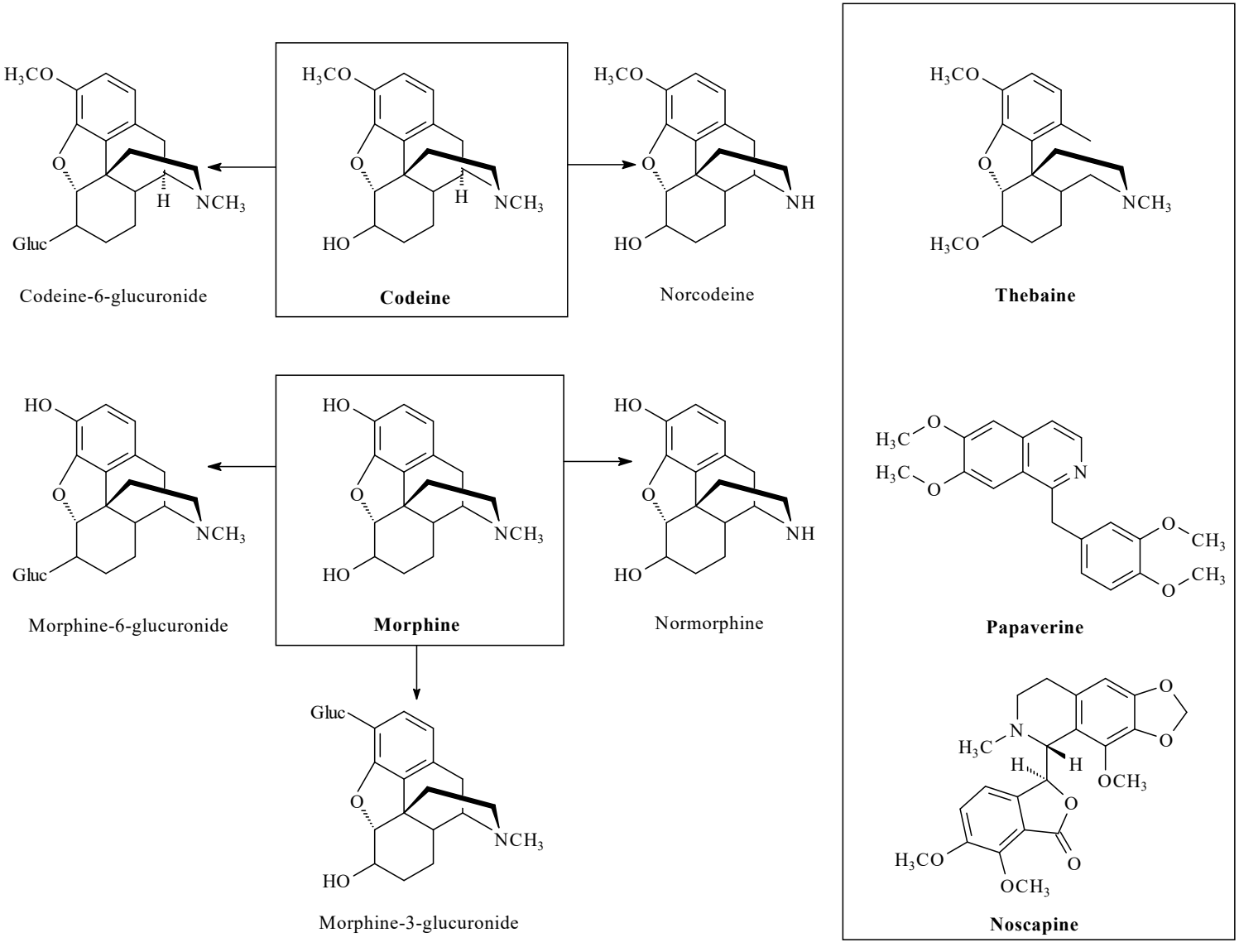
The metabolism of the major alkaloids in opium, such as morphine and codeine, has been well studied (Dinis-Oliveira, 2019). However, there are few reports on the pharmacokinetic properties of opium (mixtures of alkaloids and other components) in humans, except in the field of forensic toxicology. The primary site of morphine biotransformation is the free phenolic hydroxyl group at position 3 via which morphine is converted to inactive morphine-3-glucuronide (M3G; 57.3%); only a small percentage of morphine is converted via the alcohol group at position 6 to active morphine-6-glucuronide (M6G; 10.4%). Both conjugations are catalysed mainly by uridine 5′-diphospho-glucuronosyltransferase (UGT)2B7, but also by UGT1A1, UGT1A3, and UGT1A9 (Dinis-Oliveira, 2019). Codeine has an alcoholic hydroxyl available for glucuronidation only at position 6, leading to the formation of active/analgesic codeine-6-glucuronide, which is the major metabolite (80%). Of an oral dose of codeine, 0–15% is O-demethylated to morphine by the polymorphic enzyme cytochrome P450 2D6 (CYP2D6) and 10–15% is N-demethylated to norcodeine via CYP3A4 (Dinis-Oliveira, 2019). The chemical structures of the five major alkaloids in opium and their metabolites, described in this section, are shown in Fig. 4.1.

4.1.1 Humans

(a) Exposed humans

Morphine was detected in all hair samples collected from 30 opium smokers (all men who had been referred to a detoxification centre).

Fig. 4.1 Structures of the five major alkaloids in opium (shown in boxes) and their metabolites



Gluc, glucuronide.
Compiled by the Working Group.

The ages of the participants ranged from 21 to 51 years and their hair colour (natural or dyed) was reported to be black, blond, light brown, or white. Each participant had smoked 1–7.5 g of opium per day for 12–92 months. Gas chromatography-mass spectrometry analyses of extracts from the hair samples revealed a morphine concentration range of 0.26–10.31 ng/mg of hair. The higher the daily dose of opium, the higher the morphine concentration in hair. In addition, higher concentrations of morphine were detected in black hair than in hair of other colours (Sabzevari et al., 2004). In a hair sample obtained from a woman aged 50 years, in the Republic of Korea, who had cultivated opium poppies in her private garden and had ingested the liquid extracted from the poppies, thebaine (0.7 ng/mg), morphine (0.4 ng/mg), codeine (0.6 ng/mg), and norcodeine (below the limit of quantification) were detected (Lee et al., 2011). In a urine sample from a man who was an "opium eater", who had been hospitalized for treatment of cancer of the oesophagus, morphine (0.64 µg/mL) was detected at nearly twice the concentration of codeine (0.37 µg/mL), while normorphine and norcodeine were detected in equal amounts (about 0.15 µg/mL). The patient had ingested approximately 1 g per day of a dark, resinous material that he identified as *sukhteh* [opium dross] from his opium pipe. After the urine sample had been treated with β-glucuronidase to hydrolyse the conjugated metabolites, the concentrations of the four compounds described above increased by more than 10 times. There were no traces of thebaine, papaverine, or oripavine after the sample had been treated (Cone et al., 1982). In the case of a sudden fatality (a man aged 32 years) involving opium consumption in a legal poppy field in Spain, thebaine (0.10, 7.12, 0.23, and 14.80 mg/L), morphine (0.13, 4.50, 0.13, and 6.60 mg/L), and codeine (0.48, 0.88, 0.17, and 1.50 mg/L) were detected in the man's peripheral blood, urine, vitreous humour, and gastric contents, respectively. Other toxicological findings included the presence of metabolites of cocaine and cannabis (Martínez et al., 2016).

Reticuline is a minor alkaloid in opium (0.001–0.3%, w/w) and it is a precursor of the principal opium alkaloids thebaine, morphine, and papaverine. Analyses from a forensic laboratory showed that 291 urine samples from opium users (their intake route was uncertain) contained reticuline and morphine. The percentage concentration ratios of reticuline : morphine (2–12) in these urine samples were higher than those in opium (0.01–3). As well as being a constituent of opium, reticuline in the urine of opium users may also result from the metabolic demethylation of the three other benzyltetrahydroisoquinoline opium alkaloids: codamine, laudanosine, and laudanine (Al-Amri et al., 2004). Extracts of 100 urine samples obtained from forensic case studies, which had previously yielded positive results in an immunoassay for opiates, were examined by gas chromatography-mass spectrometry. Neopine was detected in urine samples obtained from both opium users and pharmaceutical codeine users but could not be detected in urine samples obtained from confirmed heroin users. Neopine, a minor opium alkaloid, has been identified as a metabolite of codeine in humans, and may be a marker of opium use or pharmaceutical codeine and heroin use (Al-Amri et al., 2005).

Urinary levels of metabolites of several toxicants and carcinogens were higher among exclusive long-term users of opium and dual users of opium and cigarettes than non-users. Urine from opium users contained high concentrations of several toxicant and carcinogen metabolites, and dual users of opiates and cigarettes had higher concentrations of all biomarkers than people who used cigarettes or opium exclusively. Opium consumption contributed substantially to the levels of many of these metabolites, particularly those of polycyclic aromatic hydrocarbons and some volatile organic compounds, namely metabolites of acrylamide, 1,3-butadiene, and

dimethylformamide. Among the toxicant and carcinogen biomarkers present at high concentrations in opium users, most were present at similar concentrations regardless of route of use (ingestion or smoking), except for a few that were associated with smoking opium (Etemadi et al., 2020).

(b) Studies on volunteers

The maxima in the hourly urinary excretion patterns of morphine occurred 2–4 hours after single doses of a medicinal opium mixture containing 2.5 mg of morphine and smaller amounts of codeine, together with a kaolin solution, were administered orally to six volunteers. The urinary excretion of morphine appeared to be a more gradual process than that observed after the consumption of medicinal morphine hydrochloride (equivalent to 1.5 mg of morphine base). The morphine concentrations in urine were generally below 1.0 μg/mL. A significant amount of codeine was also detected in each urine sample. The codeine:morphine ratio ranged from 0.1 to 0.7. In total, the amount of morphine (free and conjugated) excreted during an 8-hour period after consumption was found to be in the range of 6–17%. Although a single dose of opium contained more morphine than a single dose of medicinal morphine, the total urinary excretion of morphine after the consumption of opium was about four times less than in the case of medicinal morphine (Yong & Lik, 1977).

Urinary excretion of both morphine and codeine reached their maxima 2–6 hours after ingestion of a single dose of either tablets or a solution of Brown Mixture (BM), which is a legal prescription drug in Taiwan, China, and contains opium powder, opium tincture, or camphorated opium tincture. Single oral doses of one, two, four, or six BM tablets (each tablet contained 281.11 μg of morphine and 32.41 μg of codeine) were administered to four volunteers. Single oral doses of 5, 10, 15, or 20 mL of BM solution (containing opium tincture, with morphine and codeine at concentrations of 134.91 μg/mL and 46.85 μg/mL, respectively) were administered to the same four volunteers, respectively, 2 weeks after completion of the first experiment. In addition, multiple oral doses (three times per day for 2 days) of one, two, or four BM tablets were administered to three additional volunteers. Multiple oral doses of 5, 10, and 15 mL of BM solution were administered to the same three volunteers, respectively, 2 weeks after the completion of the first experiment. Urine was collected at 0, 2, 4, 6, 8, 10, 12, 14, and 16 hours, and then every 4 or 8 hours until both codeine and morphine became undetectable (< 0.05 μg/mL). Morphine concentrations found in urine specimens collected from the volunteers were always < 4 μg/mL. Depending on the dose administered, morphine became undetectable 24–42 hours after a single dose, while codeine disappeared more quickly (8–18 hours). Morphine:codeine ratios observed in urine specimens with morphine concentrations of < 300 μg/mL were: (i) less than 3.0 for volunteers ingesting BM solution and (ii) greater than 3.0 (mostly > 5.0) for volunteers ingesting BM tablets (Liu et al., 2006).

