Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for Asbestos

ECHA/RAC/A77-O-0000006981-66-01/F

10 June 2021

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR ASBESTOS

Commission request

The Commission asked the Committee for Risk Assesment (RAC) to assess the scientific relevance of the current occupational exposure limit (OEL) for asbestos, in view of the preparation of the proposals for amendment of Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work.

In accordance with Article 8 of Directive 2009/148/EC "employers shall ensure that no worker is exposed to an airborne concentration of asbestos in excess of 0.1 fibres per cm^3 as an 8-hour time-weighted average (TWA)". Therefore, on 08/01/2020 the Commission requested ECHA with RAC, in accordance with the Service Level Agreement (SLA) (Ares(2019)18725), to review the current OEL for asbestos.

The SLA further specified that:

- The scientific evaluation shall include, where appropriate, review of/or proposals for OEL(s), biological limit value(s) and/or appropriate notations.
- It shall include an evaluation of different types of asbestos fibres (as defined in Art 2, Dir 2009/148/EC) and take into account the nature of the health effects due to these differences.
- It shall include an assessment of whether a differentiated limit value may be appropriate for the different types of asbestos fibres.".

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for asbestos with a deadline of 08/07/2021.

Chemical name(s): asbestos

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values for asbestos at the workplace. In the preparatory phase of making this report, a call for evidence was started on 02/03/2020 to invite interested parties to submit comments and evidence on the subject by 02/06/2020.

This scientific report was made publically available[1] on **01/02/2021** and interested parties were invited to submit comments by **01/04/2021.**

The Committee for Risk Assessment (RAC) developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to the RAC opinion to ensure alignment.

[1] https://www.echa.europa.eu/web/guest/oels-prev-pc-on-oel-recommendation/-/substance-rev/27203/term

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Dick Heederik and Tiina Santonen**

The opinion was adopted by **consensus** on **10 June 2021.**

RAC Opinion on an updated risk assessment for asbestos to inform derivation of an OEL

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of the current Occupational Exposure Limit (OEL) for asbestos is set out in the table below (Table 1) and in the following summary of the evaluation and supported by Annex 1.

SUMMARY TABLE

Asbestos is a non-threshold carcinogen and consequently, no health-based OEL can be identified. Instead, an exposure-risk relationship (ERR) is derived, expressing the excess risk for lung cancer and mesothelioma mortality (combined) as a function of the fibre concentration in the air. This will facilitate the setting of an OEL by the relevant EU bodies, taking an acceptable level of excess risk into account.

The exposure-risk relationship was calculated for all types of asbestos by combining all studies, regardless of the asbestos fibre type the working population are exposed to. The exposure-risk relationship focuses on air concentrations, at and below the current OEL of 0.1 fibre per cm^3.

The table below presents the details of the exposure-risk relationship.

Table 1: Derived Limit Values[2]

<table>
<tr><td rowspan="9">OEL as 8-hour TWA:</td><td colspan="2">Air concentration of asbestos as measured by PCM[3]</td><td>Excess life-time cancer risk (cases per 100 000 exposed)</td></tr>
<tr><td>Fibres/cm^3</td><td>Fibres/m^3</td><td></td></tr>
<tr><td>0.001</td><td>1000</td><td>1.2</td></tr>
<tr><td>0.002</td><td>2000</td><td>2.5</td></tr>
<tr><td>0.005</td><td>5000</td><td>6.2</td></tr>
<tr><td>0.01</td><td>10000</td><td>12</td></tr>
<tr><td>0.02</td><td>20000</td><td>25</td></tr>
<tr><td>0.05</td><td>50000</td><td>62</td></tr>
<tr><td>0.1</td><td>100000</td><td>125</td></tr>
<tr><td>STEL:</td><td colspan="3">No STEL is proposed</td></tr>
<tr><td>BLV:</td><td colspan="3">No BLV is proposed</td></tr>
<tr><td>BGV:</td><td colspan="3">No BGV is proposed</td></tr>
</table>

Notations

Notations:	none

[2] The naming conventions of limit values and notations used here follow the 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7) and the Joint ECHA/RAC – SCOEL Task Force report (2017b). [https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145].

[3] The exposure-risk relationship is based on fibre measurements according to the Phase Contrast Microscopy (PCM) method of WHO (1997).

RAC OPINION

Background

This opinion concerns asbestos. This evaluation, takes previous reviews into account, in particular:

- Reviews of the complete body of evidence by NFA (2019), IARC (2012), DECOS (2010), Afsset (2009a,b) and AGS (2008). This has been complemented by a literature search of published papers from the last ten years.
- Meta-analyses conducted earlier and published in the peer review literature.
- Published papers were in particular reviewed for quantitative exposure response relations for cancers known to be related to asbestos exposure.

