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Critical Reviews in Toxicology

ISSN: 1040-8444 (Print) 1547-6898 (Online) Journal homepage: www.tandfonline.com/journals/itxc20

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**To cite this article:** Andrey A. Korchevskiy & Ann G. Wylie (2025) The IARC re-classification of talc carcinogenicity: a move in the wrong direction?, Critical Reviews in Toxicology, 55:9, 867-889, DOI: 10.1080/10408444.2025.2585870

**To link to this article:** https://doi.org/10.1080/10408444.2025.2585870

CRITICAL REVIEWS IN TOXICOLOGY
2025, VOL. 55, NO. 9, 867–889
https://doi.org/10.1080/10408444.2025.2585870

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REVIEW ARTICLE

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# The IARC re-classification of talc carcinogenicity: a move in the wrong direction?

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**ABSTRACT**

The paper explores a content of the recent International Agency for Research on Cancer (IARC) Monograph (Volume 136) where pure talc was reclassified from the Group 2B ("Possibly carcinogenic to humans") to the Group 2 A ("Probably carcinogenic to humans"). The Monograph is considered in the context of the history of the IARC program for classification of carcinogens as well as in the framework of basic principles of toxicological science. It is demonstrated that reclassification was made not based on any new scientific information available, but rather because of a change in some of the methodological approaches or preferences employed by IARC. In particular, it is demonstrated that there are significant mineralogical issues in characterization of talc by the recent IARC Monograph. It is shown why weight-of-evidence for carcinogenicity of pure talc in experimental animals cannot be estimated higher than "limited", and in human study higher than "inadequate". It will also be argued that utilization of separated mechanistic criteria (key characteristics of carcinogens) without contextual analysis and proven mode-of-action (MoA) can cause significant uncertainties in the determination of carcinogenicity in humans. There is a need for comprehensive risk assessment for various agents and processes, rather than just hazard identification that the IARC continues to exercise with questionable relevance for global cancer prevention.

**Abbreviation:** AOP: adverse outcome pathways; IARC: International Agency for Research on Cancer; IRIS: Integrated Risk Information System; KC: key characteristic; MoA: mode-of-action; MTD: maximum tolerated dose; NAM: new approach method; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NTP: National Toxicology Program; PCA: principal component analysis; SVF: synthetic vitreous fibers; US EPA: United States Environmental Protection Agency; CART: Classification and Regression Trees methodology

**ARTICLE HISTORY**
Received 22 August 2025
Revised 27 October 2025
Accepted 31 October 2025

**KEYWORDS**
talc; IARC; carcinogenicity; classification; mechanistic criteria; mode-of-action (MoA)

## Table of contents



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Supplemental data for this article can be accessed online at https://doi.org/10.1080/10408444.2025.2585870.

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

## 1. Introduction

The International Agency for Cancer on Research (IARC) recently published the first part of Volume 136 of Monographs on the Evaluation of Carcinogenic Risks to Humans, dedicated to talc (IARC 2025a). The new assessment by IARC changes the conclusions of the previous evaluation for the same mineral issued in Volume 93 in 2010 (IARC 2010), elevating the weight-of-evidence category for talc from "Possibly carcinogenic to humans" (Group 2B) to "Probably carcinogenic to humans" (Group 2 A). Both Groups 2 A and 2B have a specific status in IARC classification that includes agents that are not yet fully proven to be human carcinogens, vs. entities from Group 1 ("Carcinogenic to humans"). Obviously, the agents in groups 2 A, 2B, and 3 are included in these categories because some necessary arguments for human carcinogenicity are lacking.

It should be emphasized that re-classification of talc by IARC was made in a specific and unique way when the new carcinogenicity group was determined not on the basis of any new information, but rather on the changing of IARC's own methodology and classification criteria.

As we will demonstrate in this paper, in Monograph 136, IARC did not change the estimation of the weight-of-evidence for cancer in humans, considering it "limited" as in Monograph 93. However, the status of the evidence in experimental animals was elevated from "limited" to "sufficient" despite using the same data (a single study with results from only one species) in 2025 as in 2010. Also, IARC utilized a new methodological approach, assigning a "strong" categorization to so-called "mechanistic evidence" for talc carcinogenicity. This was done without attempts to demonstrate the relationships between separate characteristics of potential carcinogens. It is noteworthy that the decision to reclassify talc was apparently not supported by the entire IARC working group. As Dr. Andrew Ghio, the member of the working group for Monograph 136, stated (Ghio 2025), "[s]everal experts did not agree with the reclassification of talc on the basis of the single animal study and an inadequacy of meeting a majority of the key characteristics and, accordingly, abstained from voting on the carcinogenicity of talc."

This recent decision by IARC provides an important opportunity to discuss once again the approaches that the agency utilizes for carcinogenicity classification of various agents and the applicability of IARC conclusions for scientifically based risk assessment. In this paper we will attempt to explore the IARC reasoning for the change of talc classification and suggest alternative interpretation of the data using the organization's own criteria. Through a toxicological overview and mathematical modeling of the data, we will demonstrate that the "key characteristics of carcinogens," as utilized by IARC for systematization of mechanistic evidence, do not in themselves constitute a scientifically sound argument for the carcinogenicity of various agents in humans. We will attempt to show that the IARC's decision to change the status of talc not contaminated by asbestos fibers may have implications for other agents. These implications arise from a potential loosening of the criteria for assigning carcinogenicity classifications and by a lower weight-of-evidence threshold for chemicals, which in turn could influence public policy changes in in the U.S. and internationally.

## 2. Materials and methods

This paper is not a systematic review of literature on talc and its potential biological effects. On the contrary, the paper assesses the IARC Monographs, which are intended to provide a systematic review of various chemicals, from the perspective of the scientific validity of their conclusions.

We employed several datasets published by IARC sources to analyze the statistical relationships between mechanistic evidence and the resulting cancer classification. We revisited various published sources on talc effects in humans and experimental animals to demonstrate them in the context of the new evaluation of talc by IARC. We also reviewed mineralogical papers cited by IARC in its evaluation of talc to identify possible omissions of important information in Monograph 136.

We collected information on the ten mechanistic characteristics of carcinogenicity for the 184 agents assessed in the most recent IARC Monographs (Volumes 112–135). For 99 of the agents (including talc), mechanistic evidence was available from Monographs. We used the combined data for each of the mechanistic characteristics from the recent IARC report (IARC 2025b). We supplemented the data with information about mechanistic characteristics of Group 1 agents from Monograph Volumes 100 A, 100B, 100 C, 100D, 100E, 100 F, 105, and 106 (as described in the 2019 IARC publication) that had been collected from various sources (the data were available for 85 agents) (IARC 2019b). No specific evaluation of the strength of evidence for each mechanistic endpoint was attempted, and the specific evidence included in the IARC analysis was assumed to be significant, as evidenced by the "yes" or "no" option for each evidence category. Three options for the weight-of-evidence on cancer in humans and animals (inadequate, limited, or sufficient) were also included for each agent. IARC's overall conclusion and final classification, based on the assigned group, 1, 2 A, 2B, or 3, was included. For each of the ten key characteristics of carcinogens (see Section 3), the code 0 was used to indicate absent evidence and code 1 to indicate evidence present in human or animal cells. The weight-of-evidence for animal and human studies was codes as 0 for inadequate, 1 for limited, and 2 for sufficient.

The data used for the study are summarized in Table S1. We used several methods to demonstrate a possible relationship between key characteristics of carcinogens with a binary outcome (if the agent was a proven human carcinogen).

First, we performed a statistical analysis and found probabilities of agents with evidence on each KCC to belong to Group 1. Bootstrap analysis was used to find confidence intervals for the probabilities.

Then we utilized Principal Component Analysis (PCA) to determine key characteristics predictive for cancer classification. PCA is a statistical method for reducing a cases-by-variables data table to its essential features, called principal components. Principal components are a few linear combinations of the original variables that maximally explain the variance of all the variables (Greenacre et al. 2022). PCA allows

for different variables, characterizing some objects, to be projected on variable planes (representing principal components), revealing the relationship between variables. Observing the distribution of variables across the four quadrants of the plant helps to understand their proximity to one another. The limitations of the approach are typical for any multivariable statistical method (e.g. data imbalances, linear distortions).

We also used the Classification and Regression Trees (CART) methodology for constructing decision trees. For binary classification and regression models, this approach recursively divides the data into two near-homogenous daughter nodes according to a split point that maximizes the reduction in sum of squares error (the impurity) along a particular variable, which is how each split in the tree is chosen. In our case, we used the so-called gini impurity coefficient. If a node is pure, meaning all samples reaching that node are of one class, the gini coefficient will be 0, while a node with mixed samples will have a higher gini coefficient (Lampa et al. 2014; Hayes et al. 2015) The tree with best statistical characteristics (lowest gini coefficients and highest balanced accuracy) was utilized to evaluate a probability that talc-related mechanistic characteristics may belong to a realistic pathway for cancer in humans.

We additionally tested all combinations of KCs (including from two to four key characteristics each) for their correlation with the "Group 1 or not" binary variable. Spearman correlation coefficients were utilized for the ranking of various combinations. The sum of the values for each combination of key characteristics was found for each agent by the formula:

$$KC_{combination}(i, j, k, l) = KC_i + KC_j + KC_k + KC_l. \quad (1)$$

Parameters i, j, k, and l changed from 0 to 10 (with KCx signifying a value of KC parameter with order number x in Table S1 for $x \geq 1$, or equal to zero for $x = 0$). Combinations of KCs with 2, 3, or 4 parameters were tested (so, at least two values from i, j, k, and l in Equation 1 should not be equal to 0). Spearman correlation was found between $KC_{combination}$ (i,j,k,l) and parameter "Group 1 or not" that was equal to 1 when the agent was in the Group 1 by IARC classification and zero otherwise.

Finally, logistic regression was used to determine the probability that an agent belongs to a certain classification, based on its key characteristics. To evaluate the applicability of logistic regression to available data, we utilized a variance inflation factor (VIF) measuring multicollinearity of the model; when this parameter was not greater than 5, we assumed multicollinearity to be controllable. The standard parameters AIC, BIC, AUC, Sommer's D, and Brier score were used to evaluate the performance of logistic regression.

Licensed Statistica 14.1 and Crystall Ball packages were used for statistical analysis.

## 3. History of IARC classification: 1970s to the twenty-first century

The Monograph program by IARC was established in 1969, signifying an important step in the international process of collecting and assessing cancer-related information for various agents. The initial efforts of the founding director of IARC, John Higginson (1966–1981), and the first director of the Monograph program, Lorenzo Tomatis (1971–1982), resulted in the launch of the series of volumes focused on various potential carcinogens. The history of the methodology for agent classification by IARC in its Monographs was recently reviewed by Baan and Straif (2022). It should be emphasized that initially, the IARC Monographs did not attempt to associate these chemicals with a specific classification group. Instead, they only indicated available information and the degree of its validity. The idea was apparently to provide the public and decision-makers with valid data for immediate actions on certain human carcinogens when such actions were warranted. The way to use results on experimental animals for conclusions on human carcinogenicity was apparently unclear for IARC at that point (Baan and Straif 2022). In 1979 (IARC 1979), the first version of the agent classification was proposed, with three initial classes:

Group 1. The chemical, group of chemicals, or industrial process is carcinogenic for humans.

Group 2. The chemical or group of chemicals is probably carcinogenic for humans. (Including groups 2 A and 2B with lower and higher weight of evidence, respectively).

Group 3. The chemical or group of chemicals cannot be classified as to its carcinogenicity for humans.

In 1987, IARC separated Group 2 A (possibly carcinogenic) and Group 2B (probably carcinogenic) and introduced Group 4 (the agents probably non carcinogenic to humans) (IARC 1987). The data for experimental animals were indicated as an important supporting source of information for Groups 2 A and 2B starting in 1979. As Baan and Straif noted, the animal data were used in IARC classification only "for practical purposes", as an "approximation", until 1987 when N-ethyl-N-nitrosourea was placed in Group 2 A with sufficient evidence in animals in the absence of human epidemiological data.

It should also be noted that since approximately 1982 (IARC 1982), IARC started labeling the levels of the available evidence for carcinogenicity as "sufficient", "limited", or "inadequate".

Parallel with its increased use of animal data in carcinogenicity assessment, IARC began discussions on incorporating mechanistic data into its classification, including data from *in vitro* studies and theoretical determinations of the agents' mode-of-action. In the 1991 Preamble, IARC established that agents can be classified as carcinogenic to humans if there is sufficient evidence in animal models and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity" (IARC 1991).

The current version of the IARC Preamble was published in 2019 (IARC 2019a). At that point, IARC introduced a new methodology to integrate animal and mechanistic data in a combined manner. IARC attempted to formalize the approach to mechanistic data analysis by introducing ten key characteristics of carcinogens (KCCs or KCs):

KC1. Is electrophilic or can be metabolically activated to be electrophile

KC2. Is genotoxic
KC3. Alters DNA repair or causes genomic instability
KC4. Induces epigenetic alteration
KC5. Oxidative stress
KC6. Chronic inflammation
KC7. Immunosuppressive
KC8. Modulates receptor-mediated effects
KC9. Causes immortalization
KC10. Alters cell proliferation, cell death, or nutrient supply
(Smith et al. 2016; IARC 2019a)

In 2019, IARC also eliminated Group 4, which was almost never used in practice, except for caprolactam that was reclassified into Group 3. It should be noted that the existence of Group 4 was useful for public health guidance and regulatory decision-making because it distinguished agents unlikely to cause cancer from those for which risks remain uncertain or have been substantiated.

Baan and Straif (2022) stated in this regard that exclusion of Group 4 finally confirms "that the IARC Monographs do not evaluate agents for which there is no evidence or suspicion of carcinogenicity." It is very important to note, however, that some agents with strong evidence of rodent-specific modes of action not relevant to humans (e.g. PPARα activation, α2u-globulin nephropathy, TSH stimulation) would be classified in Group 3 by the available criteria. This reveals an apparent asymmetry in IARC's methodology: it applies KCCs to elevate a hazard classification while also assigning Group 3 ("not classifiable as to its carcinogenicity in humans") to chemicals with substantial evidence that they are unlikely to be human carcinogens.

The main criteria for IARC classification, as promulgated in the most recent Preamble in 2019 (IARC 2019a), is pictorially expressed in Figure 1.

In addition to information provided in Figure 1, there are several options for classification that are indicated in the Preamble. In particular, classification to Group 2 A can be used when there is strong evidence, based on mechanistic considerations, that the agent belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2 A. 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 tumor sites. Specifically, the remaining tumor sites should still support an evaluation of sufficient evidence in experimental animals for this evaluation to be used to support an overall classification in Group 2 A.