Plasma morphine concentrations differed significantly across dosing groups (6.66, 13.3, and 20 mg of morphine equivalents, twice per day) in a study of 45 opium-dependent Thai participants who were allocated to one of three different dosing groups depending on their self-reported prior opium use. On day 5 of the dosing period, an interdosing interval study was conducted in which blood samples were taken from participants, and their withdrawal scores, heart rates, and blood pressure were assessed at 0, 1, 3, and 8 hours. Plasma morphine concentrations changed significantly across the interdosing interval for all three doses ($P = 0.0001$), increasing to a maximum 1 hour after administration and then decreasing rapidly to a minimum 8 hours after ingestion. The mean ratios of the morphine glucuronides M3G and M6G were: M3G:M6G,

7.7; M3G:morphine, 35.6; and M6G:morphine, 4.9 (Somogyi et al., 2008).

4.1.2 Experimental systems

Thebaine, codeine, norcodeine, and morphine were detected in the dark grey hair of three male lean Zucker rats given an opium suspension, prepared by shaking opium in saline, at a dose of 100 mg/kg, once per day for 2 weeks. Before dosing began, areas of dark grey and white hair were separately shaved. These areas were shaved again and hair collected 2 weeks after administration of the final doses. The mean concentrations of thebaine, codeine, norcodeine, and morphine in the dark grey hair were 3.2, 2.6, 0.6, and 1.2 ng/mg, respectively. Normorphine was also detected in the dark grey hair but was below the limit of quantification. No opiates were detected in the white hair (Lee et al., 2011).

There was only one report that described compounds in vapour derived from the volatilization of opium, and the urinary excretion of these compounds after inhalation of volatilized opium by experimental animals (Kikura-Hanajiri et al., 2003). In three male Wistar rats exposed to opium by vapour inhalation for 20 minutes, the following compounds were detected in urine collected over a 72-hour period: M3G (5.45–14.38 μg), morphine (2.27–4.65 μg), meconin (4.60–5.06 μg), codeine (0.54–1.85 μg), noscapine (0.34–0.40 μg), and papaverine (0.01–0.04 μg). Only a trace level of thebaine was observed.

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether opium consumption is genotoxic; alters cell proliferation, cell death, or nutrient supply; induces chronic inflammation; is immunosuppressive; or induces oxidative stress. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is genotoxic

Table 4.1 and Table 4.2 summarize the identified studies relevant to whether opium is genotoxic.

(a) Exposed humans

Abedi-Ardekani and co-workers characterized the mutation pattern of the oncosuppressor gene *TP53* in tumour biopsies collected from 119 patients with oesophageal squamous cell carcinoma who were enrolled in a case–control study in Golestan, a north-eastern province of the Islamic Republic of Iran, an area where the incidence of oesophageal squamous cell carcinoma is one of the highest in the world (Abedi-Ardekani et al., 2011). Only 15 (12.6%) and 21 (17.6%) of the participants reported using opium or both tobacco and opium, respectively. The molecular analysis of the mutational spectrum revealed the highest rate of *TP53* mutation (89.9%) ever reported to date, anywhere and in any cancer (107/119 cases, 15/15 opium users, and 17/19 opium and tobacco users had at least one mutation). Direct sequencing of *TP53*, exons 2 through 11, showed a heterogeneous pattern of mutations likely due to the additive action of several environmental carcinogens (Abedi-Ardekani et al., 2011).

Specifically, GC→AT transitions, not located at cytosine-phosphate-guanine (CpG) sites, were the most common mutations (25%) followed by GC→TA transversions (16.7%). GC→AT transitions can be the result of exposure to several mutagens, such as alkylating agents, nitrosoamines, and nitric oxide (NO), therefore preventing the assignment of this mutation to a single category of mutagens. However, GC→TA transversions are the most common mutations induced by polycyclic aromatic hydrocarbons, which

Table 4.1 Genetic and related effects of opium in exposed humans

End-point	Tissue, cell type	Location, setting, study design	Exposure level and number of exposed and controls	Response[a]	Covariates controlled	Comments	Reference
Gene mutation, *TP53* exons 2 through 11 (direct sequencing)	Biopsies of 119 oesophageal squamous cell carcinomas	Golestan, Iran (Islamic Republic of), case–control study	15 opium users 21 opium and tobacco users, 67 neither Lower numbers for specific mutations	(–)	Age, sex, ethnicity, tobacco consumption (ever/never), tea temperature, and residence (urban/rural)	Mutation patterns differed with temperature of tea consumed, but not with opium use. Small number of opium users, especially for specific mutations. Opium exposure was poorly defined and specified.	Abedi-Ardekani et al. (2011)

[a] (–), negative in a study of limited quality.

Table 4.2 Genetic and related effects of opium in human cells in vitro and in experimental systems

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Human cells						
Sister-chromatid exchange	Human PBMCs	+	+ (0.5% S9 mix)	Opium pyrolysates or *sukhteh* [opium dross], 30 µg/mL	Small sample size (three healthy donors). Dose–response relationships.	Perry et al. (1983)
Non-human mammalian cells						
Sister-chromatid exchange	Chinese hamster ovary cells	+	+ (0.5% S9 mix)	Opium pyrolysates or *sukhteh* [opium dross] (approximate dose range, 5–100 µg/mL) LEC, 5 µg/mL	Dose–response relationships.	Perry et al. (1983)
Non-mammalian systems						
Base substitution (TA100) and frameshift mutations (TA98) (Ames test)	*Salmonella typhimurium* TA100 and TA98	NR	± (TA98)	Crude opium	Crude opium, six samples.	Malaveille et al. (1982)
		NR	– (TA100)			
		±	+	*Sukhteh* [opium dross]	*Sukhteh*, 21 samples; TA98 > TA100.	
		+	+	Opium pyrolysates	Opium pyrolysates from four countries all + in both strains with and without activation; concentration-dependent relationships with activation; TA98 > TA100.	
Frameshift mutations (Ames test)	*Salmonella typhimurium* TA1538	NT	+	*Sukhteh* [opium dross]		Malaveille et al. (1982)
		NT	+	Opium pyrolysates		
Base substitution (TA100) and frameshift mutations (TA98) (Ames test)	*Salmonella typhimurium* TA100 and TA98	–	+	*Sukhteh* [opium dross]: LEC, 2080 µg/plate (TA100) LEC, 800 µg/plate (TA98)	Concentration-dependent relationship for mutagenic effect of *sukhteh* in both strains; T98 > TA100	Hewer et al. (1978)
		–	–	*Shireh* [a minimally refined opium product]: HIC, 6250 µg/plate	Non-mutagenicity of *shireh* may be due to preassay processing.	
		–	± (TA98)	Crude opium	Questionable purity of some crude opium samples.	
		–	– (TA100)			

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; PBMC, peripheral blood mononuclear cell.

[a] +, positive; –, negative; ±, equivocal (variable response in several experiments within an adequate study).

are human carcinogens produced by pyrolysis, including during opium smoking. [The Working Group noted that the number of opium-only users was small, especially for analyses of specific *TP53* mutations, and opium exposure was poorly defined and specified.]

(b) Human and other mammalian cells in vitro

In vitro cell culture studies show that *sukhteh* [opium dross] and opium pyrolysates induce sister-chromatid exchanges in both human peripheral blood mononuclear cells and Chinese hamster ovary cells. A clear dose–response relationship was observed in both cell types with or without metabolic activation, indicating the presence of direct clastogenic agents in opium pyrolysates (Perry et al., 1983).

(c) Non-mammalian experimental systems

Assays for mutagenicity or genotoxicity in bacteria using *Salmonella typhimurium* strains TA98 and TA100 have been performed for various opium products. In an early study, six samples each of *sukhteh* [opium dross] and *shireh* [a minimally refined opium product], and three samples of crude opium, were collected in villages in the north-east of the Islamic Republic of Iran and in Transkei, South Africa, and three samples of crude opium from other countries were obtained from the French Ministry of Health (Hewer et al., 1978). A concentration-dependent increase in mutagenesis was observed for *sukhteh* in both strains with rat liver microsomal activation. At each tested concentration, the mutagenicity induced by *sukhteh* was higher in the TA98 than in the TA100 strain (Hewer et al., 1978). Although it sometimes contains *sukhteh*, *shireh* exhibited little mutagenic activity in either strain, possibly due to processing before the assay was conducted (Hewer et al., 1978). The crude opium samples showed no mutagenic activity, with the exception of three of the village samples, which may have been contaminated with *sukhteh*, which is often mixed with crude opium (Hewer et al., 1978). These early results were confirmed by a larger study, which tested 21 samples of *sukhteh* [opium dross] and 6 of raw opium, as well as opium pyrolysates from four different countries (Malaveille et al., 1982). In addition, *sukhteh* and opium pyrolysates induced frameshift mutations in *Salmonella typhimurium* strains TA98 and TA1538 (Malaveille et al., 1982).

4.2.2 Alters cell proliferation, cell death, or nutrient supply

Table 4.3 summarizes the identified studies relevant to whether opium alters cell proliferation, cell death, or nutrient supply.

(a) Exposed humans

Compared with those from non-tobacco smokers, smears of buccal mucosa and mouth floor samples obtained from smokers and opium-addicted participants were characterized by an increase in both nuclear diameter and nuclear:cytoplasmic ratio, as well as by a decrease in cellular size. The smears were collected from a cohort of 300 men (100 controls, 100 tobacco smokers, and 100 opium addicts). (Hashemipour et al., 2013). [The Working Group noted that the cigarette-smoking status of the opium user group was not reported and as such there was no attempt to distinguish the effects of cigarette smoking. Cytomorphometry may not represent cell proliferation.]

The effect of opium consumption on argyrophilic nucleolar organizer region (AgNOR) changes in buccal mucosa cells was evaluated in a cohort of men and women that included non-smokers, tobacco smokers, and opium addicts. The opium addicts included tobacco smokers, with the average cigarette consumption per day being similar in the two groups (18.7 in opium addicts vs 18.4 in tobacco smokers). Exfoliative cytological analysis showed a higher AgNOR count in smokers than in controls and

Table 4.3 End-points relevant to cell proliferation and death in exposed humans

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)[a]	Covariates controlled	Comments	Reference
Cytomorphometry	Smears of buccal mucosa and mouth floor	Kerman City, Iran (Islamic Republic of), cross-sectional	100 opium addicts (≥ 4 g/day during ≥ 3 of the last 6 yr; selected by DSM-IV-TR criteria for addiction), 100 tobacco smokers, 100 non-smokers; ≥ 4 g opium/day	+ Different rate of keratinization and significant[b] differences in cellular size of epithelial cells in opium addicts vs non-smokers	Tobacco; users of alcohol and drugs affecting oral epithelium excluded	Questionnaire, no details of questions or whether administered or self-completed. Well-defined opium use except that type of opium is not presented; had to be recent opium use and ≥ 4 g/day; grams per day and duration of addiction collected; also collected tobacco smoking per day and duration; alcohol users excluded.	Hashemipour et al. (2013)
AgNOR count	Smears of buccal mucosa	Tehran, Iran (Islamic Republic of), cross-sectional	25 opium addicts (exposure level NR; average duration 12.8 yr), 25 tobacco smokers (average cigarette consumption/day similar, 18.7 in opium addicts vs 18.4 in tobacco smokers), 25 non-smokers	+ ($P < 0.0001$) Opium addicts (9.21 ± 2.95) > tobacco smokers (5.68 ± 2.17) > non-smokers (4.3.5 ± 1.62)	Opium addicts include tobacco smokers, then opium addicts are compared with tobacco smokers	Assessment method not given; very little information on exposure, which is poorly defined and characterized; many of the opium addicts also smoked.	Kadivar & Attar (2008)

AgNOR, argyrophilic nucleolar organizer region; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; NR, not reported; vs, versus; yr, year.