Based on both global and national European estimates asbestos-related cancers are currently the leading fatal occupational diseases. The burden of disease related to asbestos exposure is expected to reduce in the coming decades. However, at present there are still categories of workers that experience exposure to asbestos, in particular during renovation or demolition activities in the construction industry exposure still occurs. In some cases, asbestos may be present naturally in some geological formations leading to environmental exposures and occupational exposures during mining or construction activities.

Key conclusions of the evaluation

- There is sufficient evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) and that asbestos causes mesothelioma and cancer of the lung, larynx, and ovary.
- Also, positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum, but there is not yet sufficient evidence to consider the associations for these three cancers as causal associations.
- Sufficient evidence exists from experimental animal studies for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).
- All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are classified as known human carcinogens (Carc. 1A) according to EC Regulation 1272/2008 and as carcinogenic to humans (Group 1) by IARC.
- Robust quantitative exposure-response relations are observed for lung cancer and mesothelioma in workers studied in epidemiological cohort studies and some case-control studies. In all these studies exposure to asbestos fibres has been monitored and related to disease experience.
- For other cancer sites no (precise) exposure-response relations have been described by cumulative or other quantitative exposure metric.
- Considerable evidence exists that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. Estimates vary between a factor 200-500. It is important to note that uncertainty exists concerning the accuracy of the relative potency estimates because of the limited power of some of these studies and the potential for exposure misclassification in the epidemiological studies.
- It is controversial whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos. In general, potency differences for the different asbestos types are considerably smaller in case of lung cancer in comparison

to mesothelioma. Earlier estimates are in a range of a factor 10-50 for the potency difference between amphiboles and chrysotile. These estimates of fibre type specific potency for chrysotile are sensitive to two influential studies. More recent estimates of potency differences, using a non-linear (spline) modelling approach to improve estimation of the exposure response curve in the low exposure range observed higher overall risks for all fibre types together in this range. The same spline models showed a lower potency difference between amphiboles and chrysotile (a 3-fold statistically non-significant difference for amphibole asbestos in comparison to chrysotile). This is likely due to the fact that predictions of risk at lower exposure levels are less affected by observations at high levels in the spline model, which are more likely affected by measurement error.

- For lung cancer there is an indication that restricting meta-analyses to studies with the highest quality provides quantitative risk estimates that are higher than when all studies are used in both linear as well as non-linear models. An effect of study quality was also observed in the updated database described in Annex 1, with 22 studies on lung cancer. Restricting the lung cancer analysis to only studies with few quality limitations leads to an epidemiological evidence base which is too sparse to draw conclusions about potency differences by fibre type.
- Asbestos and some other mineral fibres are still the only established causal factor identified for mesothelioma. The majority of mesothelioma cases (>90%) can be explained by occupational or environmental asbestos exposure. Smoking is not a risk factor for mesothelioma.
- There is a long latency time from first exposure to occurrence of mesothelioma, at least 10 years but typically 30 to 40 years or more.
- The current occupational exposure to asbestos in Europe is generally mixed exposure to different types of asbestos and it is not possible to estimate the current relative contributions of chrysotile and amphiboles to the exposure. Neither is the proportion of chrysotile in the available epidemiological cohorts with mixed exposure known.
- Studies on lung cancer and smoking show a variable pattern ranging from supra-multiplicative to less than additive effects, which is considered to possibly reflect the fact that both tobacco and asbestos are complex carcinogens that can affect more than one stage of lung carcinogenesis.
- There are some indications that fibre dimensions may influence the risk of mesothelioma and lung cancer, with potency increasing with increasing length and decreasing width. However, based on human and animal data, it is not possible to exclude an asbestos associated risk of cancer for any fibre width or length category studied. These observations are nearly exclusively based on optical microscopy and thus concern fibres with dimensions detectable with that method.
- For cancers of the larynx and ovaries, there is insufficient data to conclude on fibre dimension specific potencies.
- Numerous (meta-)analyses have quantitatively estimated the asbestos associated risk of mesothelioma and lung cancer dependent on exposure. The EPA (1986) absolute risk model has been used for mesothelioma. This model estimates the excess risk on the basis of exposure expressed as the concentration of asbestos in the air, duration of exposure and time since first exposure. The excess lung cancer risk is usually calculated using exposure response relations estimated with relative risk models, either linear or non-linear in combination with life table analysis to calculate lifetime (absolute) risk.
- Meta-regression analysis for lung cancer, considering all available quantitative exposure response studies, indicates that the exposure-response relation is not linear. The actual risk at levels around and below the current EU OEL may be higher than the risk that would be calculated with linear extrapolation from the historical industrial cohorts with much higher exposures.

