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Kennisnotitie

Health risks associated with ultrafine (d≤0.2 µm) asbestos fibres – state of knowledge

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Introduction

It has long been known that asbestos causes cancer, including mesothelioma, lung cancer and ovarian cancer (IARC 1977, 2012). It is also known to cause asbestosis and non-malignant pleural diseases. Legal requirements for protection of workers from risk related to asbestos exposure are laid down in the European Directive 2009/148/EC (Asbestos Directive)[1] and have been adopted in the Netherlands under its Working Conditions legislation[2]. Under this ruling workers' exposures are to be kept as low as possible.

Background

The size of durable mineral asbestos fibres is a determining factor for developing mesothelioma, asbestosis and other asbestos-related diseases following inhalation. Besides density of the asbestos containing material, diameter and length of the fibres play key roles in dose-delivery and bio-persistence with diameter being an important dimension for exposure via inhalation and translocation (IARC 2012). Small fibre diameter facilitates translocation from the lung into pleural, peritoneal and other tissues.

In this note the term 'regulatory fibres' is consistent with the World Health Organisation's 1997 specification for fibres that are considered hazardous (WHO 1997). These are fibres that are >5 µm in length that have widths between 0.25 and 3 µm and a length:diameter aspect ratio ≥3. Fibre counting for regulatory purposes is currently based on the visibility of fibres by phase contrast light microscopy (PCM). PCM can only detect fibres >0.20 µm. It therefore excludes thinner fibres that contribute to total asbestos exposure.

Upon realising that the current approach for regulatory compliance may exclude biologically-relevant fibres the European Commission amended their Asbestos Directive in 2023 (Directive (EU) 2023/2668)[3]. The revised version states that:

"*Current available technologies for measuring asbestos fibres do not allow for the measurement at very low concentrations when thin fibres are counted. In order to ensure a high level of protection of workers' health while duly considering the feasibility of measuring, when using such technologies, it is therefore necessary to choose whether to count thin fibres or to apply low concentration limits. Some Member States have opted for a lower limit value without counting thinner fibres, while others have opted for a higher*

[1] Directive 2009/148/EC of the European Parliament and of the Council on the protection of workers from the risks related to exposure to asbestos at work.
[2] Arbeidsomstandighedenbesluit
[3] Directive (EU) 2023/2668 of the European Parliament and of the Council of 22 November 2023 amending Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work.

limit value and count thin fibres. With a view to guaranteeing a balanced approach, different limit values should be established, depending on the fibre size taken into consideration for the purpose of measuring asbestos fibres in the air, namely fibres with a breadth of between 0,2 and 3 micrometres (µm) as well as, from the moment of technological transition to electron microscopy, fibres with a breadth of less than 0,2 µm.
"Taking into account the relevant scientific expertise and a balanced approach that ensures, at the same time, the adequate protection of workers at Union level, revised limit values should be established, which, depending on the fibre counting method used in a particular Member State, should be equal to 0,002 fibres per cm^3 when counting fibres with a breadth of between 0,2 and 3 µm, or 0,01 fibres per cm^3 , when also counting fibres with a breadth of less than 0,2 micrometres (200 nm), as an 8-hour time-weighted average (TWA)."

Additionally, in 2010, the Health Council of the Netherlands (HC) (Gezondheidsraad, 2010) noted that:
"Recent epidemiological analyses also suggest a more important role for longer and thinner fibers, but the precise relationship could not be reliably deduced; therefore, information on the apportionment of fiber length and -diameter is insufficiently documented in most studies."

Given that 15 years have passed since the HC's report the Ministry of Social Affairs and Employment (SZW) has commissioned the RIVM to determine whether there are any recent scientific studies that provide new insights into the role of fibre diameter on the potency of asbestos. In this knowledge update we assess recent studies that have looked at ultrafine asbestos and its link to asbestos-related health effects. For the remainder of this report ultrafine asbestos is defined as asbestos fibres with a diameter below or equal to 0.2 µm.

Research question

The research question as posed to RIVM by The Ministry of Social Affairs and Employment (SZW) is:

- What do the scientific studies published after the publication of the HC advice in 2010 add to the state of knowledge on the health risks of ultrafine asbestos fibres?

In this knowledge update we report on findings and limitations of studies on this subject that were published after 2010. We provide our conclusion on what those studies add to the current state of knowledge and put forward our recommendation based on the overall findings.

Method

We conducted a literature review to identify the studies that have looked at ultrafine asbestos and its link to asbestos-related health effects.

