Dear Danish Working Environment Authority,

Thank you for the opportunity to comment on the evaluation from the Quality Committee of the report: Respirable quartz. 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 suggested risk levels.

Below, 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 Anne Thoustrup Saber, Nicklas Raun Jacobsen, Niels Hadrup, Pernille Danielsen, Sarah Søs Poulsen, Karin Sørig Hougaard and Ulla Vogel

December 1st, 2021.

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

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 June 30th 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.

Response: The quality of table 1 has been 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.

Response: Thank you!

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).

Response: The title refers to respirable quartz because we were asked by the Danish Working Environment Authority to reassess the documentation for the Danish occupational exposure limit for respirable quartz. However, based on the literature review the present working group concluded that quartz and two other silica polymorphs, namely cristobalite and tridymite, have similar toxicity and carcinogenic potency. We have renamed the report "Respirable quartz and other crystalline silica polymorphs".

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.

Response: We note that we have used the same approach as in our previous reports. We always rely on the conclusions by IARC, when available, as part of the mutual data acceptance for WHO institutes. The selection of studies were based on the report by OSHA (and a literature search by NFA for the period after the OSHA evaluation), but the OSHA key studies were evaluated by the working group.

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.

Response: We agree that information on exposure is important. However, our report is focused on a toxicological evaluation and not exposure. Therefore, our literature search did not capture the paper by Kirkeskov et al (2016) and we had not included information on the number of persons exposed. The reported geometric mean of respirable crystalline silica dust levels for demolition workers by Kirkeskov et al., 2016[1] (0.12 mg/m³) were higher than in the Swedish study by Hedmer et al. (2017) that

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[1] Kirkeskov L, Hanskov DJA, Brauer C. Total and respirable dust exposures among carpenters and demolition workers during indoor work in Denmark. J Occup Med Toxicol 2016; 11:45. doi: 10.1186/s12995-016-0134-5

we have referred to in our report. In that study, the geometric mean value for quartz was 0.02 mg/m^3, while the highest measured concentration was 17 mg/m^3.

We have now included a small paragraph about the study by Kirkeskov et al. (2016) in the revised report "In a Danish study from 2016, measurements of total and respirable dust and respirable crystalline silica were performed by personal sampling among demolition workers doing different indoor work tasks in 5 companies. In total, 20 measurements of total dust, and 11 measurements of respirable and 11 of respirable crystalline silica were performed. The geometric mean of total dust was 22.3 mg/m^3 (geometric standard deviation 11.6), respirable dust concentrations of 1.06 mg/m^3 (0.10–10 mg/m^3), and for respirable crystalline silica of 0.12 mg/m^3 [<0.01 (no detectable crystalline silica) to 0.92 mg/m^3]. The authors calculated 8-h-TWA for respirable crystalline silica to be 0.08 mg/m^3 for all the measurements and found that 45 % of the 8-h-TWA of respirable crystalline silica for demolition workers exceeded OEL (by up to 2.4 times the present Danish OEL of 0.1 mg/m^3). The authors stressed that the concentrations of respirable crystalline silica were above the OEL even though the respirable dust level was below the OEL for respirable dust. Only a few of the workers used respiratory protection (Kirkeskov et al, 2016)." and adapted the summary in the chapter on "Human Exposure" to take the Swedish study into account."

Furthermore, we have adapted the exposure part of both the Executive summary and the Conclusion to take the Kirkegaard study into account.

The ph.d. dissertation by Signe Boudigaard is not included in the report because our literature search was finalized end of 2019 and the ph.d. defence took place February 2021.

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?

Response:

Thank you for this comment.

Since an extensive literature on epidemiological studies of high quality was available, we did not evaluate individual animal experiments. Instead, we chose to rely on IARCs classification on cancer in experimental animals. We have added some extra comments below.

We searched the document for the use of the term "no or limited evidence". As far as we can see, in addition to the use of "limited evidence" on p.23 it only occurs on p.35 in the paragraph on IARC in "Previous evaluations". Since the intention with the paragraph on previous evaluations is just to provide the conclusions made by other organizations, we will only comment on the use of limited evidence on p.23.

IARC uses the classification "limited evidence of carcinogenicity in experimental animals" in the following cases: "The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs". If no data are available, IARC classifies the compound as having "inadequate evidence of carcinogenicity".

In general, most of the referred studies are studies in rats. However, some studies are in hamsters and mice as well. We have added the following text: "The present working group notes that most of the referred studies in the IARC monography are studies in rats. However, some studies are in hamsters and mice as well. IARC report the following inhalation studies: mouse (1 study, no significant increase in lung tumours), rat (4 studies, significant increase in lung tumours in all studies) and hamster (1 study, no significant increase in lung tumours).) In general, hamsters and mice are more resistant than rats to the induction of lung cancer following exposure to particles. Furthermore, the present working group notes that only a few animal experiments with tridymite and cristobalite dust have been performed. In a single experiment tridymite and cristobalite induced lymphomas.". (

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.

Response: IARC mentions three suggested mechanisms for carcinogenicity of crystalline silica in rats and states that the mechanism in humans is unknown: 1) inflammation-induced carcinogenicity, 2) extracellular generation of free radicals by crystalline silica resulting in depletion of antioxidants and cell injury followed by epithelial cell proliferation, and 3) direct, primary genotoxicity caused by generation of free radicals by crystalline silica particles taken up by epithelial cells (IARC, 2012). IARC considers "the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown, which of these mechanisms occur in humans exposed to crystalline silica dust" (IARC, 2012). As mentioned in the report (p.26) IARC conclude that one of the proposed mechanisms for carcinogenicity of crystalline silica in rats is that crystalline silica particles are taken up by epithelial cells followed by generation of free radicals that can induce direct genotoxicity by interaction