- The epidemiological data does not allow identifying a threshold for asbestos-related risk of lung cancer or mesothelioma. A recent meta-regression analysis does not give an indication of the existence of an exposure threshold.
- Asbestos fibres may transfer from the mother to the foetus. Data on developmental effects is, however, limited. Developmental effects have been reported in one animal study with intraperitoneal administration of chrysotile, amosite or crocidolite fibres. There are no human data available and this limits clear conclusions about potential human risks.
- Pulmonary fibrosis (asbestosis) and pleural plagues are also well-known asbestos related disease entities. Asbestosis occurs only at higher exposure levels than current OELs and although pleural plaques may occur already at lower exposure levels their clinical relevance is unclear.
- Asbestos fibres can be measured using either phase contrast optical microscopy (PCM) or scanning or transmission electron microscopy (SEM or TEM).
- Epidemiological data and dose-responses are based on studies that measured exposure by PCM or expressed exposure in PCM levels (for instance in case of historic exposure studies using other approaches than measuring fibres by PCM). SEM/TEM represent modern techniques and are able to detect thinner and shorter fibres than PCM and to characterise the elemental composition or crystal structure of the fibres.
- Considering that also thinner fibres (<0.2 µm) are carcinogenic, RAC is of the opinion that these fibres should be considered when measuring exposure in the workplace. However, harmonisation work is required at EU level, covering the dimensional fibre definitions, counting rules and other factors that influence the EM asbestos fibre counts.
- No conversion factors applicable to all situations to convert PCM derived risk estimates to EM based risk estimates can at present be given.

Carcinogenicity and mode of action (see section(s) 7.6, 7.7 and 8.1 of the Annex 1 for full discussion).

There is significant animal and epidemiological evidence showing that asbestos fibres are carcinogenic. The carcinogenicity mode of action of asbestos is related to the asbestos fibre dimensions (length) and biopersistence, and probably also surface reactivity. Inability of macrophages to engulf the long fibres, leading to the formation of frustrated macrophages, sustained inflammation, reactive oxygen species and nitrogen species play a significant role in this pathologic process. This results in activation of intracellular signalling pathways, indirect genotoxicity, and epigenetic changes. Different fibre properties of chrysotile asbestos when compared to the amphiboles result in more effective decomposition of chrysotile fibres and may explain the potency differences observed in epidemiological studies. Although from mechanistic point of view it might be possible to speculate on the possible threshold for the carcinogenicity of chrysotile, taking into account that the current exposures to asbestos are mixed exposures to amphiboles and chrysotile, and that the current epidemiological evidence on the carcinogenicity dose-response of asbestos fibres do not support the existence of the threshold, asbestos fibres should be considered as non-threshold carcinogens.

Cancer Risk Assessment (see section(s) 7.7.1 and 9.1 of the Annex1 for full discussion)**.**

Cancers diagnosed currently reflect exposures that started decades ago, and data sources used for burden of disease estimates make use of relatively crude historic exposure data to predict present or future burden of disease and do not contain sufficiently granular data to provide risk estimates that would link the risk to a given measured or estimated

cumulative exposure in a known cohort or exposed population. Therefore, such data are not suitable for quantitative risk assessment of setting an OEL or deriving an exposure risk relationship which require information on the relation between (cumulative) exposure and excess risk of cancer in the exposed population. For the same reasons it is not possible to compare data from such burden of disease and health impact type of approaches with results from quantitative risk assessments used for setting regulatory standards. The same methodological restrictions apply to data reported in the worker compensation systems, where, in addition to the above mentioned limitations, also the level of under-recognition of occupational diseases is an unknown parameter that limits quality of the information.

In contrast, risk assessments for occupational asbestos exposure, as presented in this opinion and further described in Annex 1, are based on the available quantitative and detailed data (on exposure level and exposure duration) and disease risk to estimate at what levels disease risk is minimal. Risk assessment may involve extrapolation to exposure levels clearly below present exposure levels. Such detailed quantitative data on exposure-response relations for asbestos related cancers comes from epidemiological studies (cohort studies or case-control studies) which have been conducted since the 1950s. In most of these studies, exposure data is available over periods of several decades measured with different techniques but converted to and expressed in Phase Contrast Microscopic measurements.

The most recent meta-analyses combining quantitative exposure-risk relationship slope factors for lung cancer and mesothelioma from the available epidemiological studies were published between 2010-2013 (Berman and Crump, 2008 a,b, van der Bij et al 2013, Lenters et al 2011, DECOS 2010). Some new studies have been published since, that provide quantitative exposure-response estimates for both lung cancer and mesothelioma. These studies concern already known studies with extended cancer follow-up, or some relatively small new cohorts and new case-control studies among which there is one very large multicentre case-control study for lung cancer. These studies were reviewed for their suitability for inclusion in an update of the previously published meta-analyses for lung cancer and mesothelioma to be able to calculate the excess risk for lung cancer and mesothelioma (combined) by level of exposure using all information that is at present available.