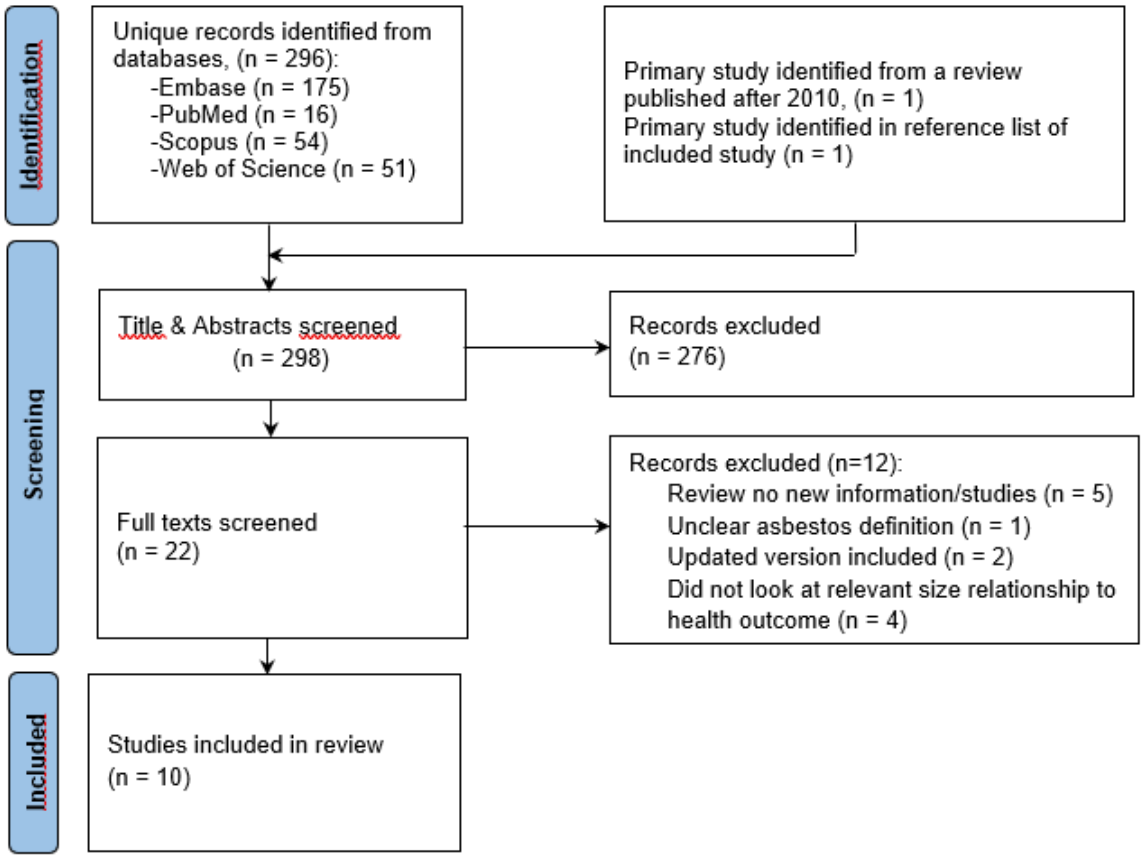
The scientific literature was searched for studies published after 2010 until December 2024 on health risks associated with asbestos fibres with diameter ≤0.2 µm. Search strings used for querying Embase are given in Appendix 1. These were adjusted for searching PubMed, Scopus and Web of Science. All unique records were screened for relevant information based on title and abstract. Selections for final inclusion were based on full text screening. Reviews published after 2010 were compared with the Health Council's 2010 report so that primary studies not considered by the Health Council or

identified by our research strategy could be identified. The reference lists of included studies were also screened to identify relevant studies.

Results

Ten studies were retained following the screening. This comprised four epidemiological studies, four studies on dimensional parameters of fibre toxicity using modelling approaches and two studies that examined pathological evidence in lung tissue. The latter included one study dated before 2010 that had not been considered in the HC 2010 report. One of the modelling studies was identified from the reference list screening. Details of the flow of information can be found in Figure 1. All selected studies relied on electron microscopy (Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM)) with which smaller fibre sizes can be identified.

Figure 1: PRISMA Flow diagram



Epidemiological studies (4)

Loomis et al. (2012) and Hamra et al. (2017) conducted epidemiological study of a retrospective pooled-cohort comprising two cohorts of textile workers from North and South Carolina.

Analyses on the single North Carolina cohort were also conducted by Loomis et al. (2010) and Hamra et al. (2014) (See Appendix 2 for further details). The single North Carolina cohort study was based on 3803 workers (64% male) who had worked at least one day between 1950 and 1973 in any one of three asbestos textile production plants in North

Carolina, USA. The retrospective pooled-cohort (n = 6136 workers; 61% male) comprised the North Carolina cohort and a cohort of workers from South Carolina who had worked at least one day in asbestos textile mills in South Carolina between 1940 and 1973.

The epidemiological studies used two different study designs and/or statistical approaches in an attempt to separately quantify the influence of particle length and diameter on asbestos-related health outcomes. They all characterised exposure by fibre size categories that were based on PCM and TEM analysis of random historical dust samples collected from the study plants. Respectively, 77 and 160 dust samples were used to define the bivariate fibre size distributions for the single and pooled-cohort studies. Overall, 24 bivariate fibre size distributions were described (Dement et al. 2008). These were combinations of four diameters (D) (<0.25, 0.25–1.0, 1.0–3.0, >3.0 µm) and six lengths (L) (≤1.5, 1.5–5, 5–10, 10–20, 20–40, >40 µm). Estimates of workers' size-specific fibre exposures were then determined based on the bivariate categories and individual worker histories.

