Dear The Danish Working Environment Authority,

Thank you for the opportunity to comment on the evaluation from the Quality Committee of the report: Asbestos. Scientific basis for setting a health-based occupational exposure limit. We are pleased to note that the Quality Committee agrees with the major decisions in our risk assessment, including selection of critical effect, selection of a non-threshold approach and the use of the Dutch DECOS report for the calculation of risk levels.

However, we retain our suggestion that the expected excess lung cancer risk in relation to occupational exposure to asbestos is 1:1 000 at 0.01 fibres/ml, 1:10 000 at 0.001 fibres/ml, and 1:100 000 at 0.0001 fibres/ml, covering amphibole asbestos. We suggest that this is the best value from a precautionary approach as workers may be exposed to asbestos containing materials made of only amphiboles.

In this document, we respond to the points raised by the Quality Committee. Each rebuttal is provided in italics just below each comment from the Quality committee.

Yours sincerely Niels Hadrup, Anne Thoustrup Saber, Nicklas Raun Jacobsen and Ulla Vogel,

November 8, 2019.

NRCWE's response to the points raised by the Quality Committee

Each rebuttal is provided in italics just below each comment from the Quality committee.)

Short report from the Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Asbestos. Scientific basis for setting a health-based occupational exposure limit.

Members of the Quality committee: Anne Mette Zenner Boisen (Miljøstyrelsen); Anoop Kumar Sharma (DTU Fødevareinstituttet); Mette Lausten Hansen (Arbejdsmedicin AUH); Jesper Bo Nielsen (Institut for Sundhedstjenesteforskning SDU); Vivi Schlünssen (NFA)

This report is based on a meeting 4th September 2019 at AT where the results from the report were discussed after the authors presented the content of the report. The members of the quality committee had the chance to ask questions to the authors.

The Report: Niels Hadrup, Anne Thoustrup Saber, Nicklas Raun Jacobsen and Ulla Vogel. Asbestos. Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA) 2019.

Overall evaluation of the report

The report reviews data relevant for assessing the hazard of asbestos in humans and animals. Furthermore, toxicokinetics and mechanisms of toxicity are reviewed, and core previous risk assessments of asbestos are summarized. The scientific basis for setting an occupational exposure limit (OEL) is presented and based on this, the authors suggest a health based OEL for asbestos.

The structure of the report is a bit challenging to follow, and the committee recommend for future reports to follow the structure used in e.g. the previous report on diesel exhaust particles. Specifically we suggest to move section 7.8 – 8 so they appear before the conclusion.

Authors' response: The structure of the report on asbestos was based on the request from The Quality committee to align structure with SCOEL reports. We will provide the next reports in the format previously used by the authors for e.g. the format used for the documentation report for Diesel exhaust particles.

Some of the scanned tables in the report include reference numbers from original studies not corresponding to the reference list in the current report (for example Table 8 and 12). These reference numbers should be removed.

Authors' response: We deliberately chose to use the reference style of author-date in order to avoid that the numbers can be confused with our references. However, we acknowledge that this point should be addressed in future reports. We suggest that copied tables from other reports are either cropped or added a sentence in the table legend: "that the reference numbers are not relevant for the current report"

The suggested OEL for asbestos is mainly based on results from a previous risk assessment from the Netherlands (DECOS 2010). Similar results were seen in a French risk assessment (Afsset 2009). This approach makes excellent use of previous work, and the quality committee support the use of earlier high quality work from other countries. It would have been a tremendous work to base the Danish OEL on the original evidence only, but would have offered a possibility for an independent evaluation. In the Danish report recent key studies are also included. There is an important paper from 2017 (Olsson 2017) the committee suggest also to add. Furthermore there is a recent paper from Denmark on mesothelioma (Dalsgaard 2019) we also recommend to include in the report.

Authors' response: We acknowledge that these articles could have been included in the current report. However, we have reviewed the two articles and found that the data in these would not have affected our conclusion. Olsson et al (2017) is a case-control study, whereas the dose-response relationship in the DECOS report was based on cohort studies. In general, we consider cohort studies to have the advantage of better exposure assessment as compared to case-control studies, and DECOS specifically had a step for selection of relevant studies, in which the quality of the exposure assessment was evaluated.

The literature search for the report was supported by research librarians, and we recommend including details of searched databases and the search strings including dates for covering of the search as an appendix in the report.

Authors' response: We acknowledge this point and will adapt future reports.

Asbestos are silicate minerals encompassing 6 different silicates, of which one, chrysotile has a serpentine (leaf like) structure and the other 5 have an amphibole structure (a chain-like crystalline structure). There is evidence from studies on humans that both serpentine and amphibole structured asbestos can cause cancer (IARC 1212), even though it is quite evident that serpentine asbestos is a less potent carcinogen for especially mesothelioma.

The authors focus on studies and reports dealing with occupational exposure by inhalation, and the committee supports that decision, as inhalation is the major route of exposure for asbestos.

The suggested health-based OEL is based on human data from epidemiological studies, but the authors also assessed asbestos hazard based on experimental animal studies in order to support the human data. The committee supports the use of epidemiological data as the best suited data for setting a health based OEL for asbestos, and we will not further evaluate the hazard assessed from animal studies. Of note, data from animal studies provided substantially higher asbestos levels for excess lung cancer risk level compared to the estimations based on the epidemiological data.

The authors regard carcinogenicity as the critical adverse effects. Interstitial lung disease caused by asbestos (asbestosis, one of more pneumoconiosis) involving inflammation and fibrotic changes is important, but the authors assessed that asbestosis does not represent the critical effect endpoint for hazard assessment due to a likely threshold mechanism of action for asbestosis in contrast to non-threshold mechanism for cancer. This judgement is supported by the committee.