It should be noted that methods of testing for carcinogenicity in experimental animals remain the central point of the interpretation for the weight-of-evidence. In the Preamble published in 1991, sufficient evidence of carcinogenicity in animals was assumed if "a causal relationship has been established between the agent or mixture and 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) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols." The document added that "exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset" (IARC 1991). The Preamble from 2006 (IARC 2006) added that increase of tumors in both sexes "in a well-conducted study, ideally under Good Laboratory Practices, can also provide sufficient evidence." Except for some rewording, the Preamble updated in 2019 kept the language from previous versions on this topic but also allowed for

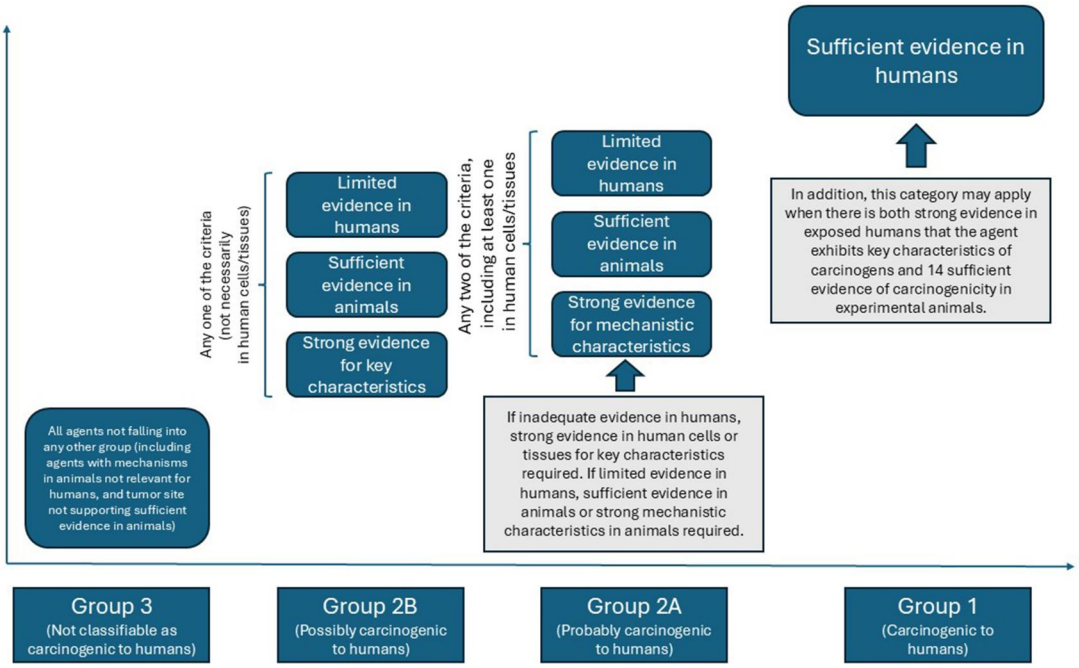


**Figure 1.** Main evidence-based criteria for IARC classification based on IARC 2019 (IARC 2019a).

"exceptional" study in one species and sex when the findings are "unusual" (IARC 2019a).

In the current classification model by IARC, sufficient evidence of carcinogenicity in humans (either from elevated cancer risk in epidemiological studies, or from mechanistic evidence in exposed humans) remains the principal determinant of carcinogens in Group 1. However, for all groups, there is a trend to gradually balance the evidence from human (epidemiological) data, evidence from experimental animals, and the key characteristics of carcinogens.

Analysis of the history of the IARC Monograph program and specifically its last Preamble reveals several facts.

First, the most important classification in the IARC schema is the determination of the Group 1 human carcinogen list. By doing this, IARC attempts to fulfill its mission of hazard identification, providing the necessary first step in the risk assessment process. Obviously, any assessment of human carcinogenicity for various agents is expected to have limitations related to limited epidemiological data, possible exposure assessment issues, biases, analytical problems, and others. What remains important, however, is a clear message regarding Group 1 carcinogens that are expected to be addressed in public policy.

Second, IARC seems to have much less certainty in defining the meaning of groups other than Group 1 in the assessment. All of them (including Group 2 A, 2B, 3 and eliminated 4) cannot be considered proven carcinogens in humans. The Preamble from 2019 specifically indicated that Group 2 contains agents with the degree of evidence of carcinogenicity in humans being "almost sufficient" (IARC 2019a). The word "almost" indicates inability of the classification model to characterize any of the agents outside of Group 1 as human carcinogens, even in the terms of "possibly" and "probably". The implications of this situation for public policy are unclear. With all agents in Groups 2 A, 2B, and 3 being "suspected" human carcinogens, with no specific "potency", but only general weight-of-evidence ranked, there are significant difficulties in applying this classification to determine policy priorities.

Third, IARC has elevated the role of mechanistic evidence for carcinogenicity, searching for toxicological information outside of the domain of traditional human epidemiological studies and tests on experimental animals. However (as we will attempt to demonstrate below using talc as an example), the ten key characteristics introduced by IARC cannot be used in isolation without determination of a mode-of-action (MoA) and confirmation in humans and animals that a chain of events leading from exposure to the specific *in vitro* test results to cancer is real.

The International Programme on Chemical Safety (IPCS), administered by both the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD) has provided an internationally accepted definition of MoA: a biologically plausible sequence of key events that are causally linked and lead to an adverse effect (Boobis et al. 2006; Meek et al. 2014). The OECD Adverse Outcome Pathway (AOP) framework incorporates principles from the WHO/IPCS MoA framework by applying a causal evaluation approach that draws on Bradford Hill considerations, including temporal and dose–response concordance, consistency, biological plausibility, and essentiality (OECD 2017). The KCC concept by IARC that disconnects separate characteristics from each other and considers each of the characteristics as evidence of carcinogenicity appears to be a significant setback in the scientific approach to the assessment of agents for their ability to produce cancer in humans. At least some of the ten KCCs listed above obviously reflect normal biological processes that do not necessarily lead to tumor development on their own (e.g. wound healing and cell proliferation for restoring tissue integrity after injury; or chronic inflammation as part of normal immune responses or tissue repair). This emphasizes the importance of determining human relevance by causal analysis, which is intended to minimize the possibility of false inferences of causation based on spurious relationships. Otherwise, the list of carcinogens in Groups 2 A and 2B can grow indefinitely, without any proof of relevance for carcinogenicity in humans. As can be seen, the current Preamble allows the agents to be potentially classified as Group 1 based on sufficient animal evidence and strong key characteristics data. It is therefore reasonable to suggest that much better formalization to avoid unjustifiable inclusion to Group 1 (which should remain the "gold standard" list of carcinogens) is needed. This formalization should include the confirmation of specific combinations of key characteristics of carcinogens as "strong" vs. "limited", or "insufficient" mechanistic data. Predictability of separate key mechanistic characteristics of carcinogenicity, promoted by IARC, for cancer in humans is not defined by IARC in any reproducible way, leaving ten characteristics as a disjointed list of parameters that may or may not serve as a support for classification.

Similar thoughts were expressed by Goodman et al. (2020) in the recommendations for further revisions on the IARC Monograph program. The authors emphasized that "without continued improvements in, and modernization of, the procedures for evaluating, presenting and communicating study quality, and in the methods used to conduct (and independently peer review) evidence-based causal decision making by Working Groups, the IARC Monographs will likely continue to generate classifications that fall short of meeting current best practices benchmarks for authoritative scientific reviews."

It also appears that the initial question that IARC tried to answer by the Monograph program has become outdated. Boobis et al. (2016) suggested that instead of the effort from the 1970s to "identify those chemicals which are capable of causing cancer so they can be eliminated from use," IARC should address the current problem which is to: "identify and characterize the carcinogenic potential of chemicals so that appropriate risk management measures can be taken to safeguard human health." Boobis et al. argued for a risk-based decision framework that integrates hazard, dose–response, and exposure to provide a balanced basis for informed risk management decisions.

We would suggest that not one, but a series of more specific questions should be addressed by IARC in the XXI century:

- Is this agent proven to be carcinogenic to humans in realistic exposure circumstances?

- If there is no direct proof of an agent's carcinogenicity to humans, and only some questionable evidence, what should be done to demonstrate or disprove carcinogenicity status for humans?
- If the agent is proven to be carcinogenic to humans, what is the MoA, and would it imply an exposure threshold or other aspects of dose-response relationship impacting public perception, along with policy and regulations?

Obviously, not every question can be fully and scientifically answered for each agent. Difficulties of "proving a negative" can be hard to overcome in assessment of potential carcinogenicity. However, without the vision for the "key questions" it is impossible to integrate fully the IARC agenda into the public policy processes.

In 2015, a group of scientists, involved in the work of IARC, responded to increasing public criticism of the program (Pierce et al. 2015). Pierce et al. specifically addressed the opinions published by Boffetta et al. (2009), Epidemiology Monitor (2012), Ioannidis (2005), Kabat (2012), and McLaughlin et al. (2010, 2011). Four main types of critique were identified: the overreliance on epidemiology (despite its inherent limitations); the issue of false positives; discontent with the IARC process (including selection of working groups); and/or focused criticism of specific evaluation. The authors of the paper argued that the IARC classification process is transparent and solid, epidemiology remains a powerful source of cancer information, and specific evaluation passed steps of the IARC process, warranting their validity.

Samet (2015) compared the IARC program with the U.S. EPA's Integrated Risk Information System (IRIS), suggesting that the two systems should be considered mutually supportive because IARC focuses on hazard identification, while IRIS provides dose-response information on risk. Currently, the future of IRIS in the U.S. is unclear; however, the lessons from IRIS can be used by IARC in reemphasizing all steps of the risk assessment process, besides just hazard identification. Hazard identification without exposure and dose-response assessment appears to be an incomplete step. For example, some agents may express certain characteristics of carcinogenicity, but if this expression would be expected only at doses irrelevant for humans, hazard identification would mislead the public. To provide scientifically based and practically applicable results, IARC should not artificially try to limit itself to the "hazard identification" part of the risk assessment process, and should include other steps including relevant exposure assessment, dose-response evaluation, and risk characterization. Also, hazard identification by IARC should also follow the principles of scientific analysis, essential for risk assessment purposes.

## 4. New evaluation of talc by IARC: Changes with no change

IARC evaluated talc in its Monographs three times. Table 1 shows the relationship between evaluation of the evidence for talc carcinogenicity in 1987, 2010, and 2025.

Not attempting a comprehensive retelling the context of IARC Monographs, we will emphasize several aspects of the differences and similarities between assessment of talc by IARC from 1987 to 2025.

### 4.1. Minerology of talc

Monograph 136 (IARC 2025a) contains a table listing 49 mines and mining districts from which talc ore has been mined. Of these 49 entries, there are 34 entries under the column labeled "Occurrences of Asbestos." This table was used by IARC to support the statements in the monograph that talc is commonly contaminated with asbestos at the mine source. However, the content of the table appears to be inconsistent with scientific understanding of talc mineralogy and the sources referenced by the monograph itself. With such poor understanding of the occurrences of talc and associated minerals, it is difficult to see how exposures were evaluated, especially with respect to possible presence of elongate particles in talc samples.

#### 4.1.1. Background

#### 4.1.2. What is talc

Talc is a naturally occurring magnesium silicate represented by the formula $Mg_3Si_4O_{10}(OH)_2$. It is the softest mineral known, defining the lowest value on the Mohs scale of relative scratch hardness. Mineral talc also has surface properties and chemical stability in the body that make it a valuable conveyer of many pharmaceuticals, and its softness and platy form make it valuable for body powders and cosmetics.

**Table 1.** The components of IARC evaluation of talc carcinogenicity.

| Component | IARC evaluation in 1987 | IARC evaluation in 2010 | IARC evaluation in 2025 |
|---|---|---|---|
| Cancer in humans | *Inadequate* for talc not containing asbestiform fibers; *sufficient* for talc containing asbestiform fibers | Inadequate for inhalation and limited for perineal pathways | Limited. (Specifically emphasized that the positive association was with cancer of the ovary.) |
| Cancer in experimental animals | *Inadequate* for talc not containing asbestiform fibers and for talc containing asbestiform fibers. | Limited | Sufficient |
| Mechanistic evidence | Absent | Absent | Strong (in human primary cells and experimental systems) |
| Overall conclusion | Talc not containing asbestiform fibers is *not classifiable as to its carcinogenicity to humans (Group 3)*. Talc containing asbestiform fibers is *carcinogenic to humans (Group 1)*. | Talc not containing asbestos fibers: Group 2B | Talc not containing asbestos fibers: Group 2 A |

Talc is also a mined commodity. The mineralogy of commodity talc varies among sources; it may contain more than 95% mineral talc or less than 30% (IARC 2025a). Other minerals that can occur in commodity talc in variable amounts include carbonates, chlorite, quartz, amphiboles, serpentine, sepiolite, and other clays, oxides, and other colorless silicates. The carbonates include dolomite, magnesite and calcite. The amphiboles include tremolite and anthophyllite. IARC (2010) provided a more complete list of associated minerals in Table 1.4. Commodity talc with more than a few percent of these impurities is used in paint, polymers, ceramics, animal feed, fertilizer, roofing and rubber, among other products. In Monograph 42 (IARC 1987), it was specifically stressed that "[e]valuation of the effects of talc is confused by the fact that talc deposits may be contaminated with various other minerals, including carbonates, quartz, serpentines and amphiboles (asbestiform and nonasbestiform)." In 1976, Rohl et al. published a study of 20 commercially available products containing talc and found as much as 35% quartz, 10% tremolite, and 11% anthophyllite in one or more samples. Shortly after, much higher standards for the purity of cosmetic and pharmaceutical talc have been put in place.

High purity talc commodities with (ideally) more than 98% mineral talc are generally referred to as cosmetic talc, and pharmaceutical talc means $>$ 99% talc (IARC 2010). All other talc commodities are generally referred to as industrial talc although their accessory minerals type and abundances will determine their utility.

The two uses of the term talc, talc as the mineral and talc as the polymineralic commodity, have brought controversies to the literature and to understanding outcomes when the exposure is to the commodity. To address this issue, in toxicological studies, the talc commodity making up the exposures should be clearly described by mineral content, proportion of each mineral component that is elongate, and the proportion that is asbestiform. Several of the categories can overlap, producing, for example, a situation in which a talc sample may contain fibers of talc and fibers of asbestiform amphiboles. The sources of the talc should be known, studied, and reported.

#### 4.1.3. Talc fibers

Although it is normally platy in shape, mineral talc can form fibers and elongate particles of talc can be found in most talc ores. However, talc has a weak atomic structure, and elongate particles are ribbon-like with a very high width to thickness ratio. In our recent paper we demonstrated that talc fibers are not likely to have sufficient rigidity to cause damage to macrophages or other types of cells (Wylie and Korchevskiy 2025).

In a few talc deposits in the world, mineral talc intergrows with amphibole and other similar chain silicates to form fibers. These transitional fibers are referred to as "fibrous talc" by Stemple and Brindley (1960) and Virta (1985), so by convention, fibrous talc refers to both fibers of mineral talc and fibers that are transitional, introducing an unfortunate confusion. Fibrous talc from Gouverneur, both talc and transitional, is asbestiform. Monograph 136 states that "crystal habit of talc is lamellar/platy … but it can be fibrous, or, more rarely, asbestiform" (IARC 2025a). IARC emphasized also that "fibrous talc is not asbestos" (IARC 2025a).

#### 4.1.4. Asbestos and asbestiform

The term asbestiform refers to a naturally occurring, polyfilamentous growth habit of minerals in which fibers are formed of parallel fibrils (single crystals) in bundles that can be separated into smaller fibers and fibrils with hand pressure. Asbestiform minerals are flexible in hand samples and fibers have higher tensile strength than other habits of the same mineral. Non-asbestiform habit is any habit that is not asbestiform. Of most concern to public health are elongate particles created by fragmentation when rock is broken. As IARC (2010) states: "Actinolite, anthophyllite and tremolite may occur in some talc deposits; when asbestiform, they constitute asbestos and when not asbestiform, they are referred to as mineral fragments or cleavage fragments (277)." Both categories of talc, containing and not containing asbestiform fibers (i.e. chrysotile, amphibole, or transitional), were considered in the initial evaluation by IARC in 1987, and possible carcinogenic effects were associated with alleged asbestos component of talc.