Using Poisson regression to correct for age (years in decades), sex, race, calendar-time and birth, Loomis et al. (2010) examined the exposure-response relationships between lung cancer mortality (10-year lag) and indicators of cumulative fibre exposure. This was based on 181 registered lung-cancer deaths. Estimates of cumulative exposure were based on different analytical approaches for measuring fibres (PCM, TEM, TEM fibres ≥5 µm and TEM fibres <5 µm) as well as on fibre size category. They found that estimates of mean cumulative fibre exposure based on TEM were 16 times higher than PCM-based estimates (989.4 vs 59.2 f-y/ml). Cumulative exposure to fibres of every length and diameter category based on TEM was associated with increased lung cancer risk. For models based on TEM-estimated exposure when both length and diameter were considered together, the strongest statistically significant associations were found with long and thin fibres (L>20 µm; D 0.25 - <1 µm). Fibres with diameter <0.25 µm were most associated with lung cancer mortality at lengths <5 µm. For lengths 5-20 and >40 µm ultrafine fibres had the second highest association (D 0.25 - <1 µm highest) and for lengths 20-40 µm the third highest association (D >3 µm first, D 0.25 - <1 µm second). The authors noted that the data did not demonstrate a clear or consistent difference in lung cancer mortality between thin and thick fibres.

In an extension of their earlier study Loomis et al. (2012) examined the association between fibre-size specific estimates of exposure and lung cancer mortality in the pooled North- and South Carolina cohort of textile workers. During follow-up 361 deaths from lung cancer were registered. Lung cancer mortality was significantly associated with all fibre diameters, but the greatest association was for fibres with diameter <0.25 µm (L 1.5-5 µm and L 10-20 µm $p<0.01$; L ≤1.5 µm, L 5-10 µm, L 20-40 µm and L ≥40 µm, $p<0.001$; all lengths $p<0.001$). Exposure to ultrafine fibres (D <0.25 µm) tended to have a higher risk of lung cancer mortality than exposure to thicker fibres.

In a nested case-control study design Hamra et al. (2014) analysed the North Carolina cohort of 3808 workers using frequentist and hierarchical Bayesian modelling approaches to model exposures to chrysotile asbestos with the different size ranges. Using a 1:10 case to control match on age they conducted unconditional logistic regression adjusting for 'age at cancer event', sex, race and year of observation. In the frequentist approach the relationship between exposure to each fibre group and lung cancer was modelled independently whereas the Bayesian model allowed them to look at the association between cumulative exposure to distinct chrysotile fibre size groups and lung cancer

within a single model. The frequentist models revealed increases in dose-response with increasing diameter/length group for most diameter and length categories. For each diameter group, except for the group >3 µm, there was an increase in dose-response with increasing length; this was likewise for each length group where the dose-response increased with increasing diameter. However, due to strong correlations between the different size groups the estimates were not considered as reliable.

When hierarchical models were used no dose-response trend with increasing or decreasing fibre diameter/length group was observed and the estimated coefficients for most of the fibre groups were similar to that of the grouped median. This means that, based on these data, there was no influence on lung cancer development by the different size categories. The authors noted that the wide length and diameter ranges that are generated during textile production result in strong correlations between all categories making it difficult to identify any association between fibre size and health effect. This was especially the case between the lowest two size categories (i.e. fibres of D <0.25 µm and L <1.5 µm and D <0.25 µm and L = 1.5-5.0 µm; Pearson's correlation coefficient, r = 0.9). The hierarchical modelling approach was used because it is capable of handling these strong correlations. However, taking this approach did not allow them to distinguish relationships between respective fibre size categories and lung cancer. The frequentist models supported the widely established finding that there is a dose-response relationship between fibre length and lung cancer.

In an update to their 2014 study, Hamra et al. (2017) repeated their analyses using the pooled cohort of 6136 workers. Associations between cumulative asbestos exposure to 21 of the 24 possible fibre categories and lung cancer were investigated using a similar design as in the 2014 study. This larger study added support to their previous findings that the association between asbestos fibre exposure and lung cancer mortality increases with fibre length but does not increase as diameter decreases. However, as noted by the study authors, the larger cohort size did not overcome issues around strong correlations between fibre groups. They found that risk estimates for lung cancer for all fibre categories were comparable and that the risk estimates for the thinnest fibre size category had the smallest margins of error. This suggests that ferruginous[4] fibres that cannot be identified using PCM contribute to lung carcinogenicity.

Studies based on pathological examination of human tissue (2)
Adib et al. (2013) explored the relationships between fibre dimensions and asbestos-related diseases among workers by examining the lung fibre burden of 123 workers (99% male) with asbestosis, lung-cancer or mesothelioma using TEM. In the absence of a control group within the study, exposed workers were compared to a non-exposed population. The same methods were used to establish fibre burden and ferruginous bodies in the exposed and control groups. They classified asbestos fibres into three broad categories of short (L 0.5 – 5 µm, D <3 µm), fine (L ≥5 µm, diameter <0.2 µm) and WHO fibres (L >5 µm, D <3 µm with a length:diameter aspect ratio >3). They found that most of the asbestos fibres found in the lungs of 124 workers diagnosed with an asbestos-related disease were short (50%) or fine fibres (30%) and that WHO fibres represented the lowest proportion of fibres (20%). Based on these findings they advised that different dimensional criteria (so not only regulatory fibres) should be considered when characterising health risks associated with asbestos exposure.