[a] +, positive

[b] Statistical significance was defined as $P < 0.05$ (Mann–Whitney test and Student's *t*-test).

in opium addicts than in smokers (Kadivar & Attar, 2008). [The Working Group noted that the AgNOR end-point lacks specificity for reflecting cell proliferation.]

(b) Human cells in vitro and other experimental systems

No data were available to the Working Group. [The Working Group noted that opium has been demonstrated to have pro-apoptotic activity in human cells in vitro (Khaleghi et al., 2016) and in rodents in vivo (Asiabanha et al., 2011; Asadikaram et al., 2013a). Opium-induced apoptosis and necrosis has also been reported in Jurkat cells (an immortalized line of human T-lymphocyte cells) (Igder et al., 2013); see Section 4.2.3.]

4.2.3 Induces chronic inflammation or is immunosuppressive

See Table 4.4.

(a) Exposed humans

(i) Cytokines

Most of the available studies in humans have compared cytokine levels in opium users and non-users.

In a study of patients with documented three-vessel coronary artery disease, 15 cigarette-smoking men with opium addiction were compared with 15 cigarette-smoking non-addicted men. Levels of interleukin (IL) 1R antagonist, an acute-phase inflammation marker, were significantly higher in the addicted group, while levels of IL6 were similar between the two groups. All patients performed a treadmill test, and levels of cytokines were measured before, immediately after, and 4 hours after the test (Saadat et al., 2012). [The Working Group noted that the exposure was defined as "patients with only opium addiction (raw opium inhalation)" and that no details were given about how the opium history was obtained. The Working Group also noted that no details regarding the levels of cigarette smoking across groups were given.]

In a study of 30 male opium addicts and matched controls, plasma levels of IL4 and interferon γ (IFNγ) were significantly lower, and IL6 and transforming growth factor β (TGFβ) were significantly higher, in opium-addicted participants than in controls. Individuals who smoked tobacco or consumed other substances (any medication, other components of opium such as morphine, heroin, and drugs for the treatment of heroin withdrawal such as methadone) were excluded (Nabati et al., 2013). The study also included in vitro evaluation of lymphocytes from both groups with and without opium treatment ("culturing with opium"), as described in Section 4.2.3b. [The Working Group noted that no details were given about how opium history was obtained, and that the publication contains few details about the characteristics of addicts and non-addicts.]

In a study by Ayatollahi-Mousavi et al. (2016) that examined the associations between cytokine concentrations and opium addiction in opium addicts with or without fungal infection, 72 individuals in four groups of 18 individuals each (opium addicts/non-opium-addicts, with/without fungal infection) were assessed. Two-way analysis of variance (ANOVA) showed that levels of IL17, TGFβ, and IFNγ in blood plasma differed significantly between opium addicts and non-addicts, whereas levels of IL4 and IL6 did not. [The Working Group noted that the analyses did not sufficiently account for fungal infection.] After excluding the 36 individuals with fungal infection, IL17 levels in opium addicts were significantly higher than those in non-addicts. The differences reported for IFNγ, TGFβ, IL4, and IL6 levels were not statistically significant based on the Working Group's analysis of opium users and non-users without fungal infection. [The Working Group noted that

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Cytokines (IL1 receptor antagonist and IL6 levels) ESR	Plasma	Tehran, Iran (Islamic Republic of), patients with three-vessel coronary artery disease (all men), cross-sectional	Exposure level, NR 15 cigarette smokers (mean age 54.7 ± 1.7 yr) with opium addiction were compared with 15 non-addicted sex-, age-, and cigarette-smoking-matched patients	Higher IL1Ra plasma levels in the addicted patients compared with the non-addicted patients (before, immediately after, and 4 h after treadmill test in all patients) ($P = 0.015$) No significant changes in IL6 plasma levels and ESR	NR	Poorly defined and poorly characterized exposure; exposure definition was "patients with only opium addiction (raw opium inhalation)". No details were given about how the opium history was obtained. All patients were current tobacco smokers; however, no details on levels of tobacco smoking across groups were provided. IL1Ra and IL6 levels were measured in conjunction with treadmill test; ESR results were based on single measurement per patient.	Saadat et al. (2012)

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans (continued)

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Cytokines (IL4, IFNγ, IL6, and TGFβ levels)	Plasma	Kerman, Iran (Islamic Republic of), opium addicts and non-addicted controls (all men), cross-sectional	30 opium-addicted individuals (aged 19–56 yr; smoking > 0.5 g/day for ≥ 1 yr) and 30 non-addicted age-, residence-, and BMI-matched controls	Lower levels of IL4 in addicts (15.11 ± 0.5561 pg/mL) compared with controls (20.57 ± 0.9420 pg/mL) ($P < 0.0001$) Lower levels of IFNγ in addicts (13.43 ± 0.5673 pg/mL) compared with controls (44.91 ± 3.995 pg/mL) ($P < 0.0001$) Higher levels of IL6 in addicts (367.2 ± 14.42 pg/mL) compared with controls (238.2 ± 8.596 pg/mL) ($P < 0.0001$) Higher levels of TGFβ in addicts (1657 ± 73.36 pg/mL) compared with controls (1028 ± 63.74 pg/mL) ($P < 0.0001$)	NR	Well-defined but poorly characterized exposure; minimum amount of opium smoked per day to enter the study, but type not presented; years of exposure not mentioned and amount of opium not presented; individuals excluded if tobacco smokers or consumers of opiates or other medications; control group non-opium users and non-tobacco smokers; source of addicts and control individuals NR. No details were given about how the opium history was obtained.	Nabati et al. (2013)

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans (continued)

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Cytokines (IL4, IL6, IL17, IFNγ, and TGFβ levels)	Plasma	Kerman, Iran (Islamic Republic of), male hospital attendees, cross-sectional	Addicted to opium (smoked and/or ingested for ≥ 3 yr) without FI (n = 18); non-addicted controls without FI (n = 18); mean age, 33.43 ± 5.22 yr	Higher levels of IL17 in addicts (159.10 ± 47.45 pg/mL) compared with controls (121.17 ± 26.62 pg/mL) (significance, NR) Lower levels of IFNγ in addicts (75.56 ± 37.23 pg/mL) compared with controls (88.74 ± 20.11 pg/mL) (significance, NR) Higher levels of TGFβ in addicts (731.05 ± 259.80 pg/mL) compared with controls (683.88 ± 94.76 pg/mL) (significance, NR) No significant changes in IL4 and IL6 plasma levels	NR	Poorly characterized exposure; opium exposure defined as addict or not, with no details on the intensity and type of opium. Questionnaire about smoking and narcotic drug use, but no details given. Exclusion criteria: being female, aged < 18 yr or > 60 yr, and taking immunosuppressive drugs Did not include statistical analysis comparing opium users and non-users with and without FI; the Working Group's analysis (t-test) showed that only the difference in IL17 was significant.	Ayatollahi-Mousavi et al. (2016)

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans (continued)

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Cytokines (TNFα)	Plasma	Mazandaran, Iran (Islamic Republic of), opium users during an MTT programme and healthy non-smoking controls (all men), cross-sectional study (baseline data from intervention study)	20 tobacco-smoking opium addicts (> 1 g/day for ≥ 1 yr). 40 controls (20 tobacco smokers/20 non-smokers)	Higher TNFα in patients before methadone therapy (199.96 ± 69.14 pg/mL) compared with the tobacco smoker (141.23 ± 96.2 pg/mL) or non-smoker (40.22 ± 25.8 pg/mL) comparison groups ($P < 0.05$) TNFα levels decreased significantly during methadone treatment	NR	Data collected at clinical interview; opium use validated by opioid detected in urine at baseline. Well-defined, validated exposure, unclear if collected intensity and duration except to confirm minimum exposure; type of opium and method of exposure not presented; comparison group clearly unexposed to opium, but source of subjects not described. Other substance users excluded by urine tests. Levels of smoking slightly higher in opium users than in tobacco-smoking controls (1.3 vs 1.1 pack-years).	Salarian et al. (2018)

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans (continued)

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Cytokines (IL4, IL10, IL17, and IFNγ levels) hs-CRP	Serum/ plasma	Arak, Iran (Islamic Republic of), opium addicts from a detoxification centre and healthy individuals with no history of drug abuse as the control group (all men), cross-sectional	44 opium addicts from a detox centre (aged 20–40 yr; mean, 31 yr) who smoked opium, > 2 g/day (range, 2000–3000 mg) for ≥ 1 yr; 44 age-, sex-, SES-, and tobacco-smoking status-matched controls	Higher levels of IL10 (95.48 ± 13.05 pg/mL) in opium users compared with controls (66.28 ± 2.62 pg/mL) ($P < 0.026$) Higher levels of IL17 (19.23 ± 0.64 pg/mL) in opium users compared with controls (16.99 ± 0.15 pg/mL) ($P < 0.001$) Higher levels of IFNγ (521.15 ± 33.08 pg/mL) in opium users compared with controls (399.44 ± 19.30 pg/mL) ($P < 0.002$) Higher levels of hs-CRP (8.93 ± 1.93 mg/mL) in opium users compared with controls (0.72 ± 0.09 mg/mL) ($P < 0.0001$) No significant changes in IL4 plasma levels	NR	No details were given about how the opium history was obtained, probably by questionnaire. Well-defined exposure consumption of opium (> 2 g/day for ≥ 1 year), which was not further characterized; confirmed by urine tests; smoked as *teriak*; years of exposure not collected. Polydrug abusers and alcohol users excluded; tobacco smokers included. Controls recruited by public announcement.	Ghazavi et al. (2013a, b)

Table 4.4 Effects of opium use on immune function and inflammation in exposed humans (continued)

End-point	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
hs-CRP	Plasma	Isfahan, (Islamic Republic of), opium addicts from a rehabilitation centre, and non-opium-addicted current smokers as controls (all men), cross-sectional	360 opium addicts (smoking opium for 5 mo to 5 yr), route of administration (orally, *vafoor*, and *sikh-sang*), all cigarette smokers; 360 non-opium addicts but current smokers, age- and cigarette/day-matched controls The mean number of smoked cigarettes/day was 15 ± 2 and 16 ± 3 in the opium-addicted and control groups, respectively The mean age was 38 ± 5 yr in the cigarette-smoking control group and 41 ± 3 yr in the opium-addicted group	Higher levels of CRP (4.11 ± 0.7 mg/dL) in opium users compared with controls (3.54 ± 0.3 mg/dL) ($P < 0.029$)	NR	Opium exposure defined as "opium addict" and assessed for oral and two inhalation routes; duration of addiction measured but not intensity. Questionnaire about smoking and narcotic drug use, no details. Study on cardiovascular risk factors.	Asgary et al. (2008)
CD4+ T-cell count		Tehran, (Islamic Republic of), HIV infected referred to an HIV/AIDS reference laboratory, Imam Khomeini hospital, case series	5 "patients who used opium" among 99 HIV-infected patients; exposure level, NR	Lower CD4+ T-cell count (245.68 ± 21.8 cells/mm^3) in opium users compared with controls (367.40 ± 40.7 cells/mm^3) ($P < 0.008$)		Study on HIV-infected patients, only 5/99 used opium; exposure poorly defined and characterized with type of opium, duration, and exposure method not presented. Common route was injection, but various drugs included. Study on clinical and laboratory profiles of patients with HIV.	Mohammadi et al. (2016)

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FI, fungal infection; h, hour; HIV, human immunodeficiency virus; hs, high-sensitivity; IFN, interferon; IL, interleukin; IL1Ra, interleukin-1 receptor antagonist; mo, month; MTT, methadone maintenance treatment; NR, not reported; SES, socioeconomic status; TGF, transforming growth factor; TNF, tumour necrosis factor; vs, versus; yr, year.

the lack of adjustment for cigarette smoking was also a major limitation.]