For completeness the report also includes a section on asbestosis which is highly supported by the committee. Asbestosis is described based on a review and a few originals studies. The report would have benefitted from a more systematic approach to the literature with a special focus on existing dose response studies on asbestosis. As an example Loomis et al also published valuable data on asbestosis from the North Carolina asbestos textile workers cohort (Loomis et al 2009). Furthermore the statement about the unofficial lower limit for recognition of asbestosis (25 fibre years) (Omland et al., 2018) is not relevant and the committee suggest to remove this information from the report.

Authors' response: We acknowledge this but also note that the quality committee agrees that carcinogenicity rather than asbestosis should be considered critical effect, and that most emphasis thus should be on this former endpoint. We agree that the sentence on 25 fibre years taken from a peer-reviewed article by (Omland et al., 2018) could have been omitted.

There is a stronger mechanistic evidence from in vitro studies than in vivo studies for a genotoxic mode of action in inducing the carcinogenic effect of asbestos, but in vitro studies are only sporadically mentioned (section 7.6.3). The author's state that the value of in vitro studies is questionable, which is not supported by the committee. Se for example Huang 2011. The reported positive in vivo studies for genotoxicity are after intratracheal instillation, intraperitoneal injection and oral exposure. There is no genotoxic evidence after the exposure route inhalation. The committee suggests that this should be stated in the report. We suggest to include a more elaborate description (1/2 – 1 page) summarizing the evidence from in vitro studies, including aneugenicity. In Huang et al. 2011 human data for genotoxicity is also provided.

Authors' response: Fibres represent a special biokinetics situation. As other insoluble particles, the interaction between cells and fibers in vivo is difficult to mimic in vitro. Rigid fibres may act in a needle-like fashion penetrating tissues and cells. Therefore, we prioritised in vivo studies reflecting the situation encountered by workers inhaling the fibres. However, we do acknowledge that in vitro studies with fibres interacting with an epithelial cell layer may contribute to the mechanistic evidence. We thus acknowledge that this information could have been included in the current report and we will consider this point for future reports on other compounds. We do note that we have reviewed the literature on in vitro genotoxicity studies with asbestos and that the inclusion of this information would not have changed our conclusion that asbestos should be assessed as having a non-threshold carcinogenic mechanism.

In figure 5, the committee suggests to add Margin of Exposure (MOE) in the box starting with Numerical risk assessment and to add BMDL in the box starting with NOAEL. Both a NOAEL value and a BMDL value can be used to set a health based exposure limit.

Authors' response: We acknowledge that figure 5 could have been adjusted in this way.

One of the studies included in DECOS evaluation (Gustavsson 2002) separates out with a substantial steeper dose-response relation compared to other include studies. The committee suggest the authors to reflect of possible reasons for this difference. It would be useful with more details about the Inserm model used in the French risk assessment report (Afssat 2008).

Authors' response: We acknowledge that these points could have been addressed in the report. DECOS' reflections on the high KL value in the Gustavsson article is as follows:

"The KL value from the study by the case-control Gustavsson68 (study 21) is much higher (a 100×KL value of 21) than that calculated in the cohort studies. This may be (at least partly) because Gustavsson's research population, unlike those in the cohort studies, was born much later (it was a postwar population). Hence, smoking habits and other confounding factors may have played a less prominent role than in the cohort studies. Gustavsson's study also concerned workers with a relatively recent and low level of cumulative exposure. Nevertheless, account must also be taken of the fact that this strong association might be a chance finding. A possible limitation of this study (and one that is inherent to case-control research) is that the characterisation of exposure took place after the event, although it was carried out independently of the epidemiological study. The large standard error for Gustavsson's results means that the study has relatively little influence (low relative weighting) on the outcome of the Committee's meta-analysis."

Setting an occupational exposure limit for Asbestos

The committee supports the decision to use the epidemiological data to derive an OEL for asbestos.

The authors use Danish life time risk of developing lung cancer (0-74 years): 4.9% for men and 4.5% for women.

The authors recommends that DECOS' K_L values are used for setting the OEL and suggest using the most conservative value for amphiboles, for lung cancer and mesothelioma combined.

Based on the assumption that the vast majority of workers in Denmark are only exposed to chrysotile, and based on the assumption that the level of amphibole contamination in chrysotile in Denmark is similar as the amphibole contamination in studies on chrysotile included in the DECOS K_L values, the committee suggest to use the DECOS recommendation for chrysotile for lung cancer and mesothelioma combined as the relevant measure (0.05 fibres/ml for 1/1000 excess cancer risk, table 23). Based on the numbers for prevalence of lung cancer in Denmark more cases are expected in Denmark, and we want to take this into account in the estimate. We suggest to use the ratio in table 24 between The Danish calculations and DECOS own results for lung cancer and asbestos in general (0.03/0.055). We therefore suggest to use 0.05 * (0.03/0.055) = 0.027 fibres/ml for 1/1000 excess cancer risk.

The quality committee therefore suggest the expected excess lung cancer risk in relation to occupational exposure to asbestos is 1:1 000 at 0.027 fibres/ml, 1:10 000 at 0.0027 fibres/ml, and 1:100 000 at 0.00027 fibres/ml.

Authors' response: In essence, the Quality Committee suggests to use data for the less hazardous chrysotile for risk assessment of all types of asbestos. From a precautionary point of view, we disagree with this approach, since we think that a health-based risk assessment of asbestos should be valid for all types of asbestos. We therefore retain the suggestion of expected excess lung cancer risk in relation to occupational

exposure to asbestos is 1:1 000 at 0.01 fibres/ml, 1:10 000 at 0.001 fibres/ml, and 1:100 000 at 0.0001 fibres/ml, covering amphibole asbestos. We suggest that this is the best value as workers may be exposed to asbestos containing materials made of only amphiboles.

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