Asbestos is a commercial term defining six minerals: chrysotile, grunerite (amosite), tremolite, anthophyllite, riebeckite (crocidolite), and actinolite in their asbestiform habit of formation. IARC previously stated that its assessment of asbestos carcinogenicity covers asbestiform fibers, but not elongate particles that are non-asbestiform (IARC 2012). Toxicological characteristics of non-asbestiform particles have been demonstrated to be significantly different from asbestiform fibers, and one explanation is the significant dissimilarity in dimensional parameters (Mossman 2008; Wylie and Korchevskiy 2023; Korchevskiy and Wylie 2025).

In Monograph 93 (IARC 2010), IARC attempted to specifically characterize talc not containing asbestiform fibers. The problem not clearly addressed by IARC is how to identify asbestiform fibers and tell them apart from nonasbestiform fibers. Examination by transmission electron microscopy makes the identification of chrysotile usually straightforward because of its tubular structure, and the unusual properties of asbestiform amphiboles are evident by polarized light microscopy (Verkouteren and Wylie 2002). However, asbestiform fibers cannot be distinguished from non-asbestiform particles just by applying counting criteria specified by recognized analytical methods because elongate amphibole particles meeting these criteria are present in all habits (Wylie 2016; Wylie et al. 2022). This ambiguity in the definition of what is an asbestos fiber makes the task of differentiating talc commodities that contain amphibole based on the presence or absence of asbestos problematic.

In Monograph 136 (IARC 2025a), IARC tried to distinguish effects caused by mineral talc vs. commodities that contain talc and other minerals by selecting the studies where only talc commodities not containing asbestiform fibers were used. This effort, however, appeared to be less than rigorous given the multitude of errors in Table 1.1 listing mine

locations and indicating the possible presence of asbestos. Those errors are listed and analyzed below.

#### *4.1.5. Amphibole asbestos in talc ores*

The extent of uncertainty and confusion underpinning the IARC assumptions about whether or not an occurrence of amphibole is asbestiform or nonasbestiform is evident in Table 1.1 from IARC (2025a). The three amphiboles of interest to IARC are tremolite, actinolite and anthophyllite. The important column is labeled "Occurrence of asbestos." A footnote explains that under this column, "Probable" means that the presence of the amphibole minerals tremolite, anthophyllite, and actinolite "has been reported, but not in the asbestiform habit." The word "Possible" means the presence "has been reported for the geological formation forming the deposit or in contact with the deposit," and "No" means that "in the surveyed literature describing that occurrence, the presence of one or more of the six mineral species classified as asbestos was not reported or that the absence of one or more of the six minerals species classified as asbestos was stated." An entry of either chrysotile or amphibole without a "Possible" or "Probable" means that asbestos was reported in the ore.

How the presence of nonasbestiform amphibole makes asbestos "Probable" is not explained, especially when, as the following discussion illustrates, the nonasbestiform amphibole is of an entirely different geological age or spatially unrelated. While amphibole makes up 6–10% of surface rock (Wylie and Candela 2015), asbestos only occurs when the conditions are right for the formation of fiber, and this is not necessarily related only to the formation in which it occurs, but to its geological history, such as faulting, folding, hydrothermal alteration or igneous intrusion. It is certainly true that where there is asbestos, there will be nonasbestiform occurrences of the same mineral, but the reverse cannot be assumed.

IARC's designation as "Possible" when the only report of one of the three amphiboles of interest is amphibole in the rock surrounding the ore body and not in direct contact with the ore, does not reflect the geological reality that rock types in contact with one another or in close proximity can change dramatically in mineralogy, age, and geologic history, and the mineralogical content of formations can vary along strike. Furthermore, there is no justification given for the idea that the surrounding rock formations are processed with the ore and enter a talc product. The occurrence of asbestos in a formation related to an igneous rock intrusion, or a fault, for example, has no bearing on the presence of asbestos elsewhere in the formation. Similarly, assuming that it is "Probable" that asbestos is present when the minerals are reported in a nonasbestiform habit is not justified (or justifiable) and the ideas that amphibole or serpentine near a talc deposit make chrysotile or amphibole asbestos probable in talc ore is not geologically sound.

In Table 1.1, there are numerous entries in which amphiboles are listed as occurring (not as possible or probable), meaning they are asbestiform. After reviewing all references supporting this habit designation, we found multiple entries where amphibole is mentioned but its asbestiform designation is not supported by the references; examples are listed below:

1. **Afghanistan, Nangarbar Province.** The first mine location listed as containing tremolite asbestos in Table 1.1 is Afghanistan, Nangarbar Province. The reference for this conclusion is included as Tahir et al. (2018). While tremolite is discussed by Tahir et al., and they describe in detail the habit of many elongate minerals, including use of the term fibrous, they do not use the terms asbestiform or asbestos to describe tremolite. In mineralogical terminology and by IARC's own terminology, *fibrous* is not a synonym for asbestiform.
2. **Brazil, Bahia District.** IARC (2025a) relied on Gondim and Jiang (2004) for the mineralogy of the Bahia district of Brazil. Both actinolite asbestos and tremolite asbestos are listed as present in the mines. However, Gondim and Jiang do not mention amphibole asbestos occurring in any of the mines.
3. **Canada, Madoc, Ontario.** At Madoc, Ontario Canada, IARC lists tremolite asbestos and references Sabina (1987). However, Sabina does not report amphibole asbestos from this mine.
4. **India, Rajasthane.** In the talc mines in Rajasthane, India, IARC lists tremolite asbestos. The reference, Shekhawat et al. (2010), does mention that tremolite asbestos exists in the same geographic area, but it is not reported as associated with talc.
5. **Korea, Dongyang, Chunjue.** In Korea, at Dongyang, Chungjue, the talc deposits contain tremolite and dolomite. IARC relies on Dongbok et al. (2004) for the conclusion that tremolite asbestos occurs there, but these authors do not describe asbestiform tremolite nor mention tremolite asbestos.
6. **Norway, Altermakr, Rana.** At Altermark, Rana, Norway, IARC asserts that both anthophyllite asbestos and tremolite asbestos accompany the ore. They rely on Karlsen et al. (2000), Wergeland et al. (1990), and Wergeland et al. (2017). These authors say that amphibole occurs in trace amounts, but there is no discussion of the amphiboles as asbestos or asbestiform.
7. **U.S.A., Georgia, Chatsworth District, Murray County.** In the Chatsworth district, Murray County, Georgia, IARC lists the presence of actinolite, anthophyllite and chrysotile asbestos. Their reference, Furcron et al. (1947), does not mention anthophyllite in the ore, although it is mentioned in surrounding rocks, and actinolite is only mentioned once as occurring in white grinding crayon. There is no mention of asbestos or the asbestiform habit of these amphiboles. (This is not to be confused with talc mines at Soapstone Ridge, Georgia, where these two amphiboles occur as asbestos.)

In some cases, the references listed do not support the presence of amphibole, yet amphibole is listed under the column "Occurrence of asbestos." Examples are given below:

1. **Allamoore Talc District.** In the Allamoore talc district, IARC relied on Van Gosen et al. (2004) for their

conclusion that talc deposits in the district contain tremolite asbestos. In fact, Van Gosen asserts that there is no tremolite in the talc mines. A reference with details on the mineralogy of the district not consulted by IARC, Edwards (1984), but referenced by Van Gosen et al. (2004), does not indicate the presence of tremolite or tremolite asbestos. There are several occurrences in the district of richterite or winchite asbestos, but these occurrences are found in inactive prospects associated with igneous rock. Neither of these minerals are reported in the ore of mines operating in the district.

2. **China, Guangxi Province**. Table 1.2 lists Guangxi Province, China, as a source of talc with possible tremolite, but tremolite is not mentioned at all in the ore from the source on which IARC relied (Schober 1998), (and to our knowledge tremolite has not been reproducibly documented from this source). Schober (1998) does report tremolite from Shandong province, but not Guangxi.
3. **China, Liang Province.** IARC (2025a) relied on Misch et al. (2018) for their conclusion that tremolite is possible, but Misch et al. report tremolite only from a magnesite mine, not a talc mine.
4. **Italy, Sa Matta, Sardinia.** Fiori and Grillo (2002) do not report tremolite in the ore at Sa Matta, Sardinia, Italy, yet IARC relies on them to say that tremolite in the ore is probable. They do report a recent discovery of a carbonate containing tremolite adjacent to the ore body.
5. **U.S.A., California, Inyo Northern Panamint Range.** In the California Inyo Northern Panamint Range district, IARC says that tremolite asbestos is probable and relies on Greene (1995), who does not mention tremolite or quartz and says these deposits lack minerals other than talc.
6. **U.S.A., Dillon-Ennis District, Yellowstone Mine.** IARC relies on Van Gosen et al. (2004) to conclude that tremolite is probable in the Dillon-Ennis district Yellowstone mine. In fact, Van Gosen et al. (2004) and another reference relied on by IARC, Buzon and Gunter (2017), also conclude that there is no tremolite in this mine.
7. **U.S.A, Montana, Dillon Ennis District, Willow Creek and Beaverhead mines.** IARC relies on Van Gosen et al. (2004) to conclude that tremolite is probable from the Willow Creek and Beaverhead mines in the Dillon Ennis district of Montana. In fact, Van Gosen et al. does not mention these two mines specifically but conclude that the district is amphibole free. This is supported by Buzon and Gunter (2017).
8. **Finland, Polvijarvi, Sotkamo and Vuonos mines.** IARC relies on Kuutila (2022) to conclude that tremolite is probable from both the Sotkamo and Vuonos mines in Polvijarvi, Finland. Kuutila wrote about sulfide mineralization in Finland, not talc, and while talc was mentioned, talc mines were not described. Sotkamo was not mentioned at all and Vuonos was described as a Cu, Zn, Co deposit. Another source, not consulted by IARC, describes many talc mines in Finland generally (Vesasalo 1965). While most are altered serpentine, some are altered mafic rocks. Many described do not contain tremolite.

The sources of talc by country are given in Table 1.16 and 1.17 from IARC 2010 and 1.3 and 1.4 from IARC (2025a). The mining districts are not clear in all cases. Although there is uncertainty, it appears that IARC provides conflicting information about the presence of amphibole. Table 1.1 shows that industrial talc from Texas, Canada, Montana, and Finland contain amphibole, but these sources are reported as amphibole free in Tables 1.3 and 1.4.

### *4.1.6. Chrysotile in talc ore*

Table 1.1 (IARC 2025a) lists 12 mine locations that might contain chrysotile. In the case of chrysotile, "Possible" means that serpentine was reported in the surrounding rock. While the "Probable" category for chrysotile is not explained, and by analogy to their treatment of amphibole, it may mean that serpentine has been reported in the ore but it is not asbestiform (not chrysotile). If the presence of chrysotile is not qualified as "Possible" or "Probable," we assume that chrysotile asbestos has been reported in the ore body by the reference provided.

Chrysotile is a thermodynamically metastable phase (Evans 2004), and it is unlikely to exist without a massive serpentine host. That prediction is borne out by observation. Review of the documents on which IARC (2025a) relied for the data in their Table 1.1, and in our review of the literature of chrysotile, we only found chrysotile reported as veins or masses within massive serpentine, i.e. an antigorite or lizardite host. Chrysotile was not listed in any talc ore by IARC in 2010, but in 2025, 24% (12 mine locations) of the deposits listed in Table 1.1 mention chrysotile as "present (3)," "probable(5)," or "possible(4)." It appears that this change has come about because "the Working Group assumed the possible presence of chrysotile when presence of serpentine was reported whether directly related to talc or not," additional mines were included, or as a result of literature misreading. The details for each possible occurrence of chrysotile listed in Table 1.1 are given below:

**1. Brazil, Bahia district, Chrysotile probable.** In the Bahai district of Brazil, IARC references Gondim and Jiang (2004) in support of their determination that chrysotile was probably a component of the ore. However, Gondim and Jiang mention chrysotile only in association with vermiculite and Archean granulite basement rocks, not associated with major talc ores, and provide no reference or data to support the identification of chrysotile[1]. Elsewhere in Brazil in the Ponta and Castro mines, serpentine is mentioned but not chrysotile.

**2. Brazil, Parana district, Ponta Gross and Castro mines, Chrysotile probable**. In the Parana District of Brazil, IARC relies on Gondim and Jiang (2004) to support the probability of chrysotile. Gondim and Jiang do not mention chrysotile although they do indicate serpentine (antigorite) can be found in the ore.

**3. China, Liaoning Province, Chrysotile probable**. Misch et al. (2018) were relied on to conclude that the industrial

talc deposits of Liaoning Province, China, have "probable chrysotile and possible tremolite" (IARC 2025a). However, the reference does not mention chrysotile at all, only mentioning serpentine as the source of jade deposits and not as a component of the ore. (The only mention of tremolite was from a magnesite mine, not a talc mine).

**4. India, Rajasthan, Chrysotile possible**. IARC states that chrysotile is possible in the Rajasthan district based on Shekhawat et al. (2010). However, Shekhawat et al. only mention chrysotile in massive serpentinite, not in talc ore.

**5. Italy, Valmalenco, Chrysotile probable**. At Valmalenco, Italy, Cavallo and Petriglieri (2020), the source relied upon by IARC (2025a), only mentions chrysotile as veins in serpentinite mined for building stone, not in talc ore. Serpentine is not reported as a component of talc ore.

**6. Sweden, Handol Koli, Asan, Chrysotile probable.** IARC relies on Bergman (1993) to conclude that chrysotile in the ore is probable. While serpentine is found in talc schists in the area, chrysotile is not mentioned. Furthermore, this reference does not discuss talc mines.

**7. USA, Georgia, Chatsworth district, Murray County, Chrysotile present.** The reference that IARC relied on for the mineralogy of the Chatsworth district is Furcron et al. (1947). Furcron et al. mentions chrysotile "associated with talc" but relied on optical properties to identify it. If in this reference "associated with talc" means that the chrysotile they report is in veins in massive serpentinite, not talc ore, an optical identification is probably valid, but if they were identifying chrysotile as a component in a talc ore, then this conclusion is questionable. The three forms of serpentine were not identified until 1956, nine years after the Furcron et al. paper, when Whittaker and Zussman (1956) published the first determinative data for the serpentine polymorphs.

**8. USA, Maryland, Piedmont belt, Chrysotile possible.** IARC relied on Cleaves et al. (1974) and Greene (1995) for the mineralogy of this set of small talc deposits. Neither Green nor Cleaves mentions chrysotile and Cleaves does not discuss talc deposits.

**9. USA, New York, Gouverneur District, St Lawrence County, Fowler, Chrysotile possible.** IARC relied on a number of sources for the mineralogy of this complex talc district including Wylie et al. (1997), IARC (2010), Van Gosen et al. (2004), and Gunter et al. (2018) to conclude that chrysotile is possible. None of the references support the presence of chrysotile. One of us, Ann Wylie, has studied the mineralogy of this deposit extensively and has never observed chrysotile. As stated earlier, the presence of serpentine alone is insufficient to conclude that chrysotile will also be present, and this is an excellent example.

**10. USA, New York, Lewis County, Natural Bridge, Chrysotile possible.** IARC relies on Van Gosen et al. (2004) who do not mention Natural Bridge nor does IARC (2010), another reference. Engel (1949) describes the mineralogy but does not mention chrysotile. As part of the Gouverneur District, Natural Bridge has similar mineralogy to the rest of the district, including the presence of serpentine, with the exception that tremolite is not abundant (Engel 1949).