A study of 60 individuals (20 with opium addiction, 20 cigarette-smoking controls, and 20 non-smoking controls) included follow-up of opium users during a methadone maintenance treatment programme designed to help them quit opium use. During transition from opium to methadone, blood and urine samples of the participants were periodically tested for opium use to ensure quitting. Opium users had higher plasma levels of tumour necrosis factor α (TNFα; an inflammation mediator) than both cigarette-smoking and non-smoking controls. During the methadone maintenance treatment programme, levels of TNFα dropped significantly until day 14 (when the study ended). Data were collected at clinical interview including diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis, and opium use was validated by blood and urine test. Users had consumed opium for an average of 9.6 years and used on average 2.9 g per day; 60% smoked opium (Salarian et al., 2018). [The Working Group noted that the characteristics of users and controls were fully described.]

Two papers have been published that concern a single study of 44 opium addicts who voluntarily enrolled for detoxification and 44 matched controls recruited by "public announcement" (Ghazavi et al., 2013a, b). Serum concentrations of IFNγ, IL10, and IL17 in opium addicts were all significantly higher than in controls, but concentrations of IL4 were similar between the two groups (Ghazavi et al., 2013a). Opium addicts in this study also had increased levels of C-reactive protein (CRP), C3 and C4 complements, and immunoglobulin A, but not immunoglobulin M (Ghazavi et al., 2013b). [The Working Group noted that these two papers contain little information about the characteristics of addicts and non-addicts, including tobacco use, although controls were described as being matched to cases for cigarette smoking.]

(ii) General inflammation markers

In addition to the above study by Ghazavi et al. (2013a), which showed higher CRP levels in opium addicts compared with healthy controls with no lifetime history of substance abuse, two other studies have investigated general inflammation responses in opium users. In one study, described above (Saadat et al., 2012), the erythrocyte sedimentation rate was found to not differ significantly between opium addicts and non-addicts. In another study of "cardiovascular risk factors" in 360 opium-addicted individuals (who were also cigarette smokers) and 360 current cigarette smokers with no opium addiction, the concentrations of CRP were reported to be higher in individuals with opium addiction (Asgary et al., 2008).

In a study of 99 HIV-positive individuals, the five opium users had significantly higher CD4 counts than other groups of HIV-infected individuals. No additional data about opium use, the method of obtaining history of opium use, and other confounders were given (Mohammadi et al., 2016).

(b) Human cells in vitro

In a study of in vitro production of IFNγ and IL10 after antigenic stimulation of whole blood cells, 10 opium addicts were compared with 10 heroin addicts and 10 healthy controls (all groups consisted of men aged 20–40 years). Compared with healthy controls, levels of IFNγ decreased and IL10 increased in the whole blood cells from both opium and heroin addicts after antigenic stimulation. The changes in IFNγ and IL10 in the cells from opium addicts were less significant than those from heroin addicts. All individuals had negative test results for HIV and hepatitis B surface antigen. The addicts had used opium for an average of 8.7 years and were enrolled in a detoxification programme (Azarang

et al., 2007). [The Working Group noted that the study provided no details about how the opium history was obtained and how the controls were selected, nor did it mention cigarette smoking in any group.]

Lymphocytes from 30 male opium addicts and their matched controls (study described in Section 4.2.3a; Nabati et al., 2013) were studied in vitro with opium treatment (2.86×10^{-5} g/mL for 48 hours; "culturing with opium") and without. The plasma concentrations of IL4 and IFNγ in opium-addicted participants were significantly lower than those in the control group, while the concentrations of IL6 and TGFβ were significantly higher. The concentrations of all four cytokines in the in vitro supernatants of lymphocytes from opium-addicted participants were significantly lower than those from the control group. In the in vitro supernatants of lymphocytes from opium-addicted participants, concentrations of IL4, IL6, and TGFβ, but not IFNγ, decreased significantly in response to opium treatment. Culturing with opium increased IFNγ secretion by lymphocytes from the control group but did not affect the levels of other cytokines (Nabati et al., 2013).

Exposure of Jurkat cells to different concentrations of opium increased the secretion of IL6, decreased the secretion of TGFβ, and initially decreased IFNγ but later increased its secretion. These effects varied according to the opium dose and duration of treatment (Asadikaram et al., 2015).

The effects of opium on the induction of apoptosis and necrosis in Jurkat cells have been studied in two publications. In the first, the cells were treated with different concentrations of opium (2.86×10^{-3} or 2.86×10^{-11} g/mL) and compared with untreated cells (controls) after 6, 24, and 72 hours (Igder et al., 2013). Some of the opium-treated cells showed increased apoptosis after 6 hours, and there seemed to be a dose–response association at 24 hours. [The Working Group noted that the 72-hour results were inconsistent with a dose–response association.] There was evidence of increased necrosis with some of the opium concentrations at 24 and 72 hours. [The Working Group noted that the necrosis was not dose-dependent, nor was it consistent across different times since exposure.] The second study showed 50% of cells had apoptotic features (messenger RNA (mRNA) for pro-apoptotic and anti-apoptotic molecules) among cells treated with different concentrations of opium after 48 hours (Arababadi & Asadikaram, 2016). [Again, the Working Group noted there was no clear correlation with the opium concentration. In addition, the results for mRNA patterns and anti-apoptotic molecules did not include adjustment for multiple testing.]

(c) Experimental systems

In rats given two daily doses of opium of 30–150 mg/kg bw administered intraperitoneally at 08:00 and 20:00 for 9 consecutive days, there was a slight decrease in levels of TGFβ in males, but a significant increase in females compared with controls (Asadikaram et al., 2010). Increased neutrophil counts and decreased lymphocyte counts in peripheral blood of male and female rats were also observed compared with controls (Asadikaram et al., 2013b).

Plasma levels of IFNγ were increased and of IL4 were decreased before and after surgical stress in opium-addicted rats. Differences in IL10 and TNFα levels were not statistically significant (Lashkarizadeh et al., 2016).

Intraepithelial lymphocytes from the ilea of guinea-pigs that had been treated with 1 mL of deodorized opium tincture (orally) 2 hours before cell collection showed deficient natural killer cytotoxicity and antibody-dependent cellular cytotoxicity, but were resistant to infection by *Shigella sonnei*. When guinea-pigs were fasted before the opium tincture was administered, further decreases in both types of lymphocyte cytotoxicity were observed, and the lymphocytes

were susceptible to *Shigella sonnei* infection (Morgan et al., 1984).

4.2.4 Induces oxidative stress

See Table 4.5.

This section describes the effects of opium on oxidative stress and on antioxidants. Findings from four studies in exposed humans are described below. No data from studies in human cells in vitro or in other experimental systems were available to the Working Group.

There are several biomarkers that are used to assess oxidative stress in studies in humans. These biomarkers assess oxidative damage to DNA, protein oxidation, and lipid peroxidation in cellular systems. No studies on opium examining DNA damage by formation of 8-oxodeoxyguanosine were available to the Working Group. [The Working Group noted that formation of 8-oxodeoxyguanosine is the most studied and abundant oxidative DNA lesion (used as a specific biomarker of oxidative DNA damage), which is characterized by inducing G→T transversions, which are mutagenic.]

Ghazavi et al. (2013b) assessed redox status by measuring NO levels in serum samples from 44 male opium smokers and 44 healthy age-, sex-, socioeconomic status-, and tobacco-smoking status-matched controls with no lifetime history of drug abuse. NO production was estimated by the Griess reaction. Levels of NO in serum samples from opium smokers were higher than in those from the controls, but this increase was not statistically significant. Salarian et al. (2018) investigated plasma malondialdehyde levels, an index of lipid peroxidation, in 20 tobacco-smoking opium users attending community clinics and 40 (20 smoking and 20 non-smoking) healthy controls. Urine tests were conducted to confirm opium use, and users of other substances were excluded. Malondialdehyde levels (assayed via thiobarbituric acid-reacting substances) did not significantly differ between the opium-user and control groups. After an intervention (quitting opium and substituting with methadone), malondialdehyde levels significantly decreased by days 7 and 14 in the intervention group after methadone therapy, compared with before methadone therapy in tobacco-smoking opium users (Salarian et al., 2018).

The activities of the antioxidant enzymes superoxide dismutase (SOD) and catalase were reported to be decreased in two studies (Safarinejad et al., 2013; Salarian et al., 2018). In the study described in the paragraph above, Salarian et al. (2018) reported that erythrocyte SOD activity (measured by the oxidation of NADP/NADPH) was lower in the 20 tobacco-smoking opium users than the 40 healthy controls (both the smoking and non-smoking groups), but the decrease was only significant when compared with the 20 non-smoking controls. Catalase activity (measured by decomposition of hydrogen peroxide) was significantly lower in patients with opioid use disorder and in the tobacco-smoking opium users and control groups than the non-smoking control group. After the 20 tobacco-smoking opium addicts received an intervention (quitting opium and substituting with methadone), levels of both SOD and catalase significantly increased by day 14 of the intervention (Salarian et al., 2018). Similarly low SOD and catalase levels in semen of opium users were reported by Safarinejad et al. (2013). This study compared 142 men who were opiate addicts with 146 men who were healthy controls. Significantly lower levels of SOD- and catalase-like activities were seen in addicts than in controls. [The Working Group noted that the latter study included 36 (25.3%) heroin users among the opiate addicts; however, Table 3 of the study reports similarly significant decreases in SOD- and catalase-like activities for users of crude and refined opium separately from the data for the heroin users.]