[4] A ferruginous body is a histopathologic finding in interstitial lung disease suggestive of significant asbestos exposure.

Suzuki et al. (2005) used pathological analysis of human mesothelioma tissue to test the validity of the Stanton hypothesis that states that longer and thinner asbestos fibres of length ≥ 8 µm and diameter ≤ 0.25 µm pose higher risk of carcinogenicity than shorter and thicker fibres. They used electron microscopy to examine 10,575 asbestos fibres from the lung and mesothelial tissue of 168 occupational cases of human malignant mesothelioma (98% male). They found that most of the asbestos fibres (93%) in these tissues were ≤0.25 µm in diameter and that the proportion of fibres that fit Stanton's hypothesis was very low, ranging from 2.3% to 4.9% depending on how the samples were prepared for microscopic analysis. Based on these results, they concluded that thin asbestos fibres contributed significantly to the induction of human malignant mesothelioma.

Studies that modelled dimensional parameters of fibre toxicity (4)
Korchevskiy, Wylie and their colleagues studied the influence of the dimensional parameters of Elongate Mineral Particles (EMPs)[5] on cancer potency. (Wylie et al 2020; Korchevskiy and Wylie (2021, 2022); Wylie and Korchevskiy 2023). They derived statistical regression models to estimate the relationship between the dimensional characteristics (length, width) of EMPs from specific locations and the cancer potency of EMPs that were estimated for those locations.

Data on dimensional characteristics were obtained from a database containing data on length and width of several hundred thousand EMPs of known composition and habit[6]. It comprised dimensional information collected by one of the authors (Prof. A. Wylie) along with datasets from the published or grey literature or other sources. This included data from air sampling, bulk materials and epidemiological and pathological studies. All data were from the mining and milling industry. The dimensional data were collected using TEM or SEM allowing ultrafine fibres to be identified. Information was listed per individual particle. Where length and width data were presented as size categories in any of the original source datasets, simulation was used to impute individual particle dimensions by assuming a log-normal distribution for every size category. Data on asbestos potency was obtained primarily from published epidemiological studies that reported mesothelioma and lung cancer potency factors. Mesothelioma potency (R_M) was calculated as the percent of all expected deaths that were due to mesothelioma per fibre/cc-year of exposure. Lung cancer potency (R_L) was calculated as the percent of the excess above expected lung cancer mortality per unit of cumulative exposure. The modelling studies in this knowledge update used different selections of datasets of amphibole fibres from this database.

Wylie et al. (2020) used dimensional data from nine mining and milling cohorts to estimate regression models that describe the relationships between fibres >5 µm long with a width of either ≤0.15 µm or ≤0.25 µm and mesothelioma potency (R_M) of amphibole. Based on linear models both size categories were found to be strong predictors of R_M (for size category ≤0.15 µm adjusted $R^2 = 0.977$, goodness-of fit (fit) – $p < 0.01148$; for size category ≤0.25 µm adjusted $R^2 = 0.978$; fit – $p < 0.0072$).

In their 2021 study Korchevskiy and Wylie used dimensional data from four of the cohorts to estimate models for predicting both mesothelioma and lung cancer potencies. They found that mesothelioma potency (R_M) correlated most strongly with the proportion

[5] Elongate Mineral Particles (EMP) are defined as substances having an aspect ratio >3. As such asbestos fibres also belong to this class of substances.
[6] A crystal's habit describes its characteristic external shape in single or aggregate form.

of fibres longer than 5 µm and thinner than 0.22 µm while lung cancer potency (R_L) correlated most strongly with the proportion of fibres longer than 5 µm and thinner than 0.28 µm. For fibres wider than approximately 0.6–0.7 µm there was no statistically significant correlation. For mesothelioma, doubling the width decreased potency by a factor of ~8, whereas doubling the length increased it by a factor of ~2.3.

In 2022 their analysis was based on 128,099 Elongate Mineral Particles (EMPs) from 77 datasets in the database. The results mirrored earlier findings that fibre width is strongly and negatively correlated with mesothelioma potency (Pearson correlation of r=-0.93 ($p<0.05$) and that there are significant thresholds for width below which the correlation with R_M is strongest and above which there is no correlation with R_M. Additionally, they showed that specific surface area (i.e. surface area per unit volume), which is heavily influenced by fibre width, shows the highest correlation with mesothelioma potency (r=0.97). This is because thinner fibres have higher specific surface area, enhancing their biological reactivity and pathogenicity. For lung cancer, the correlation with width was less strong.

In their most recent work Wylie and Korchevsky (2023) supplemented published data with new information from their database. Based on statistical analysis of 341,949 records compiled from 59 datasets they derived models that confirmed previous findings of fibre width as a strong predictor of cancer risk and its greater influence on potency than length. The correlation between potency and dimensional parameters was vastly more dependent on width (explaining 70-83% of the variability) than on length (explaining only 7-18%). They defined critical width thresholds below which fibres pose the greatest risk. For mesothelioma this was fibres within the width range 0.11 and 0.21 µm (≤0.25 µm) for which the highest correlations with R_M were obtained. However, fibres thinner than 0.15 µm were the most predictive of R_M. For lung cancer the predictive width was 0.3 µm. Based on these analyses they suggested that width is key in explaining the strong difference in cancer potency between asbestiform and non-asbestiform EMPs since non-asbestiform particles are wider, more brittle and contain a much lower fraction of the hazardous, thin fibres seen in the asbestiform habit.