**11. USA, Texas, Llano district, Chrysotile present.** IARC relies on Van Gosen et al. (2004) for the presence of chrysotile. Chrysotile is mentioned as a component of some "serpentine masses," not as a component of the ore.

**12. USA, Vermont (Blackwall talc), Chrysotile present.** To support the conclusion that chrysotile is present in the talc ore from Vermont, IARC relies on IARC (2010), Van Gosen et al. (2004), Gunter et al. (2018), and Egilman et al.(2020). Van Gosen et al. mention that chrysotile may be found in massive serpentinite but not in talc deposits. Gunter et al. report it possible to find antigorite in some mine products. IARC (2010) does not list serpentine as a component of the Vermont talc ores. The only reference to support chrysotile in talc is Egilman et al. who rely on supposed data NIOSH declined to publish and to legal proceedings, not peer reviewed literature for their conclusions.

IARC discusses studies of commercially available talc products or commodities used for personal care products (pages 84–88). Of these, several list chrysotile, including Bird et al. (2021), Paoletti et al. (1984), and Rohl et al. (1976). Although Bird et al. was published in 2021, this paper relies on company documents from many years before, not independent studies. Lewin (1972) also report chrysotile in 7 out of 102 commercial products studied by XRD. When analyzing talc containing small amounts of serpentine by XRD it is not possible to tell in what form the serpentine occurs. (The criteria set out by Whittaker and Zussman in 1956 require a complete pattern, often not attainable with mineral mixtures.) The report states that optical examination was used to confirm the presence of fibers, but no details as to what type of optical microscopy was used, what criteria were applied to identify particles as fibers, and how "fibers" were identified as chrysotile vs. other forms of serpentine or other minerals. Given that antigorite is not uncommon in some talc ores, it is most likely that Lewin incorrectly identified antigorite as chrysotile by XRD. Other studies that IARC lists were negative for chrysotile including Pi-Puig et al. (2020), Delgado et al. (2020), Cralley et al. (1968), and Ferret and Moreau (1990) and the lung burden study of Gordon et al. (2014).

The U.S. FDA routinely analyzes talc-based consumer products. In 2019, the FDA reported finding three chrysotile fibrils in a single TEM mount of talcum powder (US FDA 2019). The laboratory routinely examines asbestos and is skilled in its identification. However, the finding was not reproduced by the laboratory or others that examined material from the same or similar batches. In such a case, sample contamination cannot be ruled out, nor can the presence of chrysotile as a component of the ore be confirmed. Otherwise, chrysotile has not been detected in FDA studies.

It may seem reasonable to assume that chrysotile is present in talc because they are both magnesium silicates and they sometimes occur in rocks of the same age and type. This is not a geologically supportable conclusion. Our review of all the references listed by IARC, as supporting the data in Table 1.1, shows that chrysotile has not been identified as a component of talc ore, and, with the single exception of the 2019 FDA study, reports of chrysotile in talc products are confined to a time when chrysotile contamination was widespread.

From an understanding of mineralogy and petrology, it is not surprising that chrysotile is absent from talc ore. One

common way mineral talc forms in nature is from the loss of water on heating serpentine. Candela et al. (2007) reports that chrysotile can transform quickly to talc when it is heated above 500 C. As serpentine is transformed and talc is formed, chrysotile, a form of serpentine, would not selectively resist this transformation based on anything we know about the behavior of minerals.

#### 4.1.7. General comments

IARC concludes that "asbestos is a common contaminant of talc" (136), and throughout the document, IARC expresses "concern about asbestos contamination" in interpreting evidence, including which studies to include or exclude based on this concern. The conclusion that asbestos is a common contaminant is not supported by the data given for the major talc deposits of the world in Table 1.1 where, of the 49 deposits listed, only 4 have documented from the literature the presence of amphibole asbestos in the ore, including the Death Valley deposits from Grantham-Warm Spring and Alexander Hills in the Southern Death Valley, Dadeville Alabama and Soapstone Ridge, Georgia, and the Gouverneur district of NY, and, as noted above, none have chrysotile.

It is questionable how IARC was able to characterize available toxicological information from the literature, clearly distinguishing all possible combinations of various categories of talc when their compilation of the mineralogy of the talc sources was so flawed. Different toxicological studies attempted to utilize talc not contaminated with asbestos fibers. For example, pure microtalc not containing asbestiform fibers was reportedly used in the NTP study in rats and mice, assessed below (NTP 1993). However, inconsistencies in Table 1.1 of the recent monograph show that unbiased characterization of all available studies is complicated and conclusions made by IARC on "pure talc" carcinogenicity lack mineralogical meaning.

The IARC definition of "pure talc" is qualitative, and there appears to be no attempts in Monograph 136 to distinguish between cosmetic and industrial talc, or to set up an analytical threshold to specify the purity of talc. It is unclear if in the case of industrial talc whether IARC was able to determine if "fibrous talc" (not considered to be asbestos) could be present in some of the tested samples and what impact could be expected from this component on the toxicity of talc. Monograph 136 has further complicated the interpretation of a "pure talc" concept instead of improving our understanding of its importance for toxicological studies.

### 4.2. Toxicokinetics of talc

The talc Monograph in 2025 recognized that there is a limited level of transfer for talc particles between various compartments of the animal or human body (IARC 2025a). The Monograph stated that inhaled talc is retained in the lungs, whereas talc that is injected intravenously is distributed systemically. In rodents, inhaled talc was not observed in other organs apart from the lungs; orally ingested talc was excreted shortly after dosing; and no or negligible intestinal absorption or translocation of talc to the liver and the kidneys was observed.

The Monograph acknowledged that in humans, talc was identified at multiple pelvic sites distant from the perineum, but in most studies in animals, no translocation from the perineal region to the ovaries was reported. The absence of concordance between observations in humans and animals is noteworthy and may demonstrate that talc data on cancer in experimental animals should not be automatically interpreted as relevant for humans. Also, the lack of information on the mineralogy of particles found in the human pelvic site, prevents a clear toxicological assessment. For example, Johnson et al. (2020) stated that in tissues resected from ovarian carcinoma patients, "many" particles were found that gave talc spectral signals on SEM/EDX microscopy. Also, "some" particles identified as talc were found in the uterine tubes of patients. It is unclear what proportion of identified particles was detected as talc, what other types of particles were found in tissues, and what the background concentrations of talc and other particles were in tissue for the general population and for females with no ovarian carcinoma.

### 4.3. Data on cancer in humans

There are no significant changes in the assessment of the evidence for cancers in humans between talc Monographs from 2010 and 2025. The recent Monograph specifically stated that little (insufficient) evidence exists regarding a causal association between exposure to talc and mesothelioma, brain, prostate, cervical, breast, thyroid, or testicular cancer, as well as uterine, lung, digestive system, urinary, or lymphatic and hematopoietic cancers. Only evidence for the relationship of talc exposure with ovarian cancer in humans was found to have "limited" status. It should be seen, however, that IARC continues to express significant and warranted caution toward the available data on the causative relationship between talc and cancer of the ovary, emphasizing that "bias and confounding by asbestos exposure could not be ruled out with reasonable confidence" (IARC 2025a).

Earlier, Boon et al. (2024) performed a systematic review of the epidemiological evidence on talc and cancer. The authors demonstrated that with only one exception (Chang et al. 2019), no studies had direct exposure measurements for any individuals, though some used semi-quantitative exposure metrics, and few studies adequately assessed potential confounders. The only consistent associations were with ovarian cancer in case-control studies, and these associations were likely impacted by recall bias. This systematic review indicated that epidemiology studies do not support a causal association between occupational or personal talc exposure and any cancer in humans. The authors also emphasized that in the only study in which the dose of talc was at least partly quantifiable (Chang et al. 2019), the risk increase was eliminated when a latency of at least 5 years from intake to the development of cancer was considered. It should be noted that the Chang et al. publication relates not to ovarian but to stomach cancer.

As Goodman et al. (2020) argued, the hypothesis that talc exposure induces ovarian cancer is only supported if one discounts the null results of the cohort studies and the fact that significant bias and/or confounding are likely reasons for the associations reported in some case-control investigations. An alternative hypothesis that talc does not produce ovarian cancer, and that bias and confounding contribute to the reported positive associations in case-control studies, is better supported by the evidence across disciplines. Goodman et al. concluded that the evidence does not support a causal association between perineal talc use and ovarian cancer. Additionally, Goodman et al. (2024), using data from the Cramer et al. (2016) case-control study, demonstrated that recall bias alone may have a large impact on risk estimates. In this case, most scenarios demonstrate that recall bias results in a bias away from the null. It is likely that this bias has affected other case-control studies in a similar manner, because they have all used similar methods to estimate exposure.

It is important that IARC performed its own quantitative analysis of the bias in the case-control studies for talc and ovarian cancer as a part of its Monograph 136. Table A2.4 from the IARC study shows that based on quantitative bias analysis, the lower 95% confidence interval of the meta-relative risk (RR) for ovarian cancer and talc usage was lower than 1 or equal to 1 (not statistically significant) for all three involved experts (who independently evaluated sensitivity and specificity estimates for 15 studies). Nevertheless, IARC concluded that there was evidence of a positive association between talc exposure (based upon the findings of studies on perineal application of talc-based body powder) and ovarian cancer and that this association was not likely to be explained by chance. However, IARC stated that, although there was adjustment for most risk factors for ovarian cancer, bias from differential exposure misclassification and confounding by asbestos contamination of the talc could not be ruled out with reasonable confidence (IARC 2025a).

It is clear that several aspects of the evaluation of ovarian cancer relationship to talc exposure remain controversial. First, no cohort studies, which remain the source of the most reliable epidemiological information, have ever confirmed the association between pure talc exposure and cancer in humans. Second, while some studies have detected the presence of talc in the tissues of ovarian cancer patients, a direct relationship between talc exposure and disease has not been established, and no statistically significant difference in talc concentrations has been found between cancer patients and control groups. Third, the IARC Monograph confirmed potential biases and confounders in case-control studies on talc.

For "limited" evidence of carcinogenicity in humans, the IARC Preamble sets the following criteria: "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."

In our opinion, "chance, bias, and confounding" significantly affect the credibility of a causal interpretation for positive association between exposure and cancer. As Wentzensen and O'Brien (2021) stated, "the epidemiological data from case-control studies and cohort studies suggest that there may be a small, positive association between genital powder use and ovarian cancer. The causal factors underlying this association are not clear. Proposed factors include talc, other minerals, such as asbestos or quartz, that are known carcinogens and may contaminate talc products, or other powder ingredients that could cause inflammation of the reproductive tracts." It is reasonable to conclude that for talc and ovarian cancer, "there are studies of sufficient quality available in humans, but their results are inconsistent or otherwise inconclusive" (IARC 2019a). For ovarian cancer in humans, this would classify pure talc as "inadequate" rather than "limited" based on IARC's own criteria. As we mentioned before, IARC acknowledged the lack of data to support any causal association for pure talc and other types of cancer.

### 4.4. Evidence on cancer in experimental animals

The IARC assessment of the weight of evidence for cancer in experimental animals exposed to talc also remains controversial. Both Monographs 93 and 136 rely on a single large-scale inhalation study on talc in rats and mice performed by the Lovelace Biomedical and Environmental Research Institute (NTP 1993). The study included talc administration by inhalation in male and female F344/N rats. In females, talc caused malignant pheochromocytoma, benign or malignant pheochromocytoma (combined), bilateral benign pheochromocytoma, and bilateral malignant pheochromocytoma of the adrenal medulla; and bronchioloalveolar carcinoma, and bronchioloalveolar adenoma or carcinoma (combined). In males, talc caused benign, malignant, or complex pheochromocytoma (combined) of the adrenal medulla. In the same study, no neoplastic outcomes were found in exposed mice.

The results of the NTP study in male and female rats are summarized in Table 2.

Monograph 136 stated that the occurrence of tumors in this study was considered "unusual" because of the following findings: (i) the significant increase in the incidence of bilateral benign pheochromocytoma and bilateral malignant pheochromocytoma of the adrenal medulla in females; and (ii) the development of tumors in the adrenal medulla after exposure to talc by inhalation in both sexes (IARC 2025a).

However, pheochromocytoma in rats is not a rare finding for inhalation studies. For example, Ozaki et al. (2002) demonstrated a correlation between inhalation exposure in similar NTP-related studies in rats and pheochromocytoma for numerous agents including nickel oxide (IARC Group 1), cobalt sulfate (IARC Group 2B), indium phosphide (IARC Group 2 A), and nickel subsulfide (IARC Group 1). In exposure to gallium arsenide (IARC Group 1) and molybdenum trioxide (IARC Group 2B), incidence of pheochromocytoma also increased with severity of lung fibrosis and inflammation. It was demonstrated that lung fibrosis, inflammation, and hypoxemia play a role in pheochromocytoma development in rats.

At the same time, Oberdörster (1995) noted that the lungs of rats in the study were overloaded by particle exposure, signifying a possible misinterpretation of the outcomes of

Table 2. Neoplasms in rats from the NTP study and estimation of lung burden.

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| Exposure concentration ($mg/m^3$) | 0 | 6 | 18 | 0 | 6 | 18 |
| Bronchioalveolar adenoma/carcinoma (cases/total animals) | 0/49 | 1/50 | 2/50 | 1/50 | 0/50 | 13/50 |
| Pheochromocytoma (benign and malignant) (cases/total animals) | 26/49 | 32/48 | 37/47 | 13/48 | 14/47 | 23/49 |
| Volumetric lung burden of talc in rats at month 24 of observations (μl/lung) (Oberdörster 1995) | 0 | 6.59 | 15.23 | 0 | 2.23 | 10.65 |

the study that were erroneously associated with talc exposure instead of general dust burden. In Table 2, the volumetric lung burden of talc can be compared to a value of 1 μl per rat lung that Morrow (1992) suggested to be an indicator of dust overload. As can be seen the exposure level of 18 mg/$m^3$, the volumetric lung burden in male rats exceeded the overload indicator by a factor of 15.23, and in female rats by a factor of 10.65.

Also, Oberdörster concluded that pheochromocytoma rates in rats were elevated in experimental groups as well as in controls, and this endpoint was unrelated to inhalation exposure. One of the author's of this paper, Dr. Ann Wylie, was a member of the IARC Panel in 2006 where the disqualification of experimental data as support for a carcinogenic designation in animals, when significant overload was a factor, was discussed and accepted. For this reason, the panel in 2006 (IARC 2010) did not rely on the NTP study to establish carcinogenicity of talc. It is noteworthy that current IARC monographs have not discussed the previous IARC assessment of pheochromocytoma as irrelevant for human carcinogenicity and just applied a new qualification to this tumor as "unusual".