Total antioxidant capacity (TAC) was reported in two studies (Ghazavi et al., 2013b; Dwivedi

Table 4.5 Effects of opium use on oxidative stress markers in exposed humans

End-points	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Redox status, TAC	Serum/ plasma	Arak, Iran (Islamic Republic of), exposed/ unexposed comparison	44 opium-addicted men from a detox centre (aged 20–40 yr; mean 31 yr) who smoked opium, > 2 g/day for ≥ 1 yr (range 2000–3000 mg); 44 age-, sex-, SES-, and tobacco-smoking status-matched controls	Serum levels of NO higher (92.90 ± 9.12 µM) in opium users compared with controls (83.92 ± 4.85 µM) but NS ($P = 0.344$) Higher FRAP values in opium users (972.75 ± 11.55 µM) compared with controls (761.95 ± 18.61 µM) ($P < 0.0001$)	NR	No details were given about how the opium history was obtained, probably by questionnaire. Well-defined exposure for consumption of opium (> 2 g/day for ≥ 1 yr), which was not further characterized; confirmed by urine tests; smoked as *teriak*; years of exposure not collected. Polydrug abusers and alcohol users excluded; tobacco smokers included.	Ghazavi et al. (2013b)
Lipid peroxidation (MDA) and antioxidant enzymes (SOD and CAT activity)	Plasma, erythrocytes	Mazandaran, Iran (Islamic Republic of), exposed/ unexposed comparison	20 tobacco-smoking opium addicts (> 1 g/day for ≥ 1 yr); 40 controls (20 smokers/20 non-smokers)	MDA level not significantly different Lower SOD activity in patients before methadone therapy (12.71 ± 10.005 U/mg haemoglobin) compared with the smoker (20.08 ± 10.34; NS) or non-smoker (25.18 ± 11.25) comparison group ($P < 0.05$) Lower CAT activity in the patients with opioid use disorder (224.56 ± 37.7 k/mL) and in tobacco-smoking group (216.82 ± 33.4 k/mL) compared with the non-smoker (274.22 ± 31.6 k/mL) group (both $P < 0.05$)	NR	Data collected at clinical interview; opium use validated by opioid in urine at baseline. Well-defined, validated exposure, unclear if collected intensity and duration except to confirm minimum exposure; type of opium and method of exposure not presented; comparison group clearly unexposed to opium. Other substance users excluded by urine tests.	Salarian et al. (2018)

Table 4.5 Effects of opium use on oxidative stress markers in exposed humans (continued)

End-points	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Antioxidant enzymes (SOD and CAT)	Semen	Iran (Islamic Republic of); patients from several addiction treatment centres; exposed/ unexposed comparison	142 male opiate users (age, 20–50 yr) selected by DSM-IV-TR criteria for addiction, reporting use of 2.7 ± 1.2 nokhods[a]/ day; 146 healthy male controls	Lower SOD-like activity in opium users (38.4 ± 1.4 U/mL) compared with controls (49.3 ± 12.2 U/mL) ($P = 0.002$) Lower CAT-like activity in opium users (316 ± 17 U/mL) compared with controls (371 ± 42 U/mL) ($P = 0.003$)	Age, BMI, occupational status, educational level, smoking status, serum testosterone, luteinizing hormone, and prolactin	Could be questionnaire or interview; opium use validated by opioid in urine, but results not presented and no individual results for opium-only use presented. Well-defined, apparently validated exposure; collected intensity and duration, type of opium, and method of exposure; cannot separate opium and heroin users. Polydrug consumers excluded by urine analysis. 36 of the opiate users were heroin users; similar results excluding the heroin users. Tobacco smokers included.	Safarinejad et al. (2013)

Table 4.5 Effects of opium use on oxidative stress markers in exposed humans (continued)

End-points	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
TAC	Serum	Rajasthan, India; addiction clinic of a tertiary care centre; exposed/unexposed comparison	90 male opiate users (≥ 100 mg/day for ≥ 1 yr) and 30 healthy controls	TAC higher in opiate-only users while opiate users who smoked tobacco had significantly lower TAC	Age, dependence years, and basic biochemical profile	"Chronic opiate abusers" diagnosed with ICD-10, recruited from addiction clinic; controls were their attendees; screened by urine opiate test; no information about type of opium or tobacco exposure was collected; severity of opiate dependence evaluated by SODQ Opium use ≥ 100 mg/day for ≥ 1 yr duration described as "chronic"; types of opium exposure combined (pure opium, opium husk, and includes heroin); included opium-only users group and opium + tobacco-smoking and chewing tobacco groups; multiple-substance abusers excluded. Well-defined exposure to opiates (note this included opium or heroin), which was not further characterized; opiate use ≥ 100 mg/day for ≥ 1 yr, duration described as "chronic"; types of opium exposure combined (pure opium, opium husk, and includes heroin); smoking and chewing tobacco, but no other exposures considered.	Dwivedi et al. (2019) See also Purohit et al. (2017)

Table 4.5 Effects of opium use on oxidative stress markers in exposed humans (continued)

End-points	Sampling matrix	Location, setting, study design	Exposure level and number of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
Lipid peroxidation (MDA), protein oxidation (protein carbonyl), antioxidant enzymes (SOD activity), and TAC	Serum	Afzalipour and Shafa, and Payambar-e-Azam hospitals, Kerman, Iran (Islamic Republic of); admissions for lead poisoning; exposed/unexposed comparison	192 opium addicts (median use 2 g/day) with symptoms of lead poisoning and 104 healthy controls with no occupational contact with lead	MDA level significantly higher in opium addicts (0.45 ± 0.3 µM) compared with controls (0.17 ± 0.16 µM) ($P < 0.001$) Protein carbonyl significantly higher in opium addicts (0.31 ± 0.09 mM) compared with controls (0.19 ± 0.09 mM) ($P < 0.001$) Significantly lower SOD activity in opium addicts (7.6 ± 1.4 U) compared with controls (28.7 ± 5.1 U) ($P < 0.001$) TAC significantly lower (0.24 ± 0.22 mM) in opium addicts compared with controls (1.04 ± 0.15 mM) ($P < 0.001$)	None	Data collection (a structured interview with questionnaire). Opium exposure defined as "addicts"; duration of exposure undefined. Route of opium use 16% inhalation, 62% oral, and 22% both. Lead co-exposure (lead-adulterated opium), and evidence of lead poisoning in the opium users. 48% of opium users smoked tobacco; smoking in unexposed group unknown.	Shojaeepour et al. (2018)
Interventions (7–14 days)							
Lipid peroxidation (MDA) and antioxidant enzymes (SOD and CAT)	Plasma Erythrocytes		20 opium addicts who quit opium use and substituted with methadone	MDA was significantly decreased from baseline on days 7 and 14 ($P < 0.05$) CAT levels significantly improved by day 7 and SOD levels by day 14 of the intervention ($P < 0.05$)		See Salarian et al. (2018) above. Quitting opium use had an immediate significant effect on oxidative stress when tested after 7 or 14 days.	Salarian et al. (2018)

BMI, body mass index; CAT, catalase; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; FRAP, ferric reducing/antioxidant power; ICD-10, International Classification of Diseases 10th Revision; MDA, malondialdehyde; NO, nitric oxide; NR, not reported; NS, not significant; SES, socioeconomic status; SOD, superoxide dismutase; SODQ, severity of opiate dependence questionnaire; TAC, total antioxidant capacity; yr, year.

[a] *Nokhod*, the local unit for opium use, approximately 0.2 g.

et al., 2019). In the study described above, Ghazavi et al. (2013b) examined TAC using the ferric reducing/antioxidant power (FRAP) test. FRAP levels were significantly higher in the 44 opium smokers than in the 44 controls, suggesting that opium smoking increased the antioxidant capacity. Dwivedi et al. (2019) conducted a study of 90 chronic opiate users who were men attending an addiction centre and 30 healthy controls in Rajasthan, India, which was validated by urine tests, and measured TAC using the 2,2′-azino-di-(3-ethylbenzthiazoline sulfonate) method. [The Working Group noted that the test method was stated in a publication by the same group (Purohit et al. (2017).] The opiate users were subdivided into three groups: opium-only users, opium users who chewed tobacco, and opium users who smoked tobacco. They reported that opium-only users had higher TAC levels than the controls.

Shojaeepour et al. (2018) reported significantly higher malondialdehyde and protein carbonyl (a marker of protein oxidation) levels, lower SOD activity, and lower TAC in 192 opium addicts with clinical signs of lead poisoning from lead-adulterated opium compared with 104 controls with no occupational exposure to lead.

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5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

Opium is a highly addictive narcotic drug that has been used for centuries for medicinal and non-medicinal purposes. It has analgesic, hypnotic, antitussive, gastrointestinal, and cognitive effects.

Opium comes from the juice (latex) of the unripe seedpod of the poppy plant (*Papaver somniferum*), and has a complex chemical composition consisting of at least 25 alkaloids (e.g. morphine, codeine, and thebaine) and other ingredients. Opium is often adulterated with compounds such as lead to enhance its weight. Illicit opium product may therefore be a combination of opium and other compounds. The types and percentages of the alkaloids in opium differ widely between different poppy cultivars. The latex can be processed by drying or boiling before consumption. Opium includes raw or crude opium, opium dross (tarry residues formed after smoking raw opium), and refined opium or opium sap (boiled opium dross with or without raw opium). All forms of opium are typically smoked or ingested. Pyrolysis products may result from combustion (smoking) of all three forms of opium. Opium derivatives (morphine, codeine, and heroin) are not considered in the present monograph.

Opium production and distribution have been controlled internationally since 1961, and 190 countries have ratified an international convention controlling the production, distribution, and use of opium.

Opium is produced illicitly in some 50 countries worldwide, and global production has increased during the last decade from 4950 to 7610 tonnes. Over 80% of the world's illicit opium comes from Afghanistan. Of the total opium produced, 15–20% is used as raw or minimally processed opium. In 2009, the Islamic Republic of Iran was estimated to be the world's largest per capita consumer of raw or minimally processed opium, representing 42% of total global opium consumption, followed by Afghanistan and Pakistan. In 2018, there were an estimated 5 million users of illicit opium worldwide.

Due to its illicit nature, "street" opium is not subject to safety standards. Legal opium is used to produce opium tincture and syrup; however, these represent a small proportion of global opium production.

Epidemiological studies have been conducted only on users of illicit forms of opium and have used questionnaires, interviews, or patient records to evaluate opium exposure. Some studies compared questionnaire/interview data on opium consumption with opium biomarkers. Opium derivatives can be detected in blood,

urine, hair, and nails for limited periods after opium exposure.

The amount of detail and the quality of exposure information varied considerably across the epidemiological studies. Some studies defined opium consumption as opium dependence using standardized tools such as those based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Multiple studies used the structured and validated Golestan Cohort Study (GCS) questionnaire (GCSQ), which defined opium exposure as use more than once per week for at least 6 months. The GCSQ incorporated questions on opium type, dose, mode of consumption, temporality of exposure, duration, intensity, and cumulative exposure. To date, cohort studies that have used the GCSQ have evaluated baseline questionnaire data only, so any time-varying changes in exposure status have not been reported. This may be important, particularly in cancers with a long latency period. Many studies asked the participants to quantify the amount of opium consumption using grams or a local unit of nokhods per day, but these estimates were likely imprecise.

The factors most strongly related to opium use across studies were sex, age, tobacco smoking, and socioeconomic status.

5.2 Cancer in humans

The studies of cancer in humans that were available for this evaluation have all investigated illicit opium consumption in the form of the minimally processed latex of the poppy plant (*P. somniferum*). Opium, as purchased and consumed by millions of people in several countries, is a complex mixture that includes alkaloids (e.g. morphine and thebaine), non-alkaloids (e.g. sugars, fats, meconic acid, and water), and impurities (e.g. lead and chromium). Several informative cohort and case–control studies have investigated the association between opium consumption (by smoking or ingestion of crude opium, opium dross, or minimally processed opium) and cancers of various sites in humans. Some of these studies, most notably the GCS, had a strong design and used several strategies to alleviate concerns about bias. Cancers of the oesophagus, urinary bladder, lung, larynx, pancreas, stomach, colon and rectum, and pharynx were studied in more depth.

A cohort study (the GCS) showed a positive association between opium consumption and risk of oesophageal cancer, with an exposure–response association. A case–control study also showed a positive association when cases were compared with neighbourhood controls, but the association disappeared when cases were compared with hospital controls. In both studies, the large majority of the oesophageal cancer cases were of squamous type. The Working Group concluded that although a positive association is credible, chance, bias, and confounding cannot be ruled out with reasonable confidence. The association observed in the cohort study was not very strong and could possibly have arisen due to residual confounding. The results of the case–control study are subject to interpretation based on the appropriateness of the control group.