For lung cancer there were 22 suitable studies (see Annex 1; Table 11, Appendix 4). They provided 124 risk estimates (i.e., study points of the RR for lung cancer at a given exposure level) over a cumulative exposure range of 0.11–4710 f–y/cm^3. In comparison to van der Bij et al. (2013) (and Lenters et al. (2011)), the lung cancer analysis used a more recent follow-up study of Pira et al. (2017) instead of Pira et al. (2009) for the Italian Balangero chrysotile mine cohort and a more recent follow-up of Larson et al. (2010) instead of the study of Sullivan (2007) for the Libby vermiculate miner cohort. The analysis also included three cohorts for which the data were not yet available at the time of the previous meta-analyses. Notably, the French asbestos textile and friction material plant cohort of Clin et al. (2011a) with mixed exposure, the Chinese chrysotile mine cohort of Wang et al. (2013b) and the Chinese asbestos factory (textiles, rubber products and asbestos cement) cohort exposed to chrysotile (Courtice et al., 2016). The Swedish case-control study of Gustavsson et al. (2002) was replaced by the more recent and considerably larger pooled case-control study of Olsson et al. (2017) which also includes the Gustavsson study data.

The spline models described the data considerably better than the linear models (see Annex 1; Table 12 and Figure 2, Appendix 4) (because spline models had the lowest AIC value). The (non-linear) spline model, adjusted for intercept (for the elevated risk at zero exposure) was used for further risk calculations.

For mesothelioma there were 13 suitable studies to estimate the potency or meta-slope factor K_M (see Annex 1; Table 13, Appendix 4). In comparison to the DECOS (2010) meta-analysis, one more study was available and was included. This study, by Loomis et al. (2019), involves a North Carolina asbestos textile cohort exposed to chrysotile. The pooled K_M value combining all studies, regardless of asbestos fibre type (x10^8 in (f–y/cm^3)$^{-1}$) was 0.337, i.e. very similar to the 0.34 calculated by DECOS (2010).

Under the current EU situation with all asbestos types being already banned, potential exposure can be assumed mixed to all types of asbestos. The rationale for this assumption is that while handling asbestos products during removal or maintenance work on a given day may concern only a certain asbestos type, e.g. amphiboles, in the long run the exposure potential is expected to reflect the share of past use of different types of asbestos. Thus, either using excess risk calculations integrating all asbestos types combined or those coming from populations with mixed exposure to various asbestos types seem most relevant. Chrysotile accounts for the largest share of asbestos produced and used globally. However, the exact share of the past use in the EU is not known, neither is the share of chrysotile in those available cohorts with mixed exposure. Consequently, it was considered justified to use the excess risk calculations based on risk estimates combining all asbestos exposed cohorts, regardless of the fibre type. The composition of this mixed exposure in terms of the ratio of amphibole and chrysotile exposure may influence the risk calculations considerably, in particular for mesothelioma, because clear differences in potency have been found for mesothelioma. The default risk assessment for mesothelioma made use of a K_M value of 0.337 (confidence interval 0.246-0.429) ($x10^8$ in $(f–y/cm^3)^{-1}$) based on all availble (n=13) studies. The K_M for amphiboles and chrysotile are 7.95 (based on two studies; confidence interval 0.015-15.891) and 0.017 ($x10^8$ in $(f–y/cm^3)^{-1}$) (based on 5 studies; confidence interval 0.004-0.031), respectively. This K_M value of 0.337 is smaller than the average K_M value of cohorts with mixed exposure to asbestos (K_M value 1.076, confidence interval (0.330-1.821); based on 6 studies) ($x10^8$ in $(f–y/cm^3)^{-1}$). This raised the question whether the overall K_M is a justified estimate of mixed asbestos exposure as it occurs at present. Therefore, alternatively, a meta K_M was also estimated by using global production data for chrysotile and amphiboles (estimated between 94-96% and 4-6%of all asbestos produced, respectively), and calculating a meta K_M value by taking the production weighted average of the K_M values of chrysotile (0.017 ($x10^8$ in $(f–y/cm^3)^{-1}$)) and amphiboles (7.95 ($x10^8$ in $(f–y/cm^3)^{-1}$)). This led to K_M values between 0.33 and 0.49 ($x10^8$ in $(f–y/cm^3)^{-1}$). These values are close to the overall meta-K_M value based on all cohort studies, considerably lower than the K_M value for cohorts with mixed exposure. The high K_M value for cohorts with mixed exposure only is explained by the fact that the share of amphibole exposure was relatively high in these cohorts; up to 20% of the asbestos used. Therefore, the average K_M value on the basis of all available mesothelioma studies was seen as a realistic estimate.

A recent meta-analysis for lung cancer indicated that small and statistically non-significant differences in potency for lung cancer exist between amphibole and chrysotile asbestos. Therefore, no adjustments or additional sensitivity analyses were considered necessary for lung cancer. The meta-exposure response relation between cumulative exposure to asbestos and lung cancer mortality was used as input in the risk assessment.