The statement that elevated pheochromocytoma in female rats is highly unusual should also be considered incorrect. Based on Ozaki et al. (2002), pheochromocytoma rates in both female and male rats were elevated in exposure to nickel subsulfide, nickel oxide, indium phosphide, and cobalt sulfate. What was unusual, however, is the rate of pheochromocytoma in control rats for the talc study. The rate of this tumor (benign, malignant, or complex) in unexposed rats was 53% for males and 27% for females, while the typical rates of spontaneous tumors in F344/N rats is 31.9% in males and 5.1% in females (Haseman et al. 1998). In a similar NTP-related study for nickel oxide, the rate of all types of pheochromocytoma in control female rats was 8% (NTP 1996), and in an indium phosphide study it was 4% (NTP 2001). It appears that all rats in the talc study were affected by some unreported factors that elevated the level of pheochromocytoma. It is noteworthy that Tischler et al. (1999) reported pheochromocytoma in rats induced by vitamin D3. Presence of an unknown dietary, environmental, or genetic factor that could affect incidence of pheochromocytoma in male and female rats in the talc study could significantly change the statistics. Also, statistically significant elevation of the pheochromocytoma rate in male and female rats was observed only at the highest dose of talc (18 mg/$m^3$), that was suggested to exceed the maximum tolerated dose (MTD) (see a the summary of technical reports review subcommittee meeting in NTP 1993) and to cause lung dust overload that would be expected to lead to significant pulmonary effects in rats (Morrow 1992). As Prueitt et al. (2024) noted in this regard, talc carcinogenicity has only been observed in one study in rats under conditions of lung particle overload, which is not relevant to human exposures. Lung particle overload is a nonspecific effect of high exposures to poorly soluble particles of low toxicity (PCPT), and lung tumors observed under such conditions are not indicative of any carcinogenic properties of the particles themselves.

Recently, ECHA RAC (ECHA/RAC 2025), in its own assessment of talc carcinogenicity, expressed certain doubts about the interpretation of dust burden in rats for the NTP study. In particular, it was suggested that the definition of lung dust overload is not fully determined in science, and also that the status of talc as a PSPT compound is questionable because of its alleged proinflammatory properties. In contrast, Bevan et al. (2018) demonstrated that inhalation of a high concentration of dust can lead to pro-inflammatory responses and pulmonary toxicity in different species, which are not predictive of human carcinogenicity.

Nevertheless, RAC concluded that the finding of pheochromocytoma in rats for talc study should be assigned "less weight" for humans (because of the absence of any epidemiological information, as well as a disproportionally high incidence of the tumor in control rats). The significant emphasis that IARC made for this rare and genetically driven condition as a reason to elevate the weight-of-evidence for the data on talc carcinogenicity in experimental animals is not supported by scientific assessment. Also, in contrast to IARC, the RAC report classified the evidence of talc carcinogenicity in experimental animals as "limited".[2]

IARC established that the following criteria constitute sufficient evidence for talc's carcinogenicity in experimental animals: "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 tumor, or age at onset, or when there are marked findings of tumors at multiple sites" (IARC 2019a). The criteria for sufficient evidence were not met because the incidence of pheochromocytoma in rats is irrelevant for evaluating inhalation exposure. Rather than elevating the limited evidence from the only available single-species GLP study, it should be agreed that "there are unresolved questions about the

adequacy of the design, conduct, or interpretation of the available studies." This would keep the classification at "limited," though the "inadequate" status may be more appropriate.

### 4.5. Mechanistic evidence

The search for mechanistic evidence of the carcinogenicity of various agents is driven by the need for expanded methodological approaches to testing, as traditional human epidemiology and animal experimentation face future limitations, especially with difficulties in organizing human studies and the international movement to limit testing on laboratory animals (Rusyn and Wright 2023; Van der Laan and Manuppello 2024).

Studies in recent decades enriched our knowledge of the mechanisms of carcinogenicity in humans and animals, suggesting that there are numerous pathways for cancer development. While the initiating or early key events (e.g. receptor binding, DNA adduct formation) vary depending on the chemical, the broader biological processes—such as mutation accumulation (whether through direct mutagenic action or by increasing the likelihood of spontaneous mutations), enhanced cell replication, and immortalization—are common features across all carcinogens. In addition, rodent mode-of-action studies show that some chemicals act through DNA reactivity and mutagenesis, others through receptor-mediated processes such as hormonal disruption or growth receptor modulation, and many through induced sustained cytotoxicity/inflammation leading to regenerative proliferation, a MoA frequently observed in different rodent tissues after sustained high chemical exposures (Basu 2018; Hwa Yun et al. 2020; Sohrab et al. 2023; Alyafeai et al. 2024). However, there is no indication that separate toxicological characteristics (like induction of inflammation) can be considered separately from other characteristics in determining carcinogenicity.

Becker et al. (2025) demonstrated that separated KCC characteristics cannot characterize chemical agents as carcinogenic or non-carcinogenic. The authors showed that as much as 50% of classified carcinogens do not exhibit KCCs, while other chemicals not known to evoke cancer often do. Furthermore, across the sets of KCCs (cardiovascular toxicants, endocrine disrupting chemicals, female reproductive toxicants, hepatotoxicants, immunotoxicants, male reproductive toxicants, and aging) there is considerable redundancy, indicating that many other toxicities unrelated to cancer may be mediated by similar toxicity pathways and biological responses.

The talc monograph by IARC attempted to assign a "strong" status to mechanistic evidence for talc carcinogenicity. IARC determined that there is strong indication of talc causing chronic inflammation (KC6) and altering cell proliferation and cell death (KC10). IARC also found "suggestive" evidence that talc can cause oxidative stress (KC5) and immunosuppression (KC7).

However, the "suggestive" characteristics mentioned for talc should be treated with caution. For example, earlier, Fontan et al. (1983) found that subcutaneous talc-induced granuloma in mice apparently secreted protein that fully protected mice against Listeria monocytogenes, indicating immunostimulatory effect. This means that talc may initiate immunostimulatory, rather than immunosuppressive effects (KC7), depending on specific conditions. For oxidative stress, IARC noted that there are limited numbers of relevant studies and some of the reported endpoints of oxidative stress are known to be of low specificity (IARC 2025a).

At the same time, based on the IARC analysis, there is no data at all that would associate other key mechanistic characteristics of carcinogens with talc exposure. In particular, IARC concludes that there is no relevant data that would confirm talc as genotoxic (KC2), causing alteration of DNA repair and genetic instability (KC3), and/or epigenetic alteration (KC4) etc. (IARC 2025a).

Apparently, IARC does not have any methodology that would require specific combinations or minimal number of mechanistic evidence characteristics to reach a conclusion about a potential carcinogenicity of the agent. Conclusions that a substance may be carcinogenic to humans should be treated cautiously when based on unspecified decision-making algorithms that permit broad differences in how the same data are interpreted.

In introducing mechanistic evidence into the classification process, IARC emphasized earlier that relying on single characteristics may be misleading for overall carcinogenicity when a mode of action is not demonstrated. In the IARC publication (IARC 2019b), it was argued that "[c]ertain types of inflammatory processes in skin, and possibly in other tissues, may serve a tumor suppressor function." Also, despite extensive inflammation, activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and abundant proliferation of bile ducts in portal spaces, *Mdr2* knockout mice rarely develop tumors of the bile duct (as was demonstrated by Nickoloff et al. 2005, quoted by IARC). It was emphasized by IARC publications (IARC 2019b) that many of the indicators of changes in cell proliferation or cell death rates are nonspecific for the induction of cancer. Also, as Nishida and Andoh (2025) stated recently, "inflammation plays a dual role in cancer biology. While it can foster tumor growth by creating an environment rich in cytokines and growth factors that enhance cancer cell survival and proliferation, it can also activate antitumor immune responses, a mechanism harnessed in cancer immunotherapy."

Another example of single mechanistic characteristics not being predictive of carcinogenicity can be found in studies on dust overload in rats. For example, exposure to a very high dose of both titanium dioxide or carbonyl iron particles was reported to cause sustained pulmonary inflammation, enhanced proliferation of pulmonary cells, impairment of particle clearance, deficits in macrophage function, and the appearance of macrophage aggregates at sites of particle deposition (Warheit et al. 1997). At the same time, titanium dioxide is an agent from Group 2B by IARC, but carbonyl iron is not mentioned in any current IARC documents.

It is not just a single key characteristic, but their interplay, that most probably is indicative of carcinogenicity. This fact can be illustrated based on a statistical analysis, which we demonstrated using several approaches, as described in the Materials and methods section and below.

#### 4.5.1. General quantitative characteristics of the variables

We found that, among the 184 substances classified as Group 1 carcinogens in our analysis, none shared the same two characteristics observed for talc (KC6 and KC10) without also having at least one other parameter (KC1, KC2, KC3, KC4, KC8, or KC9), characteristics that have not been identified or suggested for talc.

For Group 2 A, there is only one agent (night shift work) that has evidence for characteristics KC6, KC10, and KC7, with no other characteristics mentioned. However, as we noted above, KC7 is not a confirmed parameter for talc (both immunostimulation and immunosuppression were reported). Talc's KCC profile does not align with the patterns observed in our analysis for agents classified as carcinogenic or probably carcinogenic to humans.

Table 3 provides probability values for Group 1 classification for carcinogens on each of the key characteristics.

As shown in Table 3, only the parameter KC2 (genotoxicity) is self-sufficient to fully predict the status of confirmed human carcinogenicity (in 9 from 97 Group 1 agents analyzed). All other key characteristics had to be accompanied by at least one additional parameter to confirm human carcinogenicity. This finding is not surprising given that the majority of the chemical agents in IARC's Group 1 are DNA reactive mutagens or direct genotoxins (albeit some Group 1 agents act through alternative mechanisms).

#### 4.5.2. Principal component analysis (PCA)

We performed a principal component analysis (PCA) for the ten key characteristics and the variable reflecting classification of the agent as Group 1 carcinogenic in humans or not.

Table 4 shows linear correlations between ten key characteristics and Group 1 (Yes/No) variable.

Table 4 shows that only one pair of parameters in our analysis can be considered as having medium strength of correlation (parameter KC2 and Group 1). Only week correlations exist between Group 1 parameter and "talc" pool of characteristics. We do not expect the linear relationship between parameters to significantly affect the outcomes of the PCA.

We used 4 principal components (factors) to project 11 initial characteristics. The result of the analysis is demonstrated in Figure 2 (a – the factor-plane $1 \times 2$, b – the factor plane $3 \times 4$). A total of 63.7% of all variation of all parameters is explained by these 2 planes, with other factors being minor. The plane $1 \times 2$ shows the coordinates of variables for components 1 and 2, and plane $3 \times 4$ for components 3 and 4.

As we demonstrated, at the main $1 \times 2$ factor plane, confirmed carcinogenicity in humans is associated with four key characteristics in the left upper quadrant (KC1, KC2, KC3, and KC9). Three parameters appear to be closest to Group 1 variable: KC2 (genotoxicity), KC3 (alteration of DNA synthesis), and KC9 (immortalization). All four talc-related key characteristics belong to another quadrant, not correlated with human carcinogenicity outcome.

For the second projection ($3 \times 4$ factor plane), Group 1 is associated with one of the possible talc-related parameters (KC7, immunosuppression), as well as with parameter KC9 (immortalization), but not with the other three parameters in the "talc list": KC5, KC6, and KC10 are all in a different quadrant. It should also be noted that the immunosuppression parameter is not confirmed for talc, and talc appears to

**Table 3.** Probability of each of the key characteristics in the group 1 carcinogens.

| Characteristic | Average probability (standard deviation), (bootstrap 95% CI) | Average probability of the characteristic if all other characteristics are absent (standard deviation), (bootstrap 95% CI) |
|---|---|---|
| KC1 | 0.38 (0.49), (0.29, 0.49) | 0 |
| KC2 | 0.96 (0.20), (0.92, 0.99) | 0.89 (0.33), (0.57, 0.98) |
| KC3 | 0.25 (0.44), (0.17, 0.35) | 0 |
| KC4 | 0.37 (0.49), (0.28, 0.48) | 0 |
| KC5 | 0.48 (0.50), (0.38, 0.59) | 0 |
| KC6 | 0.36 (0.48), (0.27, 0.46) | 0 |
| KC7 | 0.23 (0.43), (0.15, 0.32) | 0 |
| KC8 | 0.12 (0.32), (0.05, 0.18) | 0 |
| KC9 | 0.31 (0.46), (0.21, 0.40) | 0 |
| KC10 | 0.53 (0.50), (0.44, 0.63) | 0 |

**Table 4.** Correlation between variables used for PCA (highlighted correlations are statistically significant at $p < 0.05$).

| | Correlations | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | KC1 | KC2 | KC3 | KC4 | KC5 | KC6 | KC7 | KC8 | KC9 | KC10 | Group 1 |
| KC1 | 1.00 | **0.41** | **0.16** | **0.26** | 0.13 | 0.07 | 0.07 | 0.01 | 0.02 | **0.25** | **0.21** |
| KC2 | **0.41** | 1.00 | **0.31** | **0.32** | **0.36** | **0.24** | 0.08 | 0.05 | **0.33** | **0.39** | **0.69** |
| KC3 | **0.16** | **0.31** | 1.00 | **0.39** | **0.35** | **0.26** | 0.11 | 0.03 | **0.34** | **0.39** | **0.33** |
| KC4 | **0.26** | **0.32** | **0.39** | 1.00 | **0.35** | **0.31** | **0.22** | **0.22** | **0.28** | **0.39** | **0.46** |
| KC5 | 0.13 | **0.36** | **0.35** | **0.35** | 1.00 | **0.37** | **0.33** | **0.23** | **0.21** | **0.36** | **0.27** |
| KC6 | 0.07 | **0.24** | **0.26** | **0.31** | **0.37** | 1.00 | 0.10 | 0.07 | 0.09 | **0.32** | **0.26** |
| KC7 | 0.07 | 0.08 | 0.11 | **0.22** | **0.33** | 0.10 | 1.00 | **0.31** | **0.16** | **0.24** | **0.20** |
| KC8 | 0.01 | 0.05 | 0.03 | **0.22** | **0.23** | 0.07 | **0.31** | 1.00 | −0.03 | **0.27** | 0.09 |
| KC9 | 0.02 | **0.33** | **0.34** | **0.28** | **0.21** | 0.09 | **0.16** | −0.03 | 1.00 | **0.34** | **0.42** |
| KC10 | **0.25** | **0.39** | **0.39** | **0.39** | **0.36** | **0.32** | **0.24** | **0.27** | **0.34** | 1.00 | **0.26** |
| Group 1 | 1.00 | 0.41 | 0.16 | 0.26 | 0.13 | 0.07 | 0.07 | 0.01 | 0.02 | 0.25 | 1.00 |

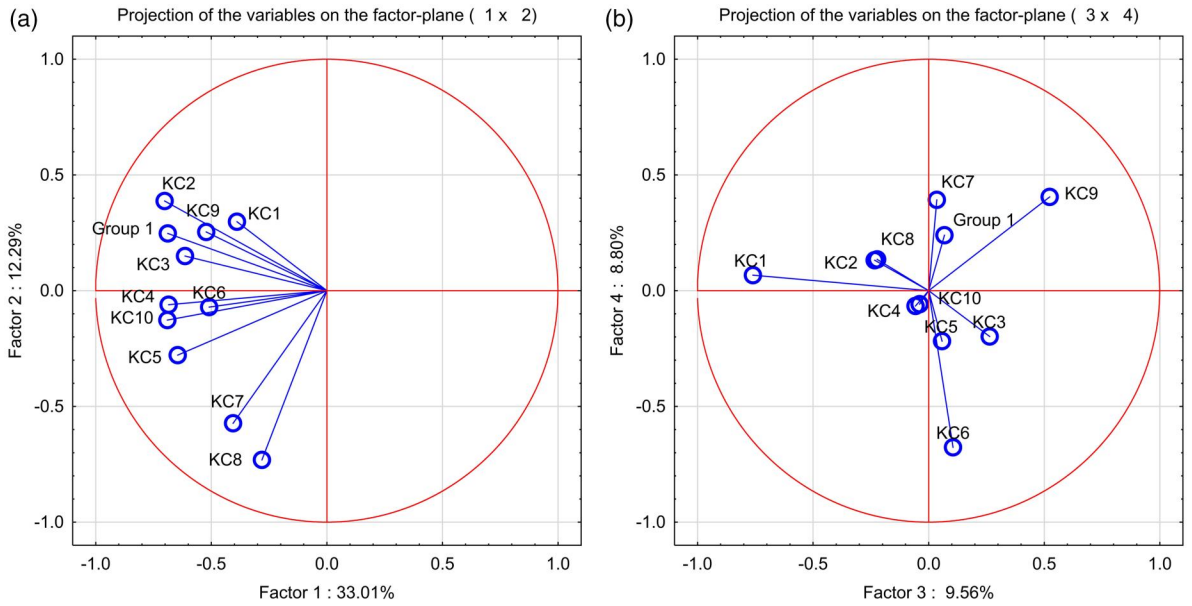


**Figure 2.** The results of principal component analysis (PCA) for key mechanistic characteristics of carcinogenicity. a) First factor plane. b) Second factor plane.