Discussion

The goal of this study was to explore the state of knowledge on health risks associated with ultrafine asbestos fibres ≤0.2 µm in diameter. This would help determine whether existing regulatory standards for airborne asbestos should be revised. The search strategy therefore included dimensional terms (“thickness”, “thin”, “diameter”) combined with terms around exposure and health outcomes known to be associated with asbestos exposure. The study period of 15 years was chosen to capture new information that became available subsequent to the Health Council’s 2010 review.

State of knowledge on asbestos dimensionality and toxicity to 2010

The Health Council had concluded in 2010 that evidence from animal experimental research supported the case that ultrafine asbestos was associated with adverse health effects. However, they noted that this could not be properly translated to humans. Additionally, they found that although epidemiological research, available at that time, suggested that longer and thinner fibres play a role in the health effects of asbestos, information about the distribution of fibre length and diameter were not sufficiently documented in most studies. This was partly because of the use of PCM for estimating exposure in earlier studies.

State of knowledge on asbestos dimensionality and toxicity to 2025
Fifteen years later we have more evidence, albeit limited, from human-based studies. All 10 publications on the subject of asbestos dimensionality and its toxicity were related to humans. This included 4 publications based on a pooled retrospective occupational cohort; 4 modelling studies conducted by one research team and 2 studies that focussed on fibre burden in human lung tissue.

An interesting finding based on the modelling studies is that fibre width appears to be the more sensitive of the two dimensional indicators (length, width) for mesothelioma potency of asbestiform amphibole once the fibre length criteria for carcinogenicity is fulfilled. This holds for fibres that are of the established biologically relevant fibre length of >5 µm and appears to be the case for ultrafine fibres <0.15 µm and fibres between 0.15 and 0.25 µm. This may not necessarily extend to chrysotile fibres seeing that these studies were primarily based on amphibole asbestos. However, the role of ultrafine fibres in asbestos carcinogenicity in humans could not be unequivocally confirmed by any of these different groups of studies.

The need for advanced methods of characterisation
PCM is one of the three fibre counting methods commonly used by EU Member States for characterising exposure to asbestos. It can detect fibres greater than 0.2 µm in diameter but it cannot be used to identify fibre types (Franken et al. 2025). The amended EU-Directive (2023/2688) calls for the transition to electron microscopy which has lower limits of visibility. For SEM, the method used in The Netherlands, this is between 0.1 and 0.2 µm (Franken et al. 2025). For TEM, detection and identification of fibre widths down to 0.01 µm are possible. By using electron microscopy all studies showed that exposure to asbestos was not limited to the PCM-based fibre sizes. Based on TEM analysis, the smallest fibres (<0.25 µm) represented 79% of the total fibre count in the epidemiological studies. Loomis et al (2010) showed that TEM-estimated exposure levels to all sizes of asbestos was 16 times higher that PCM-based estimates indicating the extent to which PCM underestimates total asbestos exposure. Franken and his colleagues compared fibre concentrations obtained using the three analytical methods. They also observed that measurements analysed by TEM resulted in higher fibre concentrations (Franken et al. 2025). Fibres of every length and diameter category were associated with increased lung cancer risk (Loomis et al. 2010; Hamra et al. 2017). This suggests that when exposure-estimates are based on the PCM method the cancer risks are wrongfully attributed to fibres >0.20 µm only.

Findings from epidemiological studies
The epidemiological studies employed electron microscopy on historical samples to obtain data on fibre-size distributions. Although this addressed one of the data limitations mentioned in the HC 2010 report it revealed the multi-collinearity between asbestos fibre size categories that can occur when trying to categorise by length and width for modelling purposes. By multi-collinearity it is meant that there were correlations between the different size categories. Consequently, the relationship between each dimensional variable (length and width) and asbestos potency could not be isolated. In other words, it was impossible to distinguish the effect of length from the effect of width on asbestos potency using these historical real-world data. In order to draw conclusions about the individual influence of fibre width and length, these parameters would need to be examined separately. This is only likely to be possible in an experimental setup.

It should be noted that while our focus was on ultrafine fibres with a diameter ≤0.2 µm, the selected epidemiological studies used <0.25 µm as the cutoff point when categorising

fibres by specific size ranges. Consequently, insights on ultrafine asbestos from these studies are not specific for fibres ≤0.2 µm.

Another consideration is that the epidemiological studies were conducted in the textile industry only and essentially based on one cohort. Given that fibre type is typical of industrial sector, the findings from studies conducted solely in the textile industry may be influenced by industry-specific characteristics and therefore may not be representative of workers in other sectors. Cement and friction manufacturing industries use short and medium length chrysotile fibres (Grades 4-7), while the textile industries require longer fibres (Grades 1-3). Grades 1-2 consist of unprocessed or crude asbestos, while 3 and 7 are milled chrysotile of decreasing fibre lengths that are produced by mechanical handling (Barlow et al. 2018). If one type of fibre predominates in an industry that has other risk factors for lung cancer, the strength of the reported relationship with asbestos is difficult to accurately quantify. There is also the possibility of variability between workplaces within the same industry due to differences in workplace factors that were also not accounted for in these studies. They also did not correct for smoking status which is strongly associated with lung cancer; this has implications for the general quality of the study.