The EPA mesothelioma model was used to estimate absolute mesothelioma risk. For estimation of lung cancer relative risk by level of cumulative exposure, both linear and non-linear (natural spline) models, with and without intercept, were run in order to identify the model with the best fit according to the Akaike information criterion (AIC). For lung cancer the excess risk associated with asbestos exposure was calculated using the so called life table analysis to adjust for the fact that at higher age mortality from other causes reduces the population at risk compared to the original population initially exposed, which influences excess risk estimates when not adjusted for.

The meta exposure response spline for lung cancer and meta-K_M value for mesothelioma were used to calculate the combined risk for lung cancer and mesothelioma mortality after a working life of exposure at several exposure levels for 8 hours per day and 5 days per week over a 40 years working life period (starting at 20 years).

The input for the life-table analysis (lung cancer and total mortality) were mortality rates, per January 2021, averaged across all EU countries for the years 2011-2016 from the Eurostat database. For this purpose, the average male and female mortality rates were calculated by age. The excess risk was calculated until 89 years of age. The analyses

focused on exposure levels at and below the current EU OEL. The resulting excess risk of lung cancer and mesothelioma (combined) by level of exposure is described in the table below (Table 2) and expressed per 100 000 exposed individuals. Lung cancer and mesothelioma contributed almost equally to the risk figures in the table below.

Table 2: Cancer exposure-risk relationship (lung cancer and mesothelioma combined) after working life exposure to given 8-hour air concentration for five working days a week as measured by PCM.

Air concentration of asbestos as measured by PCM		
fibres/cm^3	fibres/m^3	Excess life-time cancer risk (cases per 100 000 exposed)
0.001	1000	1.2
0.002	2000	2.5
0.005	5000	6.2
0.01	10000	12
0.02	20000	25
0.05	50000	62
0.1	100000	125

The above exposure-risk relation is based on studies which used fibre counting protocols which were based on or converted to phase contrast optical microscopy counts (PCM).

Uncertainties in the risk estimates (see Appendixes 4 and 6, Annex 1 for a full discussion)

A few issues are expected to contribute most to the uncertainties in the risk estimates presented:

- **Statistical estimation error and model assumptions.** Exposure response relations have been estimated on the basis of 22 studies on lung cancer and 13 studies on mesothelioma. Uncertainties arise because of limited statistical precision in the risk estimates due to limited quality of the exposure estimates, differences in design, conduct and analysis of the studies, leading to heterogeneity between studies. Some studies have a small sample size contributing to random estimation error. All these factors together lead to uncertainty in the meta-exposure-response relation and risk calculations. In all risk calculations, point estimates for the exposure response slope (lung cancer) or potency factors (K_M in case of mesothelioma) have been used. The confidence intervals around these point estimates indicate that for both lung cancer and mesothelioma, variation around these point estimates can be up to a factor 1.5-2. When considering specific types of asbestos, statistical uncertainties increase considerably, because inferences about potency differences are based on a very limited number of studies (for mesothelioma and amphiboles, only two studies are available and five study are available with chrysotile exposure only). Choices made in modelling of exposure-response relations, used to calculate lifetime risks may contribute to larger differences in risk estimates. A spline model described the exposure response relation for lung cancer best. Use of a more conventional linear model led to a shallower exposure response relation at low exposure levels, and this would have led to 35% lower lifetime risk estimates for lung cancer and mesothelioma combined. Further sensitivity analyses indicated that the spline gave a robust description of the available data for lung cancer and exposure. Changes in the spline

modelling approach (knot placement) changed the exposure response slope at exposure levels to a limited extent (10% maximally).