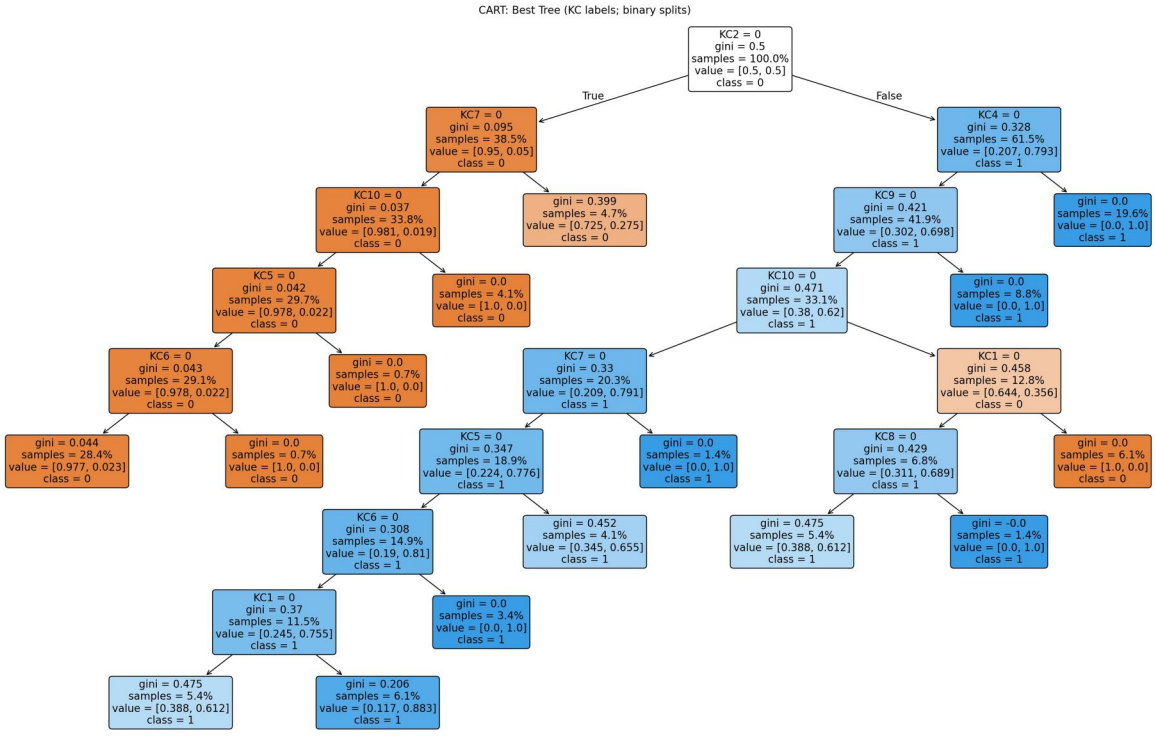


**Figure 3.** The CART analysis for key characteristics and group 1 cancer outcome.

express itself as both immunostimulating and immunosuppressing (see section 4.5.1).

While PCA does not conclude that specific combinations of variables (key mechanistic characteristics) are predictive of cancer outcomes, it does illustrate the minor role of the "talc" combination of variables, and emphasize that a MoA function (relationship between separate variables) is lacking in any assessment that would claim parameters KC6 and KC10, along with KC5 and KC9, as predictors of cancer development.

### *4.5.3. CART analysis*

The results of CART analysis with 5-fold cross-validation are demonstrated in Figure 3. The obtained tree shows a balanced accuracy of 0.76.

As we noted above, the CART approach recursively divides the data into two near-homogenous daughter nodes according to a split point that maximizes the reduction in impurity along a particular variable.

The following parameters are listed in the diagram in Figure 3:

Gini: Coefficient that determines the heterogeneity of the samples that reached a given node. A higher gini implies a more heterogeneous sample.

Samples %: Out of all samples, specifies the percent that reached a given node.

Value: The first number is the fraction of samples belonging to class 0, and the second is the fraction belonging to class 1, when reaching the specified node.

Class: predicted class.

5-fold CV: We divided the data into 5 equally sized "folds." We trained on 4 of the folds, using the remaining one to validate. Then, we rotated until each fold had been used to validate, using the average score between all fold combinations to evaluate the model's performance. In our case, we used the "balanced accuracy" method to score each tree, meaning equal weight was given to each class when evaluating accuracy.

As shown in the diagram, parameter KC2 plays the major role in the classification of the agents as class 0 (not a Group 1 carcinogen) vs. class 1 (Group 1 carcinogen). The combination of KC2 = 0 and KC7 = 1 provides classification of talc as non-Group 1 agent. The combination of KC2 = 0, KC = 0, and KC10 = 1 also provides a classification of talc as non-Group 1 agent.

#### 4.5.4. Correlations between various combinations of key characteristics and the group 1 outcome

In addition, we can compare different combinations of mechanistic characteristics to elucidate possible pathways of carcinogenicity in humans, vs. the concept of "isolated" parameters employed by IARC. We tested all possible combinations containing 2 to 4 parameters. Then we calculated a "score" for every agent, as a sum of all parameters in a combination. The result was correlated with the variable indicating that the agent is classified as a Group 1 carcinogen. All combinations were sorted by Spearman rank correlation (used because of unwarranted normality of the variables).

The results of the analysis are demonstrated in Table S2.

The highest correlation ($R = 0.76$, $p < 0.05$) was achieved for the combination of KC2 (genotoxicity), KC4 (epigenetic alteration), and KC9 (immortalization). The combination of three parameters that we determined as being close to the Group 1 variable (KC2, KC3, and KC9) by PCA is in the 9th place for Spearman correlation with $R = 0.72$, $p < 0.05$. The combination of KC5, KC6, KC7, and KC10 (as for worst-case assumption on talc) has the rank 311 among 375 combinations, with a weak correlation coefficient of $R = 0.38$. The combination of KC6 and KC10, which was estimated as carrying "strong" mechanistic evidence by IARC, is in the 352nd place for relevancy ($R = 0.33$).

#### 4.5.5. Logistic regression

We also constructed a combined "scores" reflecting the number of positive parameters for each agent from the pool of key characteristics (KC5, KC6, KC7, KC10), and from the pool of all other characteristics.

Logistic regression can be developed to predict carcinogenicity outcome for each agent based on the scores, as well as on the level of evidence for cancer in humans and animals.

The logistic regression is applicable to the available data by using two "scores" ("talc" characteristics and "non-talc" characteristics"), and weight-of-evidence data from human and animal studies. The outcome variable (Group 1 or not Group 1) is binary. Also, we found that all independent variables in our model had a variance inflation factor (VIF) of less than 5.

The results of the logistic regression are provided in Table 5.

The following diagnostics for the logistic regression have been derived:

Log-Likelihood: −17.7531
AIC: 45.5062 BIC: 61.5808
AUC (c-statistic): 0.9937
95% CI for AUC (bootstrap, $n = 2000$): [0.9844, 0.9992]
Somers' D: 0.9875
Brier Score: 0.027286

Only the "cancer in humans" variable and second pool of characteristics (not found in talc studies) appear to be predictive of the Group 1 classification.

#### 4.5.6. Review of the mechanistic evidence

Our statistical analysis confirms that not every one of the key characteristics is predictive of cancer outcomes. However, specific combinations of mechanistic characteristics can be indicative of cancer outcomes. These combinations should reflect specific MoA for cancer, such as genotoxicity, disruption of DNA repair, and cell immortalization. It is also obvious that statistical analysis can play only a supportive role in determining possible pathways to cancer, and only toxicological studies can confirm that a specific chain of events would actually exist in each case.

The IARC Monograph on talc has not provided any hypothesis on the chain of events, or MoA, for the alleged carcinogenicity of talc. It can be assumed that chronic inflammation is seen by IARC as a possible key event in the alleged talc-related carcinogenicity, with cell proliferation and inhibition of apoptosis seen as cancer promoting effects. However, this combination of these events without other confirmed characteristics (like genotoxicity, genomic instability, alteration of DNA repair, epigenetic alteration, modulation of receptors, and/or immortalization of cells) is an outlier among

Table 5. Logistic regression for prediction of confirmed carcinogenicity of various agents (Group 1 vs. other) (statistically significant parameters highlighted).

| Variable | Coefficient | 95% CI, lower | 95% CI, upper | Standard error | *Z* | *P* value |
|---|---|---|---|---|---|---|
| **Intercept** | **−7.52** | **−11.74** | **−3.30** | **2.15** | **−3.49** | **0.0005** |
| **Cancer in humans-evidence** | **4.38** | **2.59** | **6.18** | **0.92** | **4.79** | **0.0000** |
| Cancer in animals-evidence | −0.12 | −1.51 | 1.27 | 0.71 | −0.17 | 0.8646 |
| First pool of characteristics (KC5, KC6, KC7, KC10) | −0.23 | −1.08 | 0.62 | 0.43 | −0.52 | 0.6013 |
| **Second pool of characteristics (KC1, KC2, KC3, KC4, KC8, KC9)** | **2.31** | **1.15** | **3.48** | **0.59** | **3.89** | **0.0001** |

other IARC-designated carcinogenic agents. This fact should call for additional studies rather than for the immediate reclassification of talc in the IARC hierarchy. Interestingly, IARC stated, for example, that though "numerous reports" described chronic inflammation in humans, allegedly caused by talc, "none of the reviewed studies directly evaluated mechanistic endpoints of chronic inflammation per se caused by exposure to talc independently of other known risk factors…" (IARC 2025a). Also, if inflammation were a key effect of carcinogenicity for a specific agent, it should imply the existence of an exposure threshold (Cox et al. 2020). This discussion should be a part of the IARC evaluation, but it is excluded along with other essential risk assessment questions. In general, it is very difficult to see the status of mechanistic evidence for talc carcinogenicity as "strong" and should be considered "limited" or "inadequate" without addition of data from studies that would explore key characteristics for this agent in their interaction, rather than separately.

There is ongoing debate in the scientific community regarding the strengths and limitations of the IARC's KCC approach to evaluating chemical mechanisms. In particular, Becker et al. (2017) demonstrated that high throughput mechanistic characteristics of carcinogens predict cancer outcomes not better than chance. Goodman et al. (2025) noted that relying on mechanistic evidence alone to classify an agent as a possible or probable carcinogen, IARC diminishes the usefulness of its classifications and makes it impossible to distinguish human carcinogens from non-carcinogenic agents. Smith et al. (2021) suggested that KCCs "seem likely to confuse the unsatisfactory correlation from testing regimes that have ignored the differences evident when cellular changes are compared in short and long-lived species, with their very different stem cell and somatic cell phylogenies. The proposed characteristics are so broad that their use will lead to an increase in the current unacceptably high rate of false positives."

While IARC claims that introduction of mechanistic evidence for its assessment is a significant step forward, we can see that the ten key characteristics provide very approximate and patchy reflection of carcinogenicity processes, not allowing for full quantitative assessment or for determination of MoA in cancer.

IARC concluded that there is strong evidence that talc exhibits key characteristics of carcinogens in human primary cells and experimental systems. There is obviously no data on key characteristics expressed directly in exposed humans (but only in human primary cells). Only for cell proliferation, cell death, or nutrient supply are there some available data on talc effects in primary human cells. For other claimed key characteristics (chronic inflammation; immunosuppression; and oxidative stress), IARC reported that "there is a paucity of data" in human primary cells (IARC 2025a).

According to IARC, the following criteria constitute the "strong" level of 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 tumor 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" (IARC 2019a). For talc, there is no confirmation of the chain of events that would make the information on key characteristics consistent in predicting cancer in humans. The majority of key characteristics are negative for talc, and several characteristics that claimed to be confirmed or suggestive do not provide a coherent pathway for cancer development. In particular, it is unclear how IARC could claim that mechanistic evidence is strong in human primary cells when limited data were available for only one key characteristic (KC 10). The "limited" status of evidence would be more reasonable by IARC's own criteria.

## 5. Summary

We explored the new evaluation of talc not containing asbestiform fibers as performed by IARC. This evaluation is one of the most recent in the series of IARC Monographs that currently includes more than 1,000 agents. As shown, the talc Monograph reflects many of the issues typical for overall process of IARC assessments.

It appears that IARC invested a lot of effort into the reevaluation of talc carcinogenicity. It is noteworthy that Volume 136 which includes talc and acrylonitrile, was initially published only partially (for talc only with no acrylonitrile) in July of 2025 with obvious attempts to announce the evaluation as early as possible. The full monograph was issued in September of 2025.

Analysis by Boon et al. (2024) demonstrated that a significant number of new epidemiological studies (about 24) have been published on the issue of talc and cancer in humans since 2010 when IARC issued its previous evaluation. However, the systematic review of data for this period indicated that epidemiological studies do not support a causal association between occupational, medicinal, or personal talc exposure and any cancer in humans. While IARC might have an interest in reviewing the new set of published human data, it is unclear if the need for reclassification existed at all. It was well known that no new major studies in animals had been performed since the publication of the last talc Monograph in 2010, and the data on cancer in humans, specifically for ovarian cancer, remained of limited quality. The facts on the mechanistic evidence for talc were also well known in 2006.

The statistical analysis performed confirmed that mechanistic evidence used by IARC to substantiate talc carcinogenicity is irrelevant for the suggested outcome. Two key characteristics that appear to be supported by IARC for evidence in the case of talc do not correlate with human carcinogenicity variable and appear not to be statistically significant when analyzed along with other characteristics. Two parameters that are claimed to be suggestive do not add to the statistical predictability for human carcinogenicity.