Notwithstanding these limitations, the epidemiological studies went a step further than previous studies by using SEM and TEM-based exposure estimates to investigate the role of ultrafine asbestos fibres in cancer potency. They showed that ultrafine asbestos fibres contribute significantly to total asbestos exposure. Although, their findings also suggests that diameter is a significant co-factor of lung cancer potency, their attempts to establish a relation between different size fractions and cancer were unsuccessful due to high collinearity between size fractions. Even after using the hierarchical model that was meant to overcome this collinearity (Hamra et al. 2014), they were still unable to estimate lung cancer risk by fibre size groups. This remained the case even after performing the analysis on a pooled cohort (Hamra et al. 2017). These studies have limited value in illustrating the role of ultrafine fibres in asbestos-related disease. Therefore, it is not possible to confirm an association or quantify the size of the effect based on these epidemiological studies only.

Findings from pathological studies - dimensional aspects of lung cancer burden
Fibres with the smallest diameters are most likely to penetrate deeply into the lung before being deposited and small fibre diameter facilitates translocation from the lung into pleural, peritoneal and other tissues. However, there are no length or width-dependent models for asbestos toxicity based on lung fibre burden. Information about lung fibre burden facilitates retrospective assessment of the retained portions of exposure and risk prediction. Both pathological studies used lung fibre burden to identify and characterise the type of fibres retained in diseased human lung tissue. The hypothesis being that the types of fibres identified in the tissue are likely to be implicated in asbestos toxicity.

Both studies reported that the fibres retained in diseased lung tissue were not predominantly regulatory fibres. Ultrafine fibres (D <0.20 µm and L >5 µm) made up 30% of the total fibre count in the study of Adib et al. and fibres <0.25 µm made up 93% in the study of Suzuki et al. This difference in percentage is caused by multiple factors. Chrysotile fibres are the thinnest fibres and made up 33% of the total fibres in Adib et al. and 61% in Suzuki et al. Furthermore, Adib et al. also examined short fibres (D <3 µm and <0.5 µm L <5 µm) that contains an unknown amount of short ultrafine fibres. In the study of Adib and colleagues, regulatory fibres represented the lowest

proportion of fibres. Suzuki et al. did not compare fibres found in lung tissue with regulatory fibres since their focus was on the influence of short, thin fibres as opposed to long, thin fibres. In both studies the majority of fibres found in human tissues were thin fibres (whether short or long). This suggest that they play a significant role in the development of asbestos-related disease. However, it is not possible to confirm an association or quantify the size of the effect based on these studies.

Findings from modelling studies
The studies by Wylie, Korchevskiy and their colleagues provide new insight into the role of ultrafine fibres in asbestos potency based on dimensional data from an extensive unique database. However, there were limitations in how the studies were conducted and due to a lack of transparency in their reporting, it is difficult to assess their full value. The simulation approach used to fill data gaps on individual particle sizes were not clearly described. There was also no description of how the use of simulated data impacted their findings; in this case a sensitivity analysis would have been informative. In their 2021 publication 82% of the 19,509 particle data used for model building included imputed data. Moreover, although all the data used for validating their 2021 models were from original data this represented 638 particles only. This is below the advisable size of 10-15% of the total dataset that is needed to accurately assess model performance.

It should be noted that the datasets used for modelling were primarily for amphibole type asbestos. This limits the transferability of findings to chrysotile asbestos since there may be other factors (e.g. chemical composition) specific to asbestos type that may also influence asbestos potency.

These studies should be considered within these limitations. Nonetheless, the findings point to width as a primary driver of mesothelioma risk and fibre widths ≤0.15 µm having the strongest predictive power for mesothelioma potency of asbestiform amphibole. That doubling the width decreased mesothelioma potency by a factor of ~8 whereas doubling the length decreased it by ~2.3, also suggest width as the more sensitive indicator of the two dimensional parameters of R_M. Their findings also suggests that ultrafine fibres of diameter ≤0.15 µm and ≤0.25 µm are relevant to the development of asbestos-related disease. This suggest that while fibre length remains an important dimensional co-factor of asbestos potency, width is more predictive of carcinogenicity under specific parameter values of other co-determinants e.g. length >5 µm. Further scrutiny of the findings in these studies and the value they may have in influencing regulatory revision is warranted.

Conclusion

The scientific studies published after the publication of the HC advice in 2010 support claims that ultrafine asbestos fibres with a diameter ≤0.2 µm are implicated in the toxicity of asbestos in humans. However, the available evidence is, as yet, inadequate to quantify the magnitude of the effect. Notwithstanding this limitation most of the relevant studies published in the last 15 years (2010 – 2025) have concluded that ultrafine asbestos fibres ≤0.2 µm (or at the very least ≤0.25 µm) in diameter should be taken into account when characterising the health risks associated with asbestos inhalation. Based on an assessment of this small body of new evidence, we agree with this conclusion. We advise the Ministry of Social Affairs and Employment (SZW) to conduct further research into the implications of this conclusion for the Dutch occupational exposure limit of asbestos (2,000 fibres/m^3). The practical feasibility of measuring ultrafine asbestos fibres ≤0.2 µm should also be considered.

