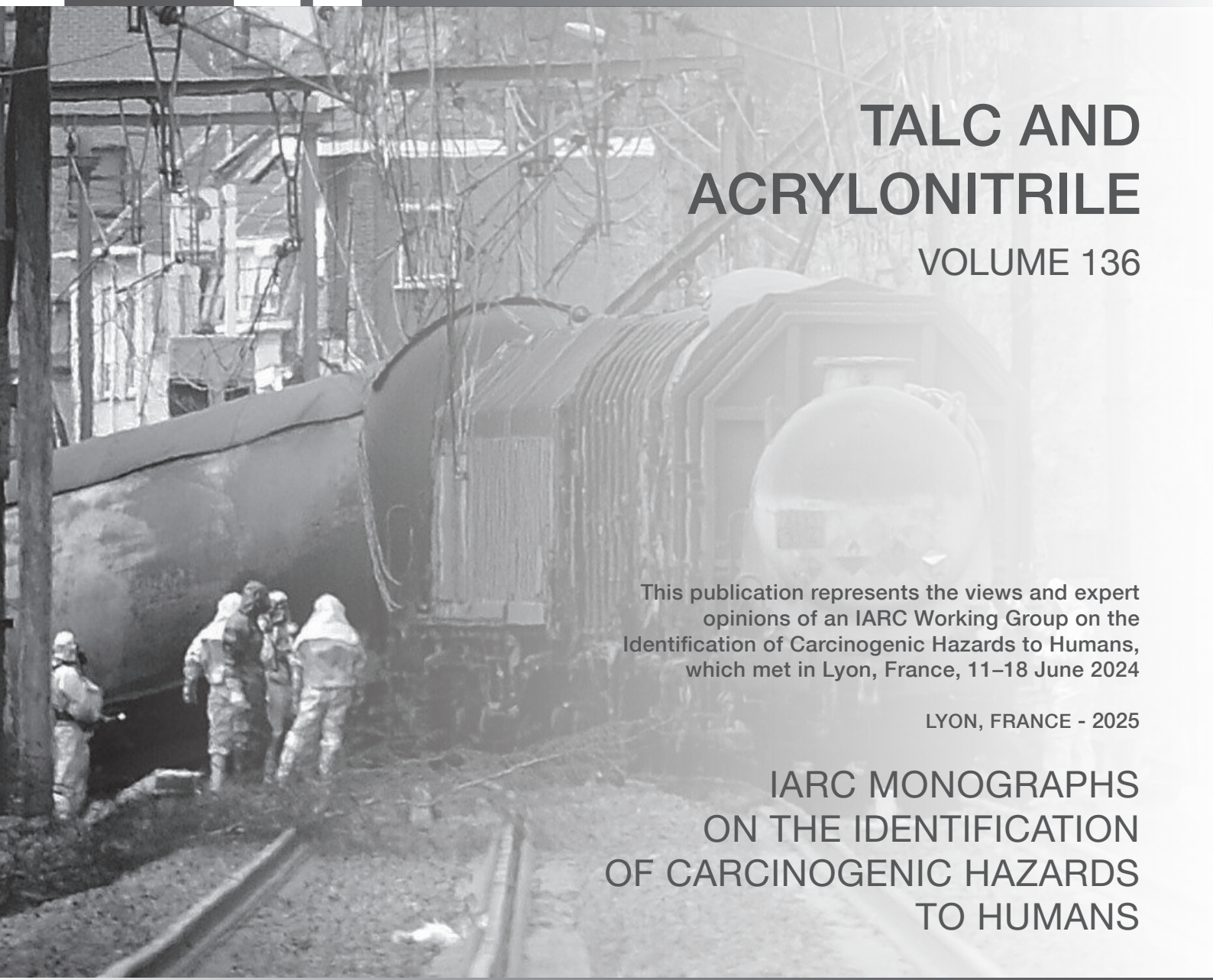
IARC MONOGRAPHS



TALC AND ACRYLONITRILE

VOLUME 136

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

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International Agency for Research on Cancer

World Health Organization

PRELIMINARY GENERAL REMARKS

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

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

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

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

Potential asbestos contamination of commercial products containing talc

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

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

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

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

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

Updated evaluation of talc and cancer in experimental animals

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

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

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

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

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

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

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

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

Scope of the systematic review

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

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

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