The GCS found a strong association between opium consumption and risk of urinary bladder cancer, with evidence of an exposure–response relation. Likewise, nearly all eight case–control studies that studied the association between opium consumption and urinary bladder cancer found higher odds of opium use among cases than in controls, with adjusted odds ratios ranging from 2 to 5. Control selection, adjustment for confounding, and definition of exposure varied among studies; however, it was notable that all studies, regardless of design, pointed in the same direction. The Working Group concluded that despite a modest number of cases in the cohort study, a positive association has been observed and that, collectively, the most informative studies rule out confounding, bias,

and reverse causation with a reasonable degree of confidence.

The association between opium consumption and laryngeal cancer has been extensively studied in a cohort study (the GCS) and six case–control studies. The GCS found a strong positive association between opium consumption and risk of laryngeal cancer, with an exposure–response association. Likewise, all six case–control studies showed substantially increased opium use among laryngeal cancer patients compared with controls, ranging from 2- to 16-fold. The quality of these studies – including adjustment for potential confounders, excluding opium use that initiated within a few years before diagnosis, and various other sensitivity analyses – varied across studies. However, the two studies that adjusted for many confounders and analysed the data in various ways also found strong associations between opium consumption and laryngeal cancer. The Working Group concluded that a positive association has been observed. The more informative studies, collectively, rule out chance, confounding, bias, and reverse causation with reasonable confidence. This inference resulted from the observation of very strong associations, exposure–response associations, consistency across studies, availability of studies with large sample sizes, and various efforts to rule out bias and confounding in at least two key studies: the GCS and IROPICAN (the Iranian Study of Opium and Cancer).

The association between opium consumption and lung cancer has been studied in a cohort study (the GCS) and three case–control studies. The cohort study found a positive association with an exposure–response trend for increasing quartiles of consumption. These results were adjusted for cigarette smoking and other potential confounders, although adjustment for cigarette smoking might have been less than ideal due to the low number of study participants with lung cancer who used opium but never smoked cigarettes. The quality of control selection, adjustment, and exposure data collection varied across the case–control studies. However, all three case–control studies, which collectively involved a large number of cases and controls, showed a positive association between opium consumption and lung cancer, with adjusted odds ratios ranging from 2 to 6. The Working Group concluded that a positive association has been observed. Given the totality of evidence and the strong association observed in the cohort study, the Working Group concluded that chance, bias, and confounding were unlikely to explain the results.

In the GCS, ever-use of opium did not show a clear association with an increased risk of pancreatic cancer. However, there was evidence of an association for participants who had very high amounts of cumulative use. A case–control study found evidence of increased risk among opium users. The controls were from the same clinic from which the cases were recruited, therefore reducing the possibility of biased reports; however, bias from data collection on the part of interviewers cannot be entirely ruled out. However, there was no exposure–response association with either duration of opium use or cumulative opium use in this case–control study. The Working Group concluded that a credible association was observed, but chance, bias, and confounding cannot be ruled out, partly because the number of studies was small. Although the only case–control study showed some evidence to support an association, the cohort study showed an association only for very high exposures.

The association between opium consumption and gastric cancer has been studied in two cohort studies (the GCS and Ardabil cohort study) and two case–control studies. All studies showed increased risk of gastric cancer. In one study, opium consumers were observed to have an increased risk of developing precursor lesions for gastric cancer, alleviating concerns about reverse causation. The GCS results showed a positive association with opium consumption,

particularly for the noncardia subtype, but the exposure–response trend was not statistically significant. In the Ardabil cohort study, opium consumption was associated with an increased risk of baseline antral and gastric body intestinal metaplasia, which are precursor lesions for gastric cancer, and subsequent incident gastric cancer. Both case–control studies also showed strong positive associations between opium consumption and odds of gastric cancer. The Working Group's assessment was that although a positive association in the body of evidence was credible, chance, confounding, and bias from potential under-reporting in case–control studies cannot be ruled out with reasonable confidence. This decision was reached partly because of lack of a clear exposure–response relation and partly because of lack of data for *H. pylori* or diet in some of these studies, which may lead to confounded results.

The association between opium consumption and cancers of the colon and rectum has been studied in a cohort study (the GCS) and two case–control studies. The GCS found no positive association between opium consumption and risk of colon cancer, nor did it find an association with cumulative opium consumption. However, two case–control studies with similar design, conducted by some of the same investigators, found evidence of strong associations between opium consumption and risk of cancer of the colon and rectum. The Working Group concluded that an association has not been established, primarily because of conflicting evidence and the lack of any positive association in the cohort study.

Only one case–control study was considered informative for cancers of the head and neck excluding the larynx. This study had a large sample size and used a variety of methods to adjust for confounding and alleviate concerns about reverse causation and under-reporting by cases and controls. This study found a strong positive association between opium consumption and cancer of the pharynx. The Working Group concluded that a positive association between opium consumption and pharyngeal cancer was credible, but that chance, bias, and confounding could not be excluded with reasonable confidence, primarily because there was only one (well-conducted) study.

5.3 Cancer in experimental animals

The available studies on opium could not be interpreted as showing either the presence or the absence of a carcinogenic effect because of major limitations, including low numbers of animals, lack of survival and body-weight data, unknown adequacy of the treatment doses, and limited reporting.

5.4 Mechanistic evidence

Evidence of opium absorption, distribution, and metabolism in humans and rodents is provided by studies on intoxication and excretion. In humans, opium metabolites have been detected in urine, hair, and blood after ingestion or smoking of opium. In rats, metabolites have been measured in hair after oral exposure and in urine after inhalation of volatilized opium.

There is consistent and coherent evidence in experimental systems that opium exhibits key characteristics of carcinogens: it is genotoxic. There is consistent evidence for *sukhteh* (opium dross) and opium pyrolysates (solid residues of combusted opium), but not for raw opium, that such forms induce clastogenicity and mutagenicity. Studies in exposed humans were uninformative. *Sukhteh* and opium pyrolysates induced dose-related increases in sister-chromatid exchange in human primary peripheral blood mononuclear cells and Chinese hamster ovary cells, with and without metabolic activation. No data for mammalian experimental systems in vivo were available. *Sukhteh* and opium

pyrolysates consistently induced mutagenicity in multiple strains of *Salmonella typhimurium* that are indicators of base-pair substitution and frameshift mutations. The studies on genetic and related effects are not numerous. However, consistent findings were seen across several test systems in different species, indicating that forms of opium containing pyrolysates are genotoxic. In multiple experimental systems, including human cells and cells from another mammalian and non-mammalian species, forms of opium containing pyrolysates induced both clastogenicity and mutagenicity. This evidence is also coherent with what is known about the genotoxicity and mutagenicity of combustion products.

There is also some evidence of increases in the incidence of precursors to chronic inflammation; however, the data are inconsistent. Evidence pertaining to oxidative stress and antioxidant status is conflicting. Information related to other key characteristics of carcinogens was sparse.

6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of opium consumption. Opium consumption causes cancers of the urinary bladder, larynx, and lung. Positive associations have been observed between opium consumption and cancers of the oesophagus, stomach, pancreas, and pharynx.

6.2 Cancer in experimental animals

There is *inadequate evidence* in experimental animals regarding the carcinogenicity of opium.

6.3 Mechanistic evidence

There is *strong evidence* in experimental systems that opium, specifically *sukhteh* and opium pyrolysates, exhibits key characteristics of carcinogens (it is genotoxic).

6.4 Overall evaluation

Opium consumption is *carcinogenic to humans (Group 1).*

6.5 Rationale

The evaluation of opium consumption (i.e. smoking or ingestion) as Group 1 is based on a determination of *sufficient evidence* of carcinogenicity in humans. In reaching this determination, the Working Group noted that in a cohort study of 50 045 adults in Golestan Province, a north-eastern province of the Islamic Republic of Iran, self-reported opium consumption was assessed at baseline, validated with urinary levels of opium metabolites, and the cohort was followed for more than a decade to ascertain incident cancers. The risk of several types of cancer – including cancers of the urinary bladder, larynx, and lung – was significantly higher among opium users than non-users and increased in an exposure-dependent fashion with cumulative opium use. The prospective cohort design minimized concerns regarding selection bias and reverse causation, and the detailed assessment of demographic, socioeconomic, and lifestyle factors addressed concerns regarding the major potential confounders of the associations of interest. These cohort study findings are supported by multiple case–control studies that provide evidence of positive associations between opium consumption and these types of cancer, often based upon larger numbers of site-specific cancer cases, ascertained over a larger geographical area in the Islamic Republic of Iran and, in many cases,

derived in studies that used similar exposure assessment tools and covariate adjustments to those used in the Golestan Cohort Study. While individually each study has its limitations, the Working Group concluded that, collectively, these studies provide a basis to rule out chance, bias, and confounding as alternative explanations for the positive association between opium use and cancers of the urinary bladder, larynx, and lung with reasonable certainty; thus, there was *sufficient evidence* of human carcinogenicity for these three cancer types. Additionally, evidence was deemed to be *limited* that opium consumption causes cancers of the oesophagus, stomach, pancreas, and pharynx. While positive associations were seen in the body of evidence for these cancers, chance, bias, and/or confounding could not be ruled out with reasonable confidence. The *sufficient evidence* of carcinogenicity in humans applies to smoking and ingestion as routes of consumption of raw, dross, and minimally refined opium.

There is also *strong evidence* in experimental systems that opium, specifically *sukhteh* and opium pyrolysates (solid residues of combusted opium), exhibits key characteristics of carcinogens. These opium forms are genotoxic. There is *inadequate evidence* in experimental animals regarding the carcinogenicity of opium consumption because all available studies had major qualitative or quantitative limitations.

LIST OF ABBREVIATIONS

AgNOR	argyrophillic nucleolar organizer region
AIDS	acquired immunodeficiency syndrome
BCE	before the Common Era
BM	Brown Mixture
BPH	benign prostatic hyperplasia
CE	Common Era
CI	confidence interval
CpG	cytosine-phosphate-guanine
CRP	C-reactive protein
DNA	deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
FFQ	food frequency questionnaire
GC-MS	gas chromatography-mass spectrometry
GCS	Golestan Cohort Study
GCSQ	Golestan Cohort Study Questionnaire
GI	gastrointestinal
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HR	hazard ratio
IFNγ	interferon gamma
IL	interleukin
IROPICAN	Iranian Study of Opium and Cancer
MDA	malondialdehyde
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
mRNA	messenger RNA
NO	nitric oxide
OR	odds ratio
RNA	ribonucleic acid
SCC	squamous cell carcinoma
SOD	superoxide dismutase
TAC	total antioxidant capacity
TGFβ	transforming growth factor beta

TNFα	tumour necrosis factor alpha
UGT	UDP-glucuronosyltransferase

ANNEX 1
SUPPLEMENTARY MATERIAL FOR SECTION 1, EXPOSURE CHARACTERIZATION

The supplementary web-only tables presented in Annex 1 (listed below and available from: https://publications.iarc.fr/600) were produced in draft form by the Working Group and were subsequently fact-checked but not edited.

Please report any errors to imo@iarc.fr.