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Appendix 1: Search (EMBASE, 13 December 2024)

No.	Query	Results
#15	#14 AND [2010-2025]/py	175
#14	#6 AND #13	681
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	17048854
#12	'carcinogen*':ti,ab,kw OR 'oncogen*':ti,ab,kw OR 'cancer*':ti,ab,kw OR 'neoplas*':ti,ab,kw OR 'tumor*':ti,ab,kw	5306187
#11	'respiratory tract disease'/exp/mj OR 'lung disease'/exp OR 'malignant neoplasm'/exp/mj OR 'lung tumor'/exp OR 'mesothelioma'/exp OR 'carcinogenesis'/exp	6096487
#10	((('health' OR 'diseas*') NEAR/2 ('hazard*' OR 'risk*' OR 'effect*' OR 'impact*')):ti,kw) OR ((('lung*' OR 'pulmonar*') NEAR/3 ('effect*' OR 'diseas*' OR 'health*')):ti,kw)	195953
#9	'inflammation'/exp/mj OR 'health hazard'/exp OR 'pathogenesis'/exp/mj OR 'epidemiology'/exp/mj OR 'toxicity'/exp OR 'risk assessment'/exp OR 'occupational disease'/exp OR 'occupational health'/exp	5894714
#8	'asbestosis':ti,ab,kw OR 'disease*':ti,ab,kw OR 'mesothelioma*':ti,ab,kw OR 'toxic*':ti,ab,kw OR 'genotoxic*':ti,ab,kw OR 'cytotoxic*':ti,ab,kw OR 'pathogenicit*':ti,ab,kw	8736221
#7	'environmental exposure'/exp/mj OR 'occupational exposure'/exp/mj OR 'inhalational exposure'/exp/mj OR ((('environment*' OR 'occupation*') NEAR/2 ('exposure*' OR 'exposed')):ti,kw)	89005
#6	#4 AND #5	860
#5	((('fiber' OR 'fibers' OR 'fibre*' OR 'fibrous') NEAR/10 ('diameter*' OR 'dimension*' OR 'width*' OR 'thick' OR 'thickness' OR 'thin*' OR 'small' OR 'fine' OR 'nano' OR 'nanosi?ed' OR 'nanometric' OR 'size*')):ti,ab) OR 'nanofiber*':ti,ab OR 'nanofibre*':ti,ab	93752
#4	#1 OR #2 OR #3	21098
#3	'asbest*':ti,kw OR 'chrysotil*':ti,kw OR 'amphibol*':ti,kw OR 'amosit*':ti,kw OR 'crocilodit*':ti,kw OR 'tremolit*':ti,kw OR 'grunerit*':ti,kw OR 'actinolit*':ti,kw	12948
#2	'chrysotile'/exp OR 'amphibole'/exp OR 'amosite'/exp OR 'crocidolite'/exp OR 'actinolite'/exp OR 'tremolite'/exp	3801
#1	'asbestos'/exp OR 'asbestos fiber'/exp	17112

Appendix 2: Overview of epidemiological studies

Study reference and title	**Study design and population**	**Exposure assessment**	**Health assessment**	**Statistical approach and confounding**	**Results and Findings**
Hamra et al. (2014) Title: Examining the association of lung cancer and highly correlated fibre size-specific asbestos exposures with a hierarchical Bayesian model.	Study type: pooled cohort Participants: 3803 textile workers (63% males) that worked in a plant for at least 1 day between January 1950 and December 1973. Location: North Carolina, USA	Exposure agent: Asbestos chrysotile fibres. Exposure metric: annual, cumulative size-specific fibre exposures expressed in fibre-years/ml (f-y/ml). Exposure assessment: TEM was used to estimate the distribution of fibres for plant/department combinations in categories defined by diameter (<0.25, 0.25–1.0, 1.0–3.0, >3.0 µm) and length (≤1.5, 1.5–5, 5–10, 10–20, 20–40, >40 µm). This assessment was performed on a stratified random sample of 160 dust samples collected in	Health outcome: Lung cancer mortality Health assessment: Causes of death, including underlying cause, immediate causes and other significant conditions, were coded to the International Classification of Diseases in effect at the time of the death.	Statistical analysis: Based on 181 cases from the cohort. Nested case-control analysis: 10:1 control/case matching on continuous age in years. Unconditional logistic regression with models adjusted for continuous age at lung cancer event or selection into the cohort; sex, race, observation year expressed in decades starting at (1950-1959). Two approaches were compared: (i) frequentist models for individual fibre size groups	Correlations across chrysotile fibres (r = 0.40 - 0.99, Med = 0.79). Highest proportion of total fibre count (53%) were group <0.25 µm diameter; 26% were group 1.5 – 5.0 µm. Frequentist model with fibre groups modelled independently: - increase in dose-response with increasing diameter/length group - within diameter group: increase in log odds of lung cancer per 100 f-y/mL additional exposure with increasing fibre length. - within length group: increase in log odds of lung cancer per 100 f-y/mL additional exposure with increasing fibre diameter. Hierarchical model with fibre groups modelled jointly: - no dose-response trend in the effect of chrysotile fibres with increasing fibre diameter/length group - the estimated coefficient for most