- **Exposure assessment methodology.** In all quantitative exposure response studies, asbestos exposure of individual workers has been estimated by combining data from measurement surveys on the level of job titles, with worker job title information and job tenure (duration of exposure). Poor quality of exposure estimates may lead to exposure misclassification and underestimation of exposure–response relationships in epidemiological studies. The magnitude of underestimation is study specific. Overall, the exposure response slope is steeper in studies on asbestos with higher quality exposure assessment as has been shown for lung cancer. Limiting exposure response modelling for lung cancer to studies with higher quality results in a exposure response slope that is 1.5-2 times higher compared to using all studies.
- **Fibre analysis.** In all epidemiological studies with quantitative exposure data fibre concentrations have been measured using PCM or converted to PCM from earlier methods. With PCM, exposure to long but thin fibres is underestimated leading to an overall underestimation of exposure. As a result, the risk from asbestos exposure in these studies is associated with exposure levels that have been underestimated leading to a higher risk per unit of exposure. This only becomes an issue of concern when, for instance in the context of compliance testing, exposure is assessed using other, more modern, techniques to assess fibre concentrations which do measure thinner fibres as well.
- **Other cancers associated with asbestos exposure.** Asbestos exposure is causally related to the occurrence of larynx and ovary cancer. These cancers have not been considered in the quantitative risk assessment and excess risk calculations. The reason for this omission is simple; no quantitative exposure-response-relations have been published that can be used in risk assessment procedures. As a result, the calculated excess risk underestimate the true risk for developing cancer resulting from asbestos exposure. It can be argued that the underestimation is relatively modest because of two reasons. First, larynx and ovary cancer are relatively rare and occur less frequently than lung cancer and mesothelioma in asbestos exposed populations. In addition, an exploratory analysis shows that not all larynx and ovary cancers can be attributed to asbestos exposure because other causes do play a role as well. It was estimated that these two cancers may maximally contribute another 10% additional cases in comparison with the ones observed for lung cancer and mesothelioma together in the excess risk calculations. It has been suggested that asbestos exposure may also lead to stomach cancer, colorectal cancer and cancer of the pharynx. Potential underestimation resulting from these cancers is expected to be in the same order of magnitude, related to asbestos exposure, but has not been considered extensively because there is still doubt whether the increased risks observed in some studies for these cancers are the result of a causal association between asbestos exposure and these cancers.
- **Estimation of the exposure response slope for mixed asbestos.** In the risk assessment process, it is assumed that at present, workers are mainly exposed to mixed asbestos. Because potential potency differences between different fibre types for lung cancer seems relatively small, the meta-estimate of the exposure response relation for lung cancer, taking all studies together, is expected to yield an acceptable meta-estimate for mixed asbestos. Differences in relative risk between the meta-exposure response estimate and the estimate for mixed asbestos types only were below 10%, using the spline model adjusted for intercept. As regards mesothelioma, the question arises what an adequate potency estimate is for mixed asbestos, against the background that clear potency differences exist between different types of asbestos for developing mesothelioma. Point estimates for the K_M

value used in the risk assessment were calculated in different ways. First, the average value of K_M values for all available studies were calculated. In addition, an asbestos use weighted average of chrysotile and amphibole asbestos was calculated. These two estimates of the K_M factor were very similar. However, the agreement depends to some extent on the assumed ratio of chrysotile : amphibole asbestos use over the second half of the previous century, which plausibly ranges between 94% and 96%. A lower contribution of chrysotile to mixed asbestos exposure, will lead to an increased risk of developing mesothelioma in case of mixed asbestos exposure. This underestimation can be as high as almost 50% for mesothelioma. These potency differences have played a considerably less important role in case of lung cancer.

- **Differences in lifetime risk related to choices in risk calculations.** Some differences in risk outcomes relate to assumptions and choices in the risk calculations for which there is no default approach agreed upon. These choices are related to using conditional (life table analysis) or simple unconditional risk calculation methods, but also the cut-off age for the lifetime risk, choice of background rates (e.g. country specific rates, EU averaged rates, both genders combined or men only), time period of reference rates (which have changed for lung cancer because of changes in smoking habits), etc., all influence the estimated risks. Some of these have been explored in the literature or in sensitivity analyses in Annex 1. The use of conditional (life table methods) leads to unbiased estimates but these can be up to a factor 2 lower than unconditional risk estimates (not adjusted for other causes of death). Calculating lifetime risk until age >100 instead of 89 (as in this opinion) leads to a 10% higher risk. The average of male and female lung cancer rates has been used for calculations. Lung cancer rates are higher for males. Use of male rates only, led to a 30% higher lifetime risk in comparison to the figures presented in the tables. It should be noted that the choice of mortality rates is only relevant for lung cancer. Mesothelioma risk has been estimated using an absolute risk model which does not require input of background mesothelioma rates.

  In particular this category of choices, arising from the lifetime excess calculations, may contribute to the explanation of differences with other risk assessments because other mortality rates or lifetime risk periods have been used.

To summarize, the use of an exposure response spline for lung cancer can be considered a relatively conservative exposure risk estimate because of the assumption of a steeper exposure response relation at lower exposure levels. The fact that other types of cancer than lung cancer and mesothelioma, causally related to asbestos exposure, could not be included in the risk assessment has led to limited underestimation of lifetime risk. Potency differences between different asbestos types contribute to uncertainty in the potency estimate for mixed asbestos exposure in case of mesothelioma, but the uncertainty seems relatively limited. Underestimation of risk resulting from exposure assessment related uncertainties and measurement error and potential other study quality issues seem dominant. The nature of these errors make underestimation of risk more plausible than overestimation of risk on top of random estimation error. Underestimation with a factor of two maximally seems plausible but it is not possible to give an accurate point estimate. Uncertainties arising from the risk calculation methodology used are generally smaller. In particular the use of average male and female mortality rates instead of male rates only may have led to upto 30% lower risk estimates for lung cancer, but does not affect mesothelioma risk estimates.