Table S1.6.2A Exposure assessment quality of studies on cancer of the oesophagus and opium consumption

Table S1.6.2B Exposure assessment quality of studies on cancer of the urinary bladder and opium consumption

Table S1.6.2C Exposure assessment quality of studies on cancer of the lung, larynx, and other cancers of the respiratory tract and opium consumption

Table S1.6.2D Exposure assessment quality of studies on cancers at "other" organ sites and opium consumption

Table S1.6.2E Exposure assessment quality of mechanistic studies on opium exposure

ANNEX 2
METHODOLOGICAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDIES ON OPIUM CONSUMPTION AND CANCER

The epidemiological evidence regarding associations between opium use and cancer includes two cohort studies and several case–control studies. Bias in estimates of associations between opium exposure and cancer can result from limitations in study design or execution. Potential biases in studies of opium–cancer associations discussed in the present Annex include reverse causation, protopathic bias, selection bias, information bias (for example, recall bias), and confounding. For each potential bias, we review possible threats to validity in the most informative cohort study (the Golestan cohort study, GCS) and in case–control studies of the association between opium use and cancer. We conclude with a summary regarding the extent to which these biases could explain the observed findings in these studies of opium–cancer associations.

Reverse causation

It has been suggested that individuals living in regions where opium is used who are diagnosed with cancer may take opium to relieve disease symptoms. "Reverse causation" is a term used when a defined outcome of interest causes a change in the exposure of interest (Fig. A1). A prospective cohort design, such as the GCS, in which participant entry to the study is conditional on being disease-free (not having had a cancer diagnosis), allows one to avoid reverse causation when assessing opium use and cancer in a population that is followed over time for subsequent cancer. Assessment of opium use at baseline is conditional on not having disease diagnosis and therefore disease must be ascertained after exposure assessment. In contrast, in case–control studies on opium use and cancer, if cancer diagnosis affects subsequent opium exposure then a statistical estimate of association derived from a model in which cancer was the outcome of interest and opium was the explanatory variable

Fig. A1 Reverse causation: the association between outcome (D) and exposure (T)

Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point during follow-up.

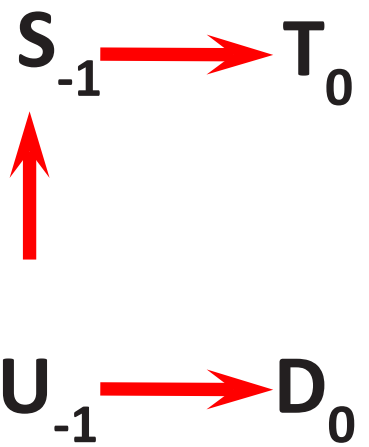
could be liable to misinterpretation about the direction of the causal association.

In a case–control study, reverse causation is not a concern if the investigator was able to reliably assess opium history before diagnosis and focus the analysis on the association between opium history before a cancer diagnosis has been made. However, when information about exposure is collected after cancer diagnosis, as in nearly all of these case–control studies of opium use and cancer, the exposure assessment for cases often fails to distinguish information regarding opium exposure before diagnosis from information about exposure after diagnosis. Aliasgari et al. (2004), Aliramaji et al. (2015), and Bakhshaee et al. (2017) provided no clear indication of the time frame relevant to history of opium use assessment (e.g. distinguishing use before an index date defined by diagnosis). In contrast, Nasrollahzadeh et al. (2008) empirically assessed the potential for this form of bias, noting that exclusion of the cases and controls who had recently started using opium from the analysis made no notable difference to the study results, and younger age at first use was a strong predictor of cancer risk. Also, in a lung cancer case–control study in which some patients started using opioids after being diagnosed with cancer, Naghibzadeh-Tahami et al. (2020) excluded both opioid consumption after cancer diagnosis, and recent opium use, defined as within 2 years of the diagnosis date for cancer cases or the enrolment date for controls.

Protopathic bias

A threat to validity that is related to reverse causation is protopathic bias (Porta et al., 2014), a form of confounding that may occur if an individual uses opium in response to a symptom of an outcome of interest that is – at the time of exposure – still undiagnosed, and if those

Fig. A2 Protopathic bias: the association between a latent factor (U), associated with a symptom (S), true exposure (T), and outcome (D)



Subscripts indicate time on study, where 0 denotes study entry and –1 represents a time-point before study entry.

with symptoms have a higher probability of the outcome. Protopathic bias refers to settings in which a symptom experienced before disease diagnosis causes a change in the exposure of interest. For example, symptoms, such as chronic cough or pain, that are associated with a particular cancer may be causes of opium use among individuals who have not yet been diagnosed with cancer. In Fig. A2, D denotes cancer status at study entry time 0 and U denotes a latent factor at time –1 (for example, a premalignant condition leading to a symptom, S, and associated with cancer, D). A cohort study design, such as the GCS, is susceptible to protopathic bias if exposure is assessed in a population that includes symptomatic individuals. If symptoms at baseline are associated with opium use at baseline and with subsequent cancer risk, then bias would occur. In the GCS, Sheikh et al. (2020) addressed the potential for such bias by conducting a sensitivity analysis that excluded events occurring in the first 24 months of follow-up.

This form of bias was also considered in some papers reporting on studies with a case–control

design. Nasrollahzadeh et al. (2008) noted that people in Golestan may start using opiates to alleviate pain before receiving a cancer diagnosis. The Working Group suggested that cough is a source of protopathic bias, noting that cough may lead to use of opium as an antitussive and cough is associated with certain cancers. Rahmati et al. (2017) noted in the GCS that, in the Islamic Republic of Iran, opium is a well-known antitussive and chronic cough is associated with laryngeal cancer. Protopathic bias could occur if people who had these symptoms used opium to suppress their cough and had a higher probability of the outcome.

Concerns about protopathic bias can be addressed by assessment of opium history in a period before the symptomatic period of disease. Unfortunately, interpretation of several of the case–control studies in the literature is complicated by potential protopathic bias. Aliasgari et al. (2004), Akbari et al. (2015), Aliramaji et al. (2015), Bakhshaee et al. (2017), and Pournaghi et al. (2019) provide no clear indication of the time frame relevant to history of opium use assessment (e.g. distinguishing use before the onset of symptoms).

Sensitivity analyses can be informative in considering the potential extent of protopathic bias under a specified scenario. For example, consider protopathic bias due to cough as an explanation for an observed opium–lung cancer association as large as a risk ratio of 3.0 (e.g. Masjedi et al., 2013). Suppose that the risk of lung cancer is higher by 20-fold among people with chronic cough, and by 2-fold in people with occasional cough, than among those who report no cough. Most people with cough do not develop lung cancer even if the majority of patients with some forms of lung cancer experience cough. Moreover, suppose that among people who never use opium the prevalence of chronic cough is 10%, occasional cough is 40%, and no cough is 50%. For a risk ratio of 3.0 to be entirely due to this type of protopathic bias, the prevalence of cough would need to be approximately reversed among people who were opium ever-users (i.e. among users of opium: a prevalence of chronic cough, 50%; occasional cough, 40%; and no cough, 10%).

Alternatively, concerns about protopathic bias can be directly addressed if the investigator solicits information specifically about opium use in the year (or years) before diagnosis. Nasrollahzadeh et al. (2008) offer a direct assessment of the potential for protopathic bias, noting that ever-use of opium was associated with oesophageal squamous cell carcinoma (SCC) (odds ratio, OR, 2.00; 95% confidence interval, CI, 1.39–2.88), as was opium use in the period more than 1 year before diagnosis (OR, 1.92; 95% CI, 1.30–2.84). Of course, this approach does not rule out protopathic bias entirely; a symptomatic period that is longer than 1 year before diagnosis is possible. However, the lack of sensitivity of results to the discounting of recent initiators of opium use reduces concern about such bias.

Finally, controlling for measured confounders in many of the published studies of opium use and cancer may also help reduce concern about protopathic bias. For example, premalignant conditions are not the only possible common causes of symptoms (such as cough) and cancer. One common reason that cough is associated with lung cancer is that smokers tend to cough and are at elevated risk of lung cancer. If the backdoor path (i.e. the presence of a common cause) from symptoms to cancer is blocked in part or entirely by conditioning on smoking, then case–control analyses that adjust for smoking will reduce the potential for protopathic bias.

In summary, it is unlikely that the results observed in the cohort and case–control studies of opium and cancer are entirely due to protopathic biases.

Selection bias

Selection bias arises when inclusion in a study sample is associated with the exposure and outcome of interest. Selection bias is not a primary concern in the GCS because entry into the study was not conditional on factors associated with opium use. However, in some case–control studies of the association between use of opium and cancer, controls were recruited from hospitals (rather than the general population) (Aliasgari et al., 2004; Masjedi et al., 2013; Aliramaji et al., 2015). Selection bias may arise if opium use is associated with being in the hospital. The controls in a case–control study are used to estimate the prevalence of opium use in the underlying study base from which the cases arose; if hospital patients are more likely than the general population to have used opium, then use of hospital-based controls may lead to a biased estimate of association. For example, in Shakeri et al. (2012), the hospital-based controls were defined as patients with injuries or illnesses that were not associated with smoking, but who may have had conditions that were affected by opium use. If the outcome defining the control series is affected by opium use, bias will occur in a case–control analysis of the opium–cancer association. As indicated in Fig. A3, conditioning on being in hospital opens a bias pathway between exposure, T, and outcome, D.

One way to assess this potential bias is to evaluate whether an estimate of the prevalence of opium use in the hospital-based control series is comparable to external information, where available, about opium use in the general population; Shakeri et al. (2012) compared the prevalence of opium use among the hospital controls in their study (28%) with that reported in the GCS and noted that opium use was higher among hospital controls than in the cohort study. Another approach is to recruit controls that are not hospital-based. Masjedi et al. (2013) recruited

Fig. A3 Selection bias: the association between true exposure (T), outcome (D), and hospital control selection

Conditioning on hospital control status opens a path between T and D
Subscripts indicate time on study, where 0 denotes study entry.

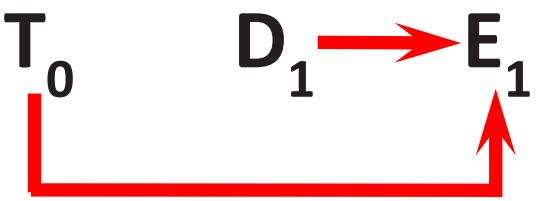
both hospital-based controls and hospital visitor controls (the latter is perhaps less susceptible to this bias), but the authors did not report analyses in which the sensitivity of the results was affected by the use of one type of control or the other. Shakeri et al. (2012) evaluated hospital versus neighbourhood controls in a case–control study on oesophageal SCC in which hospital-based controls were patients with other conditions thought to be unrelated to tobacco use, alcohol consumption, or diet. Evidence of bias to the null was reported by Shakeri et al. (2012) in study findings comparing hospital-based controls with neighbourhood controls, where opium use was associated with a significantly increased risk of oesophageal SCC (OR, 1.77; 95% CI, 1.17–2.68) in analyses using neighbourhood controls, while this was not the case (OR, 1.09; 95% CI, 0.63–1.87) in the study using hospital controls. The authors noted that, "Hospital controls may not be representative of the population because in this area opium has traditionally been used to treat pain and numerous ailments". Neighbourhood controls offer a source of information with which to address such concerns about selection bias; for example, Alizadeh et al. (2020) used neighbourhood controls in a case–control study on head and neck cancers.

In summary, selection bias in hospital-based case–control studies may have led to bias to the null in those studies.