**Table 6.** The IARC arguments for carcinogenicity of pure talc and evaluation of their validity.

| IARC argumentation | Factual assessment |
|---|---|
| The monograph addressed pure talc not containing asbestos fibers | Mineralogical assessment of talc by IARC (Table 1.1) contains inconsistencies that could affect the qualitative and quantitative evaluation of the evidence in available literature. |
| The monograph estimated the evidence for the carcinogenicity of talc from human epidemiological studies as "limited" (only ovarian cancer included). | The data on the relationship between ovarian cancer and pure talc exposure lacks sufficient scientific credibility to be classified as "limited," and should be categorized as "insufficient." |
| The monograph estimated the evidence for carcinogenicity of talc from experimental animal studies as "sufficient." The conclusion was made based on single species results (significantly elevated bronchioalveolar adenoma/carcinoma only in female rats, but not in male rats, or in mice). Elevated pheochromocytoma rates in rats were used as an "unusual" finding justifying the use of single species data for human carcinogenicity reasoning. | The highest level of exposure in rats study (18 mg/m$^3$) was apparently too high to evaluate specific effects of the agent, and not just effects of dust exposure. Pheochromocytoma in female rats was irrelevant for possible extrapolation to humans, rather than additional evidence of human carcinogenicity. Because there are unresolved questions about the adequacy of the design, conduct, or interpretation of the one available study on talc and cancer in experimental animals, this should be put into the "limited" or "inadequate" status category. |
| The monograph claimed strong evidence on key mechanistic characteristics in primary human and animal cells. | The information on key characteristics' expression in human primary cells exposed to talc is scarce. The key characteristics found for talc do not demonstrate a consistent MoA. The "limited" status of evidence would be more reasonable by IARC's own criteria. |

In its assessment, IARC clearly distinguished pure talc from talc contaminated with asbestiform elongate mineral particles. It should be emphasized that non-asbestiform elongate particles (so-called "cleavage fragments") that can be occasionally detected in some of talc samples are not carcinogenic (as IARC clearly stated in its Monograph 100 C) (IARC 2012). IARC also correctly stated in Monograph 136 that fibrous talc particles are "not asbestos" (IARC 2025a). This is why pure talc, independent of the morphology of its particles, does not produce mesothelioma in humans. However, IARC has not scientifically demonstrated that pure talc can cause ovarian cancer or any other type of malignant neoplasm in humans, either.

Table 6 summarizes the information that Monograph 136 used for determination of pure talc carcinogenicity, with our assessment of its validity.

Our review has obvious uncertainties and limitations. While talc appears to be a good example of some of the issues typical for IARC assessment it cannot be considered comprehensive or entirely representative. Further analysis of IARC monographs for various agents would be useful to determine if the organization systematically tends to elevate its previous estimations for carcinogens (that is apparent, for example, from the complete elimination of Group 4).

Among the limitations of our analysis, it should be mentioned that quantitative analysis of mechanistic and other types of evidence for the determination of Group 1 in this paper assumed that the current classification of agents for this group is correct (both inclusion or exclusion). While it might not always be the case, we used Group 1 carcinogens as a benchmark to compare the available data on talc with corresponding information for confirmed human carcinogens. We demonstrated that it is highly unlikely that talc expresses combinations of mechanistic parameters, typical for carcinogens, included in the highest IARC group (Group 1), and therefore its consideration as a "probable" human carcinogen is not justified by the mechanistic data.

We anticipate that further analysis of key characteristics of carcinogens is needed to develop better methodology for the use of KCCs in hazard identification and risk assessment. Our study covered only 184 carcinogens, about 18% of all carcinogens assessed by IARC since its inception. Our analysis, however, provided arguments against the consideration that several key characteristics, allegedly associated with talc, can produce strong evidence of carcinogenicity in humans without other characteristics being involved.

Future studies are needed to explore toxicological characteristics of various mineralogical categories of talc. For example, next generation new approach method (NAMs) can be an efficient way to estimate risk of cancer for specific agents based on comprehensive and toxicologically based methods. Recently one of the commendable outlines of such assessment was proposed by Madl et al. (2024) for synthetic vitreous fibers (SVFs). The authors used the adverse outcome pathways (AOPs) concept as an expansion of the mode-of-action paradigm, proposing testing methods for various toxicity pathways instead of a single chain of events. Applying this methodology to pure talc and to other common minerals should reveal useful information about the toxicological properties of these agents.

The unlimited expansion of the IARC list of carcinogens, particularly in Groups 2A and 2B, presents a challenge for risk assessment when it is unclear whether these classifications have substantial health implications for the population. The title of the IARC Monographs until 2019 include the term "carcinogenic risk." Since 2019, the word "risk" has been dropped from the title, and instead, the monographs address only the "identification of carcinogenic hazards." For toxicological evaluation, it is important to develop scientifically based approaches that would expand current hazard identification in the IARC agenda to actual risk assessment including exposure assessment, dose-response assessment, and risk characterization. Otherwise, there would still be a limited, or inadequate, applicability of IARC classification for practical purposes.

## 6. Conclusions

Reclassification of talc from Group 2B to Group 2 A is not supported by available scientific information.

The results of animal experiments for talc exposure remain limited and therefore cannot confirmation the status of talc as a carcinogen.

There is no mode-of-action demonstrated for talc that would prove it to be a human carcinogen. The Key Characteristics of Carcinogens (KCCs) for talc do not plausibly support a reasonable MoA.

## Notes

1. Eric Chatfield reports scrolled vermiculite that closely resembles chrysotile.
2. The overall conclusions of the RAC report on talc also appear to be not fully consistent with available data, but this assessment is outside the scope of our paper.

## Acknowledgements

The authors gratefully acknowledge the comments received from independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript.

The authors acknowledge Debbie Vaughan, for her administrative assistance in the preparation of the paper for journal submission. No other person performed a review of the draft version of the paper prior to submission.

The authors also acknowledge Arseniy Korchevskiy, an employee of Chemistry & Industrial Hygiene, Inc., who supported the statistical analysis used in this paper.

## Declaration of interest

Andrey Korchevskiy is a co-owner and salaried employee of Chemistry & Industrial Hygiene, Inc. (Lakewood, CO). Since 2023, Ann Wylie has served as part time Senior Scientific Adviser for Chemistry & Industrial Hygiene, Inc. in the role of mineralogy consultant. She is also a Professor Emerita of University of Maryland. She has never received compensation for writing papers or giving professional presentations.

Both authors participated in litigation related to asbestos and talc as experts and/or consultants.

Chemistry & Industrial Hygiene, Inc. is involved in a research project on toxicological characterization and human health risk assessment for potential associated minerals in the cosmetic grade talc deposits, supported by Johnson & Johnson.

Both authors serve as members of the Scientific Advisory Board (SAB) of the National Sand, Stone, and Gravel Association (NSSGA). NSSGA sponsored the creation of a database for dimensional characteristics of various elongate mineral particles. Chemistry & Industrial Hygiene, Inc. has NSSGA as a client for various other consulting projects. None of them included compensation for any part of this paper.

In general, no time for writing this paper was billed to any clients of the authors. No copies of the paper were provided to any clients of the authors prior to publication. No feedback or comments were received from any party outside of the authorship team during the paper preparation.

The paper reflects only opinions of the authors and not the organizations that they represent.

Debbie Vaughan performed only administrative tasks and helped to organize references in this paper. She performs different tasks as a researcher for projects with various clients of C&IH, but she has never communicated any information about this paper to any of the clients.

Arseniy Korchevskiy, as a statistician, supported some of the studies used in this paper, but he did not take part in writing the paper and did not have access to its drafts.

## Funding

No funding was received by the authors for the preparation and writing of this paper, or for the study of the IARC timeline and classification methodology included in the paper. At the same time, Chemistry & Industrial Hygiene, Inc. is involved in a research project on toxicological characterization and human health risk assessment for potential associated minerals in the cosmetic grade talc deposits that is supported by Johnson & Johnson. Specifically, no funding from this project was received or used by the authors to prepare or write this paper.

## Supplemental material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/10408444.2025.2585870.

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## References

Alyafeai E et al. 2024. Molecular dynamics of DNA repair and carcinogen interaction: implications for cancer initiation, progression, and therapeutic strategies. Mutat Res. 829:111883. https://doi.org/10.1016/j.mrfmmm.2024.111883

Baan RA, Straif K. 2022. The Monographs Programme of the International Agency for Research on Cancer: a brief history of its preamble. ALTEX. 39(3):443–450. https://doi.org/10.14573/altex.2004081

Basu AK. 2018. DNA damage, mutagenesis and cancer. Int J Mol Sci. 19(4):970. https://doi.org/10.3390/ijms19040970

Becker RA et al. 2017. How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? Regul Toxicol Pharmacol. 90:185–196. https://doi.org/10.1016/j.yrtph.2017.08.021

Becker RA, Dourson M, Onyema CG, Ryman J. 2025. Beyond key characteristics of carcinogens: an archetypal MOA-based evidence system for hypothesis testing to advance carcinogen risk assessment. JTRP. 1(1):1–15. https://doi.org/10.69982/JTRP-24-0011

Bergman S. 1993. Geology and geochemistry of mafic-ultramafic rocks (Kohl) in the Handol area, central Scandinavian Caledonides. Nor J Geol. 73:21–42.

Bevan RJ, Kreiling R, Levy LS, Warheit DB. 2018. Toxicity testing of poorly soluble particles, lung overload and lung cancer. Regul Toxicol Pharmacol. 100:80–91. https://doi.org/10.1016/j.yrtph.2018.10.006

Bird T, Steffen JE, Tran TH, Egilman DS. 2021. A review of the talc industry's influence on federal regulation and scientific standards for asbestos in talc. New Solut. 31(2):152–169. https://doi.org/10.1177/1048291121996645

Boffetta P et al. 2009. Authors' response. A further plea for adherence to the principles underlying science in general and the epidemiologic enterprise in particular. Int J Epidemiol. 38(3):678–679. https://pubmed.ncbi.nlm.nih.gov/19147704/. https://doi.org/10.1093/ije/dyn362

Boobis AR et al. 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol. 36(10):781–792. https://doi.org/10.1080/10408440600977677

Boobis AR et al. 2016. Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society. Regul Toxicol Pharmacol. 82:158–166. https://doi.org/10.1016/j.yrtph.2016.10.014

Boon D, Goodman JE, Colonna KJ, Espira LM, Prueitt RL. 2024. A systematic review of the epidemiology evidence on talc and cancer. Crit Rev Toxicol. 54(6):394–417. https://doi.org/10.1080/10408444.2024.2351081

Buzon ME, Gunter ME. 2017. Current issues with the purported "asbestos" content of talc: hydrothermal-hosted talc ores in southwest

Montana. Trans Soc Min Metall Explor. 342(1):62–71. https://doi.org/10.19150/trans.8109
Candela PA, Crummett CD, Earnest DJ, Frank MR, Wylie AG. 2007. Low pressure decomposition of chrysotile as a function of time and temperature. Am Mineral. 92(10):1704–1713. https://doi.org/10.2138/am.2007.2559
Cavallo A, Petriglieri JR. 2020. Naturally occurring asbestos in Valmalenco (central Alps, northern Italy): from quarries and mines to stream sediments. Environ Eng Geosci. 26(1):47–52. https://doi.org/10.2113/EEG-2270
Chang CJ et al. 2019. Stomach cancer and exposure to talc powder without asbestos via Chinese herbal medicine: a population-based cohort study. Int J Environ Res Public Health. 16(5):717. https://doi.org/10.3390/ijerph16050717
Cleaves ET, Fisher DW, Brincker OP. 1974. Chemical weathering of serpentinite in the eastern Piedmont of Maryland. Geol Soc Am Bull. 85(3):437–444. https://doi.org/10.1130/0016-7606(1974)85%3C437:CWOSIT%3E2.0.CO;2.
Cox LA, Goodman JE, Engel AM. 2020. Chronic inflammation, Adverse Outcome Pathways, and risk assessment: a diagrammatic exposition. Regul Toxicol Pharmacol. 114:104663. https://doi.org/10.1016/j.yrtph.2020.104663
Cralley LJ, Key MM, Groth DH, Lainhart WS, Ligo RM. 1968. Fibrous and mineral content of cosmetic talcum products. Am Ind Hyg Assoc J. 29(4):350–354. https://doi.org/10.1080/00028896809343015
Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. 2016. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. Epidemiology. 27(3):334–346. https://doi.org/10.1097/EDE.0000000000000434
Delgado R et al. 2020. The quality of Spanish cosmetic-pharmaceutical talcum powders. Appl Clay Sci. 193(:105691. https://doi.org/10.1016/j.clay.2020.105691
Dongbok S, Lee I, Sang-Mo K. 2004. Mineral chemistry of talc from different origins in the Dongyang talc deposit. J Miner Soc Korea. 17(4):357–364.
ECHA/RAC. 2025. Committee for Risk Assessment (RAC). Opinion. Proposing harmonized classification and labelling at EU level of Talc (Mg3H2(SiO3)4). EC238-877-9, CAS:14807–14896. 6.
Edwards G. 1984. Petrography and geochemistry of the Allamoore formation, Culberson and Hudspeth Counties.
Egilman D, Madigan D, Yimam M, Tran T. 2020. Letter to the editor: response to Vermont talc-miners cohort study update. J Occup Environ Med. 62(1):e17–18–e18. https://doi.org/10.1097/JOM.0000000000001783
Engel AEJ. 1949. Industrial mineral and rocks. American Institute of Mining and Metallurgical Engineers. Chapter 48, Talc and Ground Soapstone; p. 1018–1041.
Epidemiology Monitor. 2012. Epidemiology Monitor. Epidemiologists Speak out about the Challenge of False Positives in Cancer Epidemiology. 33(11):9–10.
Evans BW. 2004. The serpentinite multisystem revisited: chrysotile is metastable. Int Geol Rev. 46(6):479–506. https://doi.org/10.2747/0020-6814.46.6.479
Ferret J, Moreau P. 1990. Mineralogy of talc deposits. In: Bignon J, editor. Health related effects of phyllosilicates. (NATO ASI Series, Vol. G21). Berlin. Springer-Verlag; p. 147–158.
Fiori M, Grillo SM. 2002. Albite-chlorite and talc-chlorite deposits in metasedimentary and granitoid rocks of central Sardinia (Italy). In: Boletim Paranaense de Geociências. Editora UFPR. n 50, p 51–57. https://doi.org/10.5380/geo.v50i0.4157
Fontan E, Fauve RM, Hevin B, Jusforgues H. 1983. Immunostimulatory mouse granuloma protein. Proc Natl Acad Sci U S A. 80(20):6395–6398. https://doi.org/10.1073/pnas.80.20.6395
Furcron A, Teague KH, Ver JLC. 1947. Talc deposits of Murray County, Georgia. Atlanta (GA). USA: department of mines, mining and geology. Geological Survey Bullet. 53:75.
Ghio AJ. 2025. Talc, pleurodesis, and cancer. Am J Respir Crit Care Med. 211(2):295–296. https://doi.org/10.1164/rccm.202407-1376RL
Gondim AC, Jiang S. 2004. Geologic characteristics and genetic models for the talc deposits in Paraná and Bahia. Brazil. Yanshi Xuebao. 20(4):829–836.
Goodman JE, Drury NL, Marchitti SA. 2025. Comment on "IARC Workshop on the Key Characteristics of Carcinogens: assessment of End Points for Evaluating Mechanistic Evidence of Carcinogenic Hazards". Environ Health Perspect. https://doi.org/10.1289/EHP17383
Goodman JE, Espira LM, Zu K, Boon D. 2024. Quantitative recall bias analysis of the talc and ovarian cancer association. Glob Epidemiol. 7:100140. https://doi.org/10.1016/j.gloepi.2024.100140
Goodman JE, Kerper LE, Prueitt RL, Marsh CM. 2020. A critical review of talc and ovarian cancer. J Toxicol Environ Health B Crit Rev. 23(5):183–213. https://doi.org/10.1080/10937404.2020.1755402
Gordon RE, Fitzgerald S, Millette J. 2014. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup Environ Health. 20(4):318–332. https://doi.org/10.1179/2049396714Y.0000000081
Greenacre M et al. 2022. Principal component analysis. Nat Rev Methods Primers. 2(1):100. https://doi.org/10.1038/s43586-022-00184-w
Greene RC. 1995. Talc Resources of the Conterminous United States. Report OF 95-586. US Geological Survey. https://pubs.usgs.gov/of/1995/0586/report.pdf
Gunter ME, Buzon ME, McNamee BD. 2018. Current issues with the purported "asbestos" content of talc: asbestos nomenclature and examples in metamorphic carbonate and ultramafic hosted talc ores. Trans Soc Min Metall Explor Inc. 344(1):15–24. https://doi.org/10.19150/trans.8744
Haseman JK, Hailey JR, Morris RW. 1998. Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. Toxicol Pathol. 26(3):428–441. https://doi.org/10.1177/019262339802600318
Hayes T, Usami S, Jacobucci R, McArdle JJ. 2015. Using Classification and Regression Trees (CART) and random forests to analyze attrition: results from two simulations. Psychol Aging. 30(4):911–929. https://doi.org/10.1037/pag0000046
Hwa Yun B, Guo J, Bellamri M, Turesky RJ. 2020. DNA adducts: formation, biological effects, and new biospecimens for mass spectrometric measurements in humans. Mass Spectrom Rev. 39(1-2):55–82. https://doi.org/10.1002/mas.21570
IARC. (International Agency for Research on Cancer). 1979. Chemicals and Industrial Processes Associated with Cancer in Humans (IARC Monographs Volumes 1 to 20). IARC Monographs Supplement 1. September 1979.
IARC. (International Agency for Research on Cancer). 1982. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC Monographs Vols. 1 to 29. Supplement 4. October p. 1982.
IARC. (International Agency for Research on Cancer). 1987. Overall Evaluations of Carcinogenicity: an Updating of IARC Monographs, Volumes 1–42. Supplement 7.
IARC. (International Agency for Research on Cancer). 1991. Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
IARC. (International Agency for Research on Cancer). 2006. IARC monographs on the evaluation of carcinogenic risks to humans. Preamble.
IARC. (International Agency for Research on Cancer). 2010. Carbon black, titanium dioxide, and talc. Volume 93. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (February 7-14, 2006).
IARC. (International Agency for Research on Cancer). 2012. Arsenic, metals, fibres, and dusts. A Review of human carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100C.
IARC. (International Agency for Research on Cancer). 2019a. 2019 IARC monographs on the identification of carcinogenic hazards to humans. Preamble. France. Amended January
IARC. (International Agency for Research on Cancer). 2019b. Tumour site concordance and mechanisms of carcinogenesis. IARC Scientific Publication No. 165. Editors. Robert A. Baan, Bernard W. Stewart, Kurt Straif. Lyon, France.