Measuring exposure to fibres (see Annex 1 Chapter 6, section 9.1.2, Appendix 5)

The above exposure-risk relations are based on studies which used fibre counting protocols which were based on phase contrast optical microscopy (PCM) or converted to PCM from earlier methods. PCM measurement protocols generally define a countable fibre as a fibre

longer than 5 µm, narrower than 3 µm, and with an aspect ratio (length/width) greater than 3:1. These rules were selected because shorter fibres were difficult to detect by optical microscopy and the 3:1 aspect ratio was used to discriminate between fibrous and non-fibrous fibrous particles in occupational settings. The PCM method does not speciate fibre types. This means that all fibres that are in compliance with the dimensional definition are counted regardless of their mineralogical composition. In historical settings asbestos fibres accounted likely for most, if not all airborne fibres.

The available human data is driven by the WHO fibre definition (fibres shorter than 5 µm were not measured) and the PCM method (fibres thinner than about 0.2 µm could not be detected). However, human and animal data indicates it is not possible to exclude an asbestos associated risk of cancer for any fibre width or length. As discussed in Annex 1, there is even indication that the carcinogenic potency of asbestos fibres increases with decreasing fibre width. Therefore, fibres thinner than those detected by PCM, should be considered when measuring dust levels in the workplace. It is commonly accepted that because of the presence of small fibres in samples with fibres with a length above 5 µm, exposure limits derived in the past implicitly cover a possible health risk linked to short fibres. However, there are no studies that assessed health effects resulting from short asbestos fibres alone. There is also little animal data on such fibres and the existing mode of action data of asbestos fibres is largely driven by studies based on the WHO fibre definition. Inclusion of short fibres in EM counting would result in higher and more variable conversion factors. Similar considerations apply to elongated cleavage fragments.

At present, PCM is not considered a state of the art measurement method for asbestos in the work environment anymore. In addition to its inability to speciate fibre types it cannot detect fibres thinner than about 0.2 µm. Nowadays measurement techniques based on electron microscopy (EM) have been introduced. These methods can detect thinner and shorter fibres than PCM and are also equipped with analysers able to characterise the elemental composition or crystal structure of the fibres.

Conversion of the relationship between epidemiologically established PCM-based exposure-risk relations into electron microscopic exposure metrics have to be based on conversion factors from correlation studies but is associated with inherent uncertainties. Several studies have shown that the ratio of fibre concentration measured by EM and PCM depends, among others, on the fibre dimensions in the sample and type of asbestos. EM/PCM ratios of on average 1.4-4.6 have been observed in a limited number of studies. The range in EM/PCM ratio's is larger in specific environments such as asbestos removal and asbestos production in comparison with mining industries. However, the number of measurements taken in these specific environments is too limited to be able to obtain an accurate conversion factor from. In particular, when non-asbestos fibres were abundant, these were counted by PCM but not by TEM leading to ratios below 1. The above-mentioned EM/PCM ratios are based on fibres thicker than about 0.25 µm and longer than 5 µm. Obviously, if thinner fibres are also considered, the difference between the two methods gets more pronounced. Short fibres are also not included in these comparisons, while the majority of fibres appear to be short fibres (< 5 µm in length).

Regulatory bodies have taken pragmatic approaches to overcome the above methodological uncertainties concerning the conversion between PCM and EM fibre counts. Some organisations proposed conversion factors between 2 and 4. Others did not consider it necessary to introduce a conversion factor to take account of different methods of fibre detection or recommended development of a TEM method.

Currently there is no uniformly accepted and used international EM method to count asbestos fibres and national bodies have set national standards. Both SEM and TEM can be used to detect fibres thinner than 0.2 µm, but the current SEM standards do not recommend the use of higher magnification which would allow visualization of thinner fibres. Therefore, although SEM is widely used, and an affordable method to quantify asbestos fibre levels in Europe, it is mainly used with a magnification of 2000x allowing the quantification of fibres thicker than 0.2 µm only. As described in Annex 1, using TEM

with a magnification of 5000-10000x fibres of 0.01-0.03 µm in diameter can be detected. When SEM is used with a magnification of 6000x, fibres of ≥0.05 µm in diameter can be detected. The detection limits of 0.001-0.004 fibres/cm^3 (depending on method) may be achieved in rural environments but not necessarily in dusty environments (for example in mines) with the methods currently used. Achieving these low limits of detection, may necessitate further development of sample treatment practises together with sampling higher volumes and an increase of the number of fields counted (i.e. the area of the filter that is analysed).

Overall, harmonisation work is required at EU level concerning the different EM methods currently used. That harmonisation concerns also the dimensional fibre definitions, counting rules and other factors that influence the EM asbestos fibre counts. The proportion of fibres thinner than 0.2 µm from all asbestos fibres present varies greatly. Consequently, it is not possible to recommend a precise conversion factor for EM measurements. Transitional provisions seem necessary before that harmonisation work has been conducted.

