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

Members of the quality committee: Nellie Anne Martin (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 an online meeting 30th June 2021 headed by 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: Anne Thoustrup Saber, Nicklas Raun Jacobsen, Niels Hadrup, Pernille Danielsen, Sarah Søs Poulsen, Karin Sørig Hougaard and Ulla Vogel. Respirable quartz: Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA), Copenhagen 2021. 978-87-7904-384-8

Erratum: table 1, page 14. The resolution could be improved

Overall evaluation of the report

This well written report reviews data relevant to assessing the hazards of airborne respirable crystalline silica (RCS) in humans, and briefly touch upon hazards in animals. Furthermore, toxico-kinetics and mechanisms of toxicity are briefly reviewed, and previous risk assessments of RCS are summarized. The scientific basis for setting an occupational exposure limit (OEL) are presented and based on this, the authors assess excess lung cancer risk based on four epidemiological studies to be 1:1,000 at 4 µg/m3, 1:10,000 at 0.4 µg/m3 and 1: 100,000 at 0.04 µg/m3 RCS.

The title of the report refers to respirable quartz only, but the report covers RCS in general, so the committee suggest to rename the report (replace quartz with crystalline silica).

Due to the substantial amount of literature the authors widely rely on existing previous risk assessments of RCS. This is clearly stated in the introduction and the committee agrees with the approach but suggests to add a statement (disclaimer) about the implications of this choice (use of conclusions from existing sources, critical appraisal limited). The literature search was performed by a research librarian, and details of searched databases and the search strings are included as an appendix in the report.

In general the included literature is sufficient, with one exception. There is no information about RCS levels in the Danish working population We are aware information is sparse, but there is a paper from 2016 (Total and respirable dust exposures among carpenters and demolition workers during indoor work in Denmark - PubMed (nih.gov), and a PhD dissertation from 2021 by Signe Boudigaard (attached). In line with that, a short section about the number of anticipated exposed workers in Denmark (in total and by occupation/industry) would be helpful, as well as reflections on the usefulness of the presented international evidence base for the Danish labor market.

For some sections it is not clear if "no or limited evidence" is due to missing data or due to studies indicating no effect. Two examples can be found on page 23: "*Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters*" And: *"there is limited evidence in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust"*Is this due to no studies or negative studies for mice/hamster, and tridymite dust and cristobalite dust respectively?

On page 25 (Mechanisms of toxicity) it is stated: *Since a non-threshold mechanism of carcinogenicity cannot be excluded, the present working group considers the mechanism of action to be a non-threshold mechanism of action in the hazard assessment of carcinogenicity*. Since the methodology of the risk calculations in the report relies on the assumption of a non-threshold mechanism, the committee recommend a more comprehensive section on this decision. As an example it would be relevant to know whether there is any animal studies suggesting a direct, primary genotoxic effect, e.g. a mutagenic effect. If these data are lacking it would be helpful to mention this in the text.

The authors focus on studies dealing with occupational exposure by inhalation, and the committee support that decision, as inhalation is the major route of exposure for RCS. We also

agree on the approach to provide a joint evaluation for the different crystalline silica polymorphs because epidemiological and experimental evidence show that quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency.

We lack an overview of the exposure assessment methodology used in the considered human studies, as well as an overview of type of RCS. We therefore suggest to add two more columns to table 9, page 46; one column on type of exposure assessment (e.g. individual measurements, Internal job exposure matrices), and one column on type of RCS (e.g. quartz, mixed RCS).
It would be relevant to reflect on why the authors chose to calculate an un-weighed mean β based for the included studies and not a weighted estimate by e.g. number of participants. Furthermore, it might be a potential problem to exclude well conducted studies due to the use of linear models (and not log linear models), for example Rice et al 2001. We acknowledge the substantial work done by the authors to calculate risk across studies in a uniform way, but still we consider it questionable to exclude high quality studies just because they use an alternative model. In large parts of the spectrum, the difference between the log-linear and the linear models probably do not differ very much.

Scientific bases for an occupational exposure limit for RCS
The authors based the suggested health-based OEL on data from human studies, and consider lung cancer and silicosis as the critical endpoint, and the Committee agree on these decisions, and also the decision to finally use the cancer studies (and not the silica studies), due to more and comparable data with a high transparency for lung cancer compared to the silicosis studies.

All the included quantitative studies on lung cancer risk provided consistent and robust dose-response relationship between cumulative exposure to crystalline silica and lung cancer. The authors chose to base the risk estimation of cancer risk on four individual studies with log-linear equations (Attfield & Costello, 2004; Hughes et al., 2001; Miller & MacCalman, 2010, and Liu et al., 2013. The equation for the log-linear relationship between relative risk (RR) and cumulative exposure (E, mg/m3*years) was: RR= exp(0.107*E)

Based on this equation, the expected excess lung cancer risk based on an un-weighed mean β was 1:1,000 at 4 µg/m3, 1:10,000 at 0.4 µg/m3 and 1: 100,000 at 0.04 µg/m3 RCS.

The quality committee agree on the suggested excess lung cancer risk. 1:1,000 at 4 µg/m3, 1:10,000 at 0.4 µg/m3 and 1: 100,000 at 0.04 µg/m3 respirable crystalline silica.

Of note, the risk estimates allowing 1: 1000 excess lung cancer cases or less are possible close to ambient air concentrations of RCS, as mention on page 16 (citation from IARC (2012). A few lines about existing ambient RCS levels would be of relevance for subsequent regulatory decisions.

References

Attfield MD, Costello J. Quantitative exposure-response for silica dust and lung cancer in Vermont granite workers. American Journal of Industrial Medicine 2004;45(2):129-138. doi:10.1002/ajim.10348

Hughes JM, Weill H, Rando RJ, Shi R, McDonald AD, McDonald JC. Cohort mortality study of North American industrial sand workers. II. Case-referent analysis of lung cancer and silicosis deaths. Annals of Occupational Hygiene 2001;45(3):201-207. doi:10.1016/S0003-4878(00)00078-8

IARC. Arsenic, metals, fibres and dusts. Lyon: International Agency for Research on Cancer, 2012. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100C.

Liu YW, Steenland K, Rong Y, Hnizdo E, Huang XJ, Zhang H, Shi TM, Sun Y, Wu TC, Chen WH. Exposure-response analysis and risk assessment for lung cancer in relationship to silica exposure: a 44-year cohort study of 34,018 workers. American Journal of Epidemiology 2013;178(9):1424-1433. doi:10.1093/aje/kwt139

Miller BG, MacCalman L. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. Occupational and Environmental Medicine 2010;67(4):270-276. doi:10.1136/oem.2009.046151

OSHA. Occupational exposure to respirable crystalline silica [Docket No. OSHA-2010-0034]. Federal Register 2016;81(58):16286-16890.