Information bias, including recall bias

Opium consumption was assessed by asking study participants about their current and past use of opium. In studies in which the outcome (cancer diagnosis) occurred before the exposure assessment, a person's outcome status may have affected their self-reported exposure status (Masjedi et al., 2013). This is referred to as "recall bias". Fig. A4 illustrates this problem, where true exposure, T, affects the outcome of interest, D, and both T and D affect the assessed exposure, E. In the GCS, recall bias is not a major concern because exposure assessment at baseline was conducted before disease diagnosis. In contrast, recall bias may be a concern in case–control studies. However, recall bias does not necessarily affect all case–control studies; for example, in a case–control study in which exposure assessment is based on records rather than self-report, recall bias may be avoided if the information in the records is constrained to information collected before diagnosis. Several of the case–control studies on opium and cancer were based on information regarding opium use that was derived from hospital records, although it was unfortunately not always clear whether this record-based information consisted solely of information collected before diagnosis of the disease of interest (in which case, disease, D, does not affect assessed exposure, E). Concerns regarding recall bias can be addressed, in part, by assessments of the reliability of self-reported opium use in the Islamic Republic of Iran. In general, evaluations of self-reported opium use in these populations are reasonably concordant with classifications based on urinary markers of opium use (Abnet et al., 2004).

Fig. A4 Recall bias: the association between true exposure (T), outcome (D), and assessed exposure (E), in an observational study with recall bias

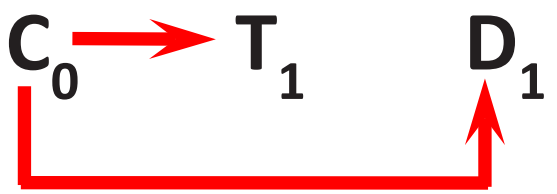


Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point.

Confounding

Unlike in randomized experimental studies, in observational studies on cancer the investigator cannot rely upon randomization to balance between exposure groups the other factors that affect risk of cancer. In an observational study, treatment is not randomized, and factors associated with cancer risk may differ between unexposed and exposed groups. Therefore, a comparison of cancer risk between the unexposed and exposed groups may potentially be distorted by baseline differences between the groups in factors other than opium use that cause cancer. This is referred to as confounding bias. Fig A5 illustrates this problem, where the confounder, C, affects true exposure, T, and affects the outcome of interest, D. An association between T and D may be observed in the absence of any true association due to C, which is a common cause of T and D. As indicated in Fig. A5, confounding bias requires an association between the confounding factor and the exposure of interest (opium use); it also requires an association between the confounding factor and

Fig. A5 Confounding bias: the association between confounder (C), true exposure (T), and outcome (D), in an observational study with classical confounding



Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point.

the outcome of interest (even in the absence of exposure to the agent of primary interest).

Confounding is a potential source of bias in analyses of the association between opium use and cancer in the GCS. A crude analysis of an association between opium use and cancer could be distorted by differences in characteristics between opium users and non-users, such as age and sex, which are also characteristics associated with cancer risk. The investigators measured many of the important potential confounding factors and subsequently accounted for them in the analysis of associations between opium use and cancer by regression modelling, or, in some cases, by restriction of their analysis to people in one stratum of the confounding factor (e.g. to men) (Sheikh et al., 2020).

From the outset of the GCS, which was motivated by an observed excess of oesophageal cancer (SCC) in the north-eastern region of the Islamic Republic of Iran, attention has been paid to tobacco use and alcohol consumption as risk factors of interest associated with oesophageal SCC. Therefore, the GCS participants were asked about tobacco and alcohol use, as well as duration, frequency, and consumption of each; in addition, the reliability of self-reported tobacco use was assessed and compared with urine cotinine. Analyses of associations between opium use and cancer in the GCS have employed regression model adjustment for tobacco and alcohol use, as well as restriction to never-smokers, to address potential confounding by smoking.

Confounding is also a potential source of bias in the case–control studies on opium consumption and cancer. Most case–control studies on opium use and cancer collected information for cases and controls about major risk factors, such as age, sex, and tobacco and alcohol use. Clearly there is a strong association between opium use and tobacco consumption, as described in Section 1.4.3. The major case–control analyses of associations between opium use and cancer have employed either stratification or restriction on age and sex, and regression model adjustment for tobacco and alcohol use, to account for these potential confounding factors. In some settings, matching in case–control studies can provide an effective approach to controlling for potential confounding factors that might be otherwise difficult to measure. The use of neighbourhood controls in a case–control study, as was done in the study by Naghibzadeh-Tahami et al. (2020) for example, implies a form of matching by which controls are sampled from the neighbourhood in which the case arose. A study design in which cases and controls are matched on neighbourhood of residence may help to control for the confounding effects of socioeconomic and environmental factors that are similar within-neighbourhood.

Another possible source of confounding may be occupational exposure to carcinogens. Such concerns about confounding may be greatest for cancers of the urinary bladder and lung, which have many occupational causes (Loomis et al., 2018). As noted in Section 2.6.6, many of the studies were conducted in rural populations, where exposure to industrial urinary bladder carcinogens is unlikely. There is little evidence that occupational exposures to lung carcinogens are associated with opium consumption, except perhaps for welding exposures (see Section 1.4.3). The magnitude of lung cancer risk associated

with exposure to welding fumes is relatively low (IARC, 2018), and even a strong association between work as a welder and opium use cannot explain the large magnitude of the association between opium and lung cancer observed in these studies.

Residual confounding

Although analyses of opium consumption and cancer conducted in the GCS and in most case–control studies adjust for potential confounders such as age, sex, and tobacco and alcohol use, it is possible that confounding bias remains in the adjusted analyses. This is referred to as "residual confounding".

The most plausible concern regarding residual confounding relates to tobacco use. This is because, in the populations under study, there is a strong association between opium use and tobacco use, and tobacco use is strongly associated with some types of cancer. Therefore, it is possible that residual confounding may remain.

One reason for residual confounding could be that the statistical control for confounding by the measured covariates was not sufficiently tight. For example, an analysis of the association between opium use and cancer might control for tobacco smoking by adjusting for ever versus never smoking tobacco. In such an analysis, differences in smoking histories between opium users and non-users might remain within the stratum of people classified as "ever-smokers". Consider the potential concern about residual confounding by smoking level among those who were ever-smokers: one way to address this concern is to conduct an analysis restricted to the stratum of study participants who were never-smokers. Among never-smokers, residual confounding by smoking is presumably minimal or non-existent, because the control for confounding by smoking is tight within the stratum of never-smokers.

Another reason for residual confounding could be that there are substantial errors in the classification of people with respect to confounding variables (for example, if the available information regarding tobacco consumption is not reliable or valid). One way to address concerns regarding errors in classification of study members by tobacco use is to undertake a validation study, as was done in the GCS, where the reliability and validity of tobacco use were assessed. Another way to address such concerns is to examine analyses restricted to women. Tobacco smoking is strongly associated with sex in these studies. Therefore, sex is a strong proxy for tobacco use and, while there may be errors in the classification of study members with regard to smoking, it is less plausible that there are substantial errors in the classification of study members by sex. Given the low prevalence of smoking among women in these studies, analyses that stratify by sex offer indirect assessment of potential residual confounding by smoking. In analyses that restrict to women, among whom smoking prevalence is very low, residual confounding by smoking is presumably minimal.

Finally, evidence of residual confounding by smoking can be assessed in cohort studies by examining patterns of association between opium use and cancer at different organ sites. Potential for bias due to confounding of the association between opium use and cancer by cigarette smoking depends, in part, upon the association between cigarette smoking and the cancer organ sites of interest. External information provides useful indications of the cigarette-smoking–site-specific cancer associations in the Islamic Republic of Iran. Consider for example: if the observed associations between opium consumption and cancers of the oesophagus and lung are entirely due to residual confounding by smoking; and suppose that the

association between smoking and oesophageal cancer in the Iranian population is smaller than the association between smoking and lung cancer; then an analysis of opium use and lung cancer in the same population, using the same methods of analysis, would be expected to be larger than the association between opium use and oesophageal cancer. In fact, tobacco smoking is a weaker risk factor for lung cancer in the Islamic Republic of Iran than is reported elsewhere; tobacco smoking increased the risk of oesophageal SCC less than 2-fold. Nonetheless, the approach, considering other smoking-related diseases, does provide a framework for indirect assessment of residual confounding by smoking.

Overall, in the GCS, the modelling of smoking was fairly tight, with statistical adjustment for pack-years of tobacco use. In addition, analyses restricted to non-smokers are reported in some publications. The GCS addresses errors in the classification of study participants with regard to smoking through the collection of reliable study information as well as the use of biomarkers of smoking. Indirect assessments of residual confounding by smoking find relatively weak evidence of an association between opium consumption and lung cancer, relatively strong evidence of an association between opium consumption and mortality from non-malignant respiratory diseases (such as asthma, chronic obstructive pulmonary disease, and pneumonia), and some positive associations with malignant diseases that also are smoking-related (such as laryngeal cancer).

The available literature from case–control studies on opium consumption and cancer provide less detailed information for evaluation of the potential for residual confounding by smoking. It is often unclear how smoking-adjusted estimates of associations between opium consumption and cancer were derived, leaving open the possibility for residual confounding due to inadequate modelling of smoking status; none of the case–control studies directly assessed the validity of tobacco use information, and few case–control studies examined results stratified by sex (in fact, some were restricted to men by design).

Summary

There are a range of concerns about bias in observational epidemiological studies. Some of the notable concerns in this literature relate to reverse causation, protopathic bias, selection bias, and recall bias in case–control studies. The most informative cohort study on opium consumption and cancer (the GCS) is unlikely to be substantially affected by these sources of bias: reverse causation, selection bias, and recall bias are not major concerns in the cohort study on opium consumption and cancer; it is also unlikely that the results observed in the cohort study on opium consumption and cancer are entirely due to protopathic biases. Of course, none of these studies were randomized trials and therefore confounding remains a potential concern. For example, the available evidence strongly suggests that opium users reported significantly higher levels of cigarette smoking than non-opium users (e.g. Aliasgari et al., 2004; Sheikh et al., 2020). However, the most informative cohort study, and nearly all case–control studies, addressed potential confounding by cigarette smoking through either adjustment or restriction; and, while residual confounding is a concern, the studies with the strongest exposure assessments also benefit from strong assessments of potential confounders.

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IARC MONOGRAPHS

This volume of the *IARC Monographs* provides an evaluation of the carcinogenicity of opium consumption.

Opium is a highly addictive narcotic drug that has been used for centuries for medicinal and non-medicinal purposes. It has analgesic, hypnotic, antitussive, gastrointestinal, and cognitive effects.

Produced from the juice (latex) of the unripe seedpod of the poppy plant (*Papaver somniferum*), opium has a complex chemical composition consisting of at least 25 alkaloids (e.g. morphine, codeine, thebaine) and other substances. There are several forms of opium (raw or crude opium, dross, refined opium, or opium sap), all of which can be smoked or ingested. Opium derivatives such as morphine, codeine, and heroin were not considered in the present monograph.

Although opium production and distribution are controlled internationally, opium is produced illicitly in some 50 countries worldwide, with more than 80% coming from Afghanistan. The world's largest per capita consumers of raw or minimally processed opium are the Islamic Republic of Iran, Afghanistan, and Pakistan. In 2018, there were an estimated 5 million users of illicit opium worldwide.

After reviewing epidemiological evidence, animal bioassays, and mechanistic data to assess the carcinogenic hazard to humans of opium consumption, the *IARC Monographs* Working Group concluded that opium consumption is *carcinogenic to humans (Group 1)*.