Derived Limit Values (see section 9.1.1 of the Annex 1 for full discussion)

The recent national approaches have assumed a non-threshold mode of action and derived an exposure-risk relationship that was then used to establish an OEL based on national conventions concerning an acceptable excess risk. Differences in concentrations estimated at a certain benchmark risk level exist, as discussed earlier in the section on uncertainties in the risk assessment. Some of the factors discussed also involve comparisons between different OELs or risk figures including the fact that different studies were chosen to derive meta-exposure response relations, excess risks were calculated from these studies in different ways, single or multiple endpoints were considered (lung cancer, mesothelioma, or both endopoints combined), etc.

Table 3: Comparison of fibre concentrations associated to given excess risk levels (lung cancer and mesothelioma combined) using the calculations of Afsset (2009b), AGS (2008), DECOS (2010), Danish NFA (2019) and Danish AT (2019)

	Excess life-time cancer risk (cases per 100 000 exposed) associated with given fibre concentrations (fibres/cm^3)		
Fibre concentration	**0.001**	**0.01**	**0.1**
Afsset, all asbestos	3.3	33	330
AGS, all asbestos	4.0	40	400
DECOS, chrysotile	2.0	20	200
DECOS, mixed	3.1	31	310
DECOS, amphiboles	9.5	95	950
DK NFA (based on DECOS amphiboles)	10	100	1000
DK AT (based on DECOS mixed)	3.7	37	370

(i) OEL - 8h-TWA

The table below (Table 4) presents the outcome of the RAC evaluation to assess the scientific relevance of the current occupational exposure limit for asbestos and to include,

where appropriate, review of/or proposals for OEL(s), biological limit value(s) and/or appropriate notations.

Table 4: Derived Limit Values[4]

<table>
<tr><td>OEL as 8-hour TWA:</td><td>Asbestos is a non-threshold carcinogen. Consequently, no health-based OEL can be identified and an exposure-risk relationship expressing the excess risk (ERR) for lung cancer and mesothelioma mortality (combined) as a function of the fibre concentration in the air is derived. The ERR was calculated for all types of asbestos by combining all studies regardless of the asbestos fibre type the working population was exposed to. The ERR focuses on air concentrations at and below the current OEL.
<table>
<tr><th colspan="2">Air concentration of asbestos as measured by PCM[5]</th><th>Excess life-time cancer risk (cases per 100 000 exposed)</th></tr>
<tr><th>Fibres/cm^3</th><th>Fibres/m^3</th><th></th></tr>
<tr><td>0.001</td><td>1000</td><td>1.2</td></tr>
<tr><td>0.002</td><td>2000</td><td>2.5</td></tr>
<tr><td>0.005</td><td>5000</td><td>6.2</td></tr>
<tr><td>0.01</td><td>10000</td><td>12</td></tr>
<tr><td>0.02</td><td>20000</td><td>25</td></tr>
<tr><td>0.05</td><td>50000</td><td>62</td></tr>
<tr><td>0.1</td><td>100000</td><td>125</td></tr>
</table></td></tr>
</table>

(ii) Short term limit value (STEL)

Acute toxicity is not relevant and therefore no STEL is given[6]. Asbestos is considered to be a non-threshold carcinogen and an exposure-risk relation is derived for these effects in Chapter 9.1.2. Asbestos also causes non-malignant pulmonary and pleural diseases following long-term exposure.

(iii) Biological guidance and limit values (BGV)

There is no biomonitoring method currently available and no BGV is proposed for asbestos.

(iv) Biological limit value (BLV)

There is no biomonitoring method currently available and no BLV is proposed for asbestos.

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[4] The naming conventions of limit values and notations used here follow the 'Methodology for the Derivation of Occupational Exposure Limits' (SCOEL 2013; version 7) and the Joint ECHA/RAC – SCOEL Task Force report (2017b). [https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145].

[5] The exposure-risk relationship is based on fibre measurements according to the Phase Contrast Microscopy method of WHO (1997).

[6] RAC notes that while some Member States use a fixed ratio between an 8-hour time-weighted average (TWA) and STEL value in absence of specific acute effects, no such convention exists at the EU level.

Biological Monitoring (see section 6 of the Annex 1 for full discussion)

Notations

No notation for 'Skin', 'Skin sensitisation' or 'Respiratory sensitisation' is warranted. Asbestos fibres are not absorbed via the dermal route and there is no reported evidence of asbestos being a skin sensitiser or respiratory sensitiser.

Other considerations

RAC acknowledges the relevance of the related issues identified by ECHA and reported in section 9.4 of Annex 1. These concern (1) health surveillance covered by Directive 2009/148/EC and (2) EU guidance on asbestos removal work. RAC notes that these issues are not directly related to scientific considerations concerning derivation of an OEL for asbestos. These considerations can support the Commission in how these aspects contribute to prevention of asbestos-related ill-health in the EU, in addition to an OEL.

ATTACHMENTS:

Annex 1 gives the detailed scientific grounds for the opinion. The list of references is included in this document.

Annex 2: Comments received on the ECHA scientific report, and responses provided by ECHA and RAC (excluding confidential information).