IARC. (International Agency for Research on Cancer). 2025a. Talc and AcrylonitrileIARC monographs on the identification of carcinogenic hazards to humans. Volume 136. Advance Publication, 30 June 2025.
IARC. (International Agency for Research on Cancer). 2025b. 2025 key characteristics-associated end-points for evaluating mechanistic evidence of carcinogenic hazards. IARC Monographs Technical Report. June
Ioannidis JPA. 2005. Why most published research findings are false. PLoS Med. 2(8):e124. https://doi.org/10.137/journal.pmed.0020124
Johnson KE, Popratiloff A, Fan Y, McDonald S, Godleski JJ. 2020. Analytic comparison of talc in commercially available baby powder and in pelvic tissues resected from ovarian carcinoma patients. Gynecol Oncol. 159(2):527–533. https://doi.org/10.1016/j.ygyno.2020.09.028
Kabat G. 2012. How Activism Distorts the Assessment of Health RisksForbes 20 November. Available: http://www.forbes.com/sites/realspin/2012/11/20/how-activism-distorts-the-assessment-of-health-risks/
Karlsen TA, Olesen O, Rian E. 2000. Overview of talc resources in the Altermark talc province, northern Norway, and possible uses of the talc ore. NGU Bull. 436:93–102. https://hdl.handle.net/11250/2674217
Korchevskiy AA, Wylie AG. 2025. The empirical metric of mesothelial carcinogenicity for carbon nanotubes and elongate mineral particles. Inhal Toxicol. 37(3):107–132. https://doi.org/10.1080/08958378.2025.2486087
Kuutila J. 2022. Outokumpu-type deposits [Bachelor's thesis]. Oulu Mining School. April 2022. Submitted on p. 21. https://oulurepo.oulufi/bitstream/10024/19672/1/nbnfioulu-202204211660. pdf.
Lampa E, Lind L, Lind PM, Bornefalk-Hermansson A. 2014. The identification of complex interactions in epidemiology and toxicology: a simulation study of boosted regression trees. Environ Health. 13(1):57. https://doi.org/10.1186/1476-069X-13-57
Lewin S. 1972. Analytical results on the mineral compositions of 102 examples of standard, commercial products containing talc. Letter to Dr Alfred Weissler, Division of Colors and Cosmetics Technology, US Food and Drug Administration. Available from https://cdn. toxicdocs.org/85/85JyymOw7EB568x1mExoqRQVe/85JyymOw7EB568x1mExoqRQVe.pdf
Madl AK, Donnell MT, Covell LT. 2024. Synthetic vitreous fibers (SVFs): adverse outcome pathways (AOPs) and considerations for next generation new approach methods (NAMs). Crit Rev Toxicol. 54(10):754–804. https://doi.org/10.1080/10408444.2024.2390020
McLaughlin JK et al. 2010. Authors' response. Re: a further plea for adherence to the principles underlying science in general and the epidemiologic enterprise in particular. Int J Epidemiol. 39(3):1679–1680. https://doi.org/10.1093/ije/dyn362
McLaughlin JK et al. 2011. Authors' response. Problems with IARC's 'expert' working groups [Letter. ]. Int J Epidemiol. 40:1728–1729. https://doi.org/10.1093/ije/dyr158
Meek ME et al. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 34(1):1–18. https://doi.org/10.1002/jat.2949
Misch D, Pluch H, Mali H, Ebner F, Huang H. 2018. Genesis of giant Early Proterozoic magnesite and related talc deposits in the Mafeng area, Liaoning Province, NE China. J Asian Earth Sci. 160:1–12. https://doi.org/10.1016/j.jseaes.2018.04.005
Morrow PE. 1992. Dust overloading of the lungs: update and appraisal. Toxicol Appl Pharmacol. 113(1):1–12. https://doi.org/10.1016/0041-008x(92)90002-a
Mossman BT. 2008. Assessment of the pathogenic potential of asbestiform vs. nonasbestiform particulates (cleavage fragments) in in vitro (cell or organ culture) models and bioassays. Regul Toxicol Pharmacol. 52(1 Suppl):S200–S203. https://doi.org/10.1016/j.yrtph.2007.10.004
Nickoloff BJ, Ben-Neriah Y, Pikarsky E. 2005. Inflammation and cancer: is the link as simple as we think? J Invest Dermatol. 124(6):x–xiv. https://doi.org/10.1111/j.0022-202X.2005.23724.x
Nishida A, Andoh A. 2025. The role of inflammation in cancer: mechanisms of tumor initiation, progression, and metastasis. Cells. 14(7):488. https://doi.org/10.3390/cells14070488
NTP (National Toxicology Program). 1993. NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(Non-Asbestiform) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser. 421:1–287.
NTP (National Toxicology Program). 1996. NTP Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344 Rats and B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser. 451:1–381.
NTP (National Toxicology Program). 2001. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Indium Phosphide (CAS No. 22398-80-7) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). NTP TR 499. July 2001.
Oberdörster G. 1995. The NTP talc inhalation study: a critical appraisal focused on lung particle overload. Regul Toxicol Pharmacol. 21(2):233–241. https://doi.org/10.1006/rtph.1995.1034
OECD. 2017. Guidance document for the use of adverse outcome pathways in developing integrated approaches to testing and assessment (IATA), Series on Testing & Assessment No. 260, Environment, Health and Safety, Environment Directorate, OECD.
Ozaki K, Haseman JK, Hailey JR, Maronpot RR, Nyska A. 2002. Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat–the National Toxicology Program experience. Toxicol Pathol. 30(2):263–270. https://doi.org/10.1080/019262302753559605
Paoletti L, Caiazza S, Donelli G, Pocchiari F. 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regul Toxicol Pharmacol. 4(3):222–235. https://doi.org/10.1016/0273-2300(84)90022-9
Pierce N et al. 2015. IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans. Env Health Perspec. 123(6):507–514. https://doi.org/10.1289/ehp.1409149
Pi-Puig T, Dante Yosafat Animas-Torices Y, Solé J. 2020. Mineralogical and geochemical characterization of talc from two Mexican ore deposits (oaxaca and puebla) and nine talcs marketed in mexico: evaluation of its cosmetic uses. Minerals (Basel). 10(5):388. https://doi.org/10.3390/min10050388
Prueitt RL, Drury NL, Shore RA, Boon DN, Goodman JE. 2024. Talc and human cancer: a systematic review of the experimental animal and mechanistic evidence. Crit Rev Toxicol. 54(6):359–393. https://doi.org/10.1080/10408444.2024.2349668
Rohl AN et al. 1976. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ Health. 2(2):255–284. https://doi.org/10.1080/15287397609529432
Rusyn I, Wright FA. 2023. Ten years of using key characteristics of human carcinogens to organize and evaluate mechanistic evidence in IARC monographs on the identification of carcinogenic hazards to humans: patterns and associations. bioRxiv [Preprint]. 2023.07.11.548354. https://doi.org/10.1101/2023.07.11.548354 Update in: toxicol Sci. 2024 198(1):141-154. doi: 10.1093/toxsci/kfad134
Sabina AP. 1987. Rocks and minerals for the collector, Hull-Maniwaki, Quebec, Ottawa-Peterborough, Ontario. Geological Survey of Canada, Miscellaneous Report. 41:141. https://doi.org/10.4095/122460
Samet JM. 2015. The IARC monographs: critics and controversy. Carcinogenesis. 36(7):707–709. https://doi.org/10.1093/carcin/bgv062
Schober W. 1998. Asia Pacific talc Ind Minerals59–63.
Shekhawat MS, Ranawat MS, Ranawat PS. 2010. Mineralogical and chemical characteristics of talc and tremolite asbestos hosting Proterozoic ultramafic rocks of Jharol area, Udaipur, Rajasthan. Int J Earth Sci Eng. 3:459–474.
Smith CJ et al. 2021. Categorizing the characteristics of human carcinogens: a need for specificity. Arch Toxicol. 95(8):2883–2889. https://doi.org/10.1007/s00204-021-03109-w
Smith MT et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–721. https://doi.org/10.1289/ehp.1509912
Sohrab SS et al. 2023. Chronic inflammation's transformation to cancer: a nanotherapeutic paradigm. Molecules. 28(11):4413. https://doi.org/10.3390/molecules28114413
Stemple IS, Brindley GW. 1960. A structural study of talc and talc-tremolite relations. J Am Ceram Soc. 43(1):34–42. https://doi.org/10.1111/j.1151-2916.1960.tb09149.x

Tahir M, Imai A, Takahashi R, Yano S. 2018. Ore genesis and geochemical characteristics of carbonate-hosted talc deposits in Nangarhar Province, Afghanistan. Resour Geol. 68(4):352–372. https://doi.org/10.1111/rge.12174

Tischler AS et al. 1999. Vitamin D3-induced proliferative lesions in the rat adrenal medulla. Toxicol Sci. 51(1):9–18. https://doi.org/10.1093/toxsci/51.1.9

US FDA. 2019. FDA advises consumers to stop using certain cosmetic products. Silver Spring (MD),. United States Food and Drug Administration. https://www.fda.gov/cosmetics/ cosmetics-recalls-alerts/fda-advises-consumers-stopusing-certain-cosmetic-products

Van der Laan JW, Manuppello J. 2024. Editorial: reducing animal use in carcinogenicity testing. Front Toxicol. 6:1538905. https://doi.org/10.3389/ftox.2024.1538905

Van Gosen BS, Lowers HA, Sutley SJ, Gent CA. 2004. Using the geologic setting of talc deposits as an indicator of amphibole asbestos content. Environ Geol (Berl). 45(7):920–939. https://doi.org/10.1007/s00254-003-0955-2

Verkouteren JR, Wylie AG. 2002. Anomalous optical properties of fibrous tremolite, actinolite and ferro-Actinolite. Am Min. 87(8-9):1090–1095. https://doi.org/10.2138/am-2002-8-905

Vesasalo A. 1965. Talc schists and soapstone occurrences of Finland. Geologinen Tutkimuslaitos, Bulletin de la Commission Geologique de Finlande. 216:73.

Virta RL. 1985. The phase relationship of talc and amphiboles in a fibrous talc sample. US Bureau of Mines Report of Investigation/1985. 198516.

Warheit DB et al. 1997. Inhalation of high concentrations of low toxicity dusts in rats results in impaired pulmonary clearance mechanisms and persistent inflammation. Toxicol Appl Pharmacol. 145(1):10–22. https://doi.org/10.1006/taap.1997.8102

Wentzensen N, O'Brien KM. 2021. Talc, body powder, and ovarian cancer: a summary of the epidemiologic evidence. Gynecol Oncol. 163(1):199–208. https://doi.org/10.1016/j.ygyno.2021.07.032

Wergeland E, Andersen A, Baerheim A. 1990. Morbidity and mortality in talc-exposed workers. Am J Ind Med. 17(4):505–513. https://doi.org/10.1002/ajim.4700170408

Wergeland E, Gjertsen F, Vos L, Grimsrud TK. 2017. Cause-specific mortality and cancer morbidity in 390 male workers exposed to high purity talc, a six-decade follow-up. Am J Ind Med. 60(9):821–830. https://doi.org/10.1002/ajim.22749

Whittaker EJW, Zussman J. 1956. The characterization of serpentine minerals by X-ray diffraction. Mineral Mag j Mineral Soc. 31(233):107–126. https://doi.org/10.1180/minmag.1956.031.233.01

Wylie A, Candela P. 2015. Methodologies for determining the sources, characteristics, distribution, and abundance of asbestiform and non-asbestiform amphibole and serpentine in ambient air and water. J Toxicol Environ Health B Crit Rev. 18(1):1–42. https://doi.org/10.1080/10937404.2014.997945

Wylie AG et al. 1997. Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. Toxicol Appl Pharmacol. 147(1):143–150. PMID:9356317 https://doi.org/10.1006/taap.1997.8276

Wylie AG, Korchevskiy AA, Van Orden DR, Chatfield EJ. 2022. Discriminant analysis of asbestiform and non-asbestiform amphibole particles and its implications for toxicological studies. Comput Toxicol. 23:100233. https://doi.org/10.1016/j.comtox.2022.100233

Wylie AG, Korchevskiy AA. 2023. Dimensions of elongate mineral particles and cancer: a review. Environ Res. 230:114688. https://doi.org/10.1016/j.envres.2022.114688

Wylie AG, Korchevskiy AA. 2025. Critical values for dimensional parameters of mesotheliomagenic mineral fibers: evidence from the dimensions and rigidity of MWCNT. Front Toxicol. 7:1568513. https://doi.org/10.3389/ftox.2025.1568513

Wylie AG. 2016. Amphiboles: fibers, fragments and mesothelioma. Can Mineral. 54(6):1403–1435. https://doi.org/10.3749/canmin.1500109