		plant surveys in 1964-1971. Estimated exposures to fibres were linked to workers' occupational histories.		(ii) a hierarchical Bayesian model that included all fibre groups to estimate the relationship of size-specific asbestos fibre groups to lung cancer mortality.	fibre groups ≈ grouped median with high standard deviations.
Hamra et al. (2017) Title: Lung Cancer Risk Associated with Regulated and Unregulated Chrysotile Asbestos Fibers.	Study type: nested case-control with each case matched to 10 controls on age at the time of lung cancer event Participants: 6136 workers (60% males) from three textile facilities in North and South Carolina (same as Loomis 2012). Location: North and South Carolina, USA	Exposure agent: Asbestos fibres (mainly raw chrysotile) 79% of total fibre count < 0.25 µm with length <1.5 to 5. Exposure metric: annual, cumulative size-specific fibre exposures (21 length/diameter groups). Exposure assessment: As for Hamra et al. (2014)	Health outcome: Lung cancer mortality; 10-year lag. Health assessment: Causes of death, including underlying cause, immediate causes and other significant conditions were coded to the International Classification of Diseases in effect at the time of the death.	Statistical analysis: Hierarchical Bayesian model that implements an order constraint to integrate a prior belief that asbestos fibres of greater length and narrower diameter may be more harmful that shorter fibres. These were compared with a model without order constraints.	For the model with order constraints: lung cancer risk increased with increasing length but not with decreasing diameter. The most precise estimates were obtained for fibres with diameter <0.25 µm in both models. Coefficient for the change in the Rate Ratio (RR) of Lung Cancer per 100 f-yr/ml change in exposure for asbestos for fibres <0.25 µm diameter: for all length categories RR ranged from 0.99 (Credible interval (CI) 0.89-1.11). For fibres <0.25 µm to 1.12 (CI: 0.89-2.03).

Loomis et al. (2010) Asbestos fibre dimensions and lunch cancer mortality among workers exposed to chrysotile.	Study design: Retrospective cohort study Population: 3803 workers from three textile facilities in North Carolina between 1950-1973. Location: North Carolina, USA	Exposure agent: Asbestos fibres (mainly chrysotile) as determined by PCM. Exposure metric: cumulative size-specific fibre exposures (21 length/diameter groups). Exposure assessment: As for Hamra et al. (2014)	Health outcome: Lung cancer mortality, 10-year lag Health assessment: Causes of death, including underlying cause, immediate causes and other significant conditions, were coded to the International Classification of Diseases in effect at the time of the death. Records that mentioned lung cancer on the death certificate were included in the analysis.	Data from all study plants were modelled simultaneously by Poisson regression with adjustment for age, sex, race and calendar time.	The strongest association with lung cancer was found for fibres with diameter >3 µm (LR 10.1) followed by diameter <0.25 µm (LR 7.8) A significant association was observed between lung cancer risk and fibres >20 µm long and 0.25-1.0 µm thick. (no p-value given) The best model fit for a length-diameter category was for fibres 20-40 µm long and >3 µm thick (LR 14.5) Fibres <1.5 µm long and <0.25 µm thick also had a strong association with lung cancer (LR 8.8) Interaction between fibre length and diameter had a non-significant inverse relationship. Fibres corresponding to the Stanton index (D<0.25µm; L≥10µm) were significantly associated with lung cancer risk (p<0.005). Association with lung cancer was less strong for fibres corresponding to the Lipmann (0.25≤D≤1µm; L≥10µm) and Berman (5 µm < length < 10 µm) indices

Loomis et al. (2012) Increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibres.	Study design: Pooled retrospective cohort study Population: 6136 workers (61% males) from three textile facilities who worked at least 30 days at asbestos textile mills between 1940-1973 Location: North and South Carolina, USA	Exposure agent: Asbestos fibres (mainly chrysotile) as determined by PCM Exposure metric: cumulative size-specific fibre exposures (21 length/diameter groups). Exposure assessment: As for Hamra et al. (2014)	Health outcome: lung cancer mortality Health assessment: Causes of death, including underlying cause, immediate causes and other significant conditions, were coded to the International Classification of Diseases in effect at the time of the death.	Data from all study plants were modelled simultaneously by Poisson regression with adjustment for age, sex, race, calendar time	Lung cancer mortality was significantly associated with all fibre diameters, but the association was strongest for fibres D<0.25um. (2 lengths p<0.01; 4 lengths p<0.001; all lengths p<0.001) Fibres with D<0.25um had the highest coefficients estimated by Poisson regression (0.03-0.04). For fibres 5-10 um long the regression coefficient was 0.041 (p<0.041) Cumulative exposure to total fibres counted by TEM and to fibres in every length and diameter category were significantly associated with lung cancer mortality (p<0.01)

PCM – Phase Contrast Microscopy; TEM – Transmission Electron Microscopy; LR – likelihood ratio, (equivalent to X^2 with 1 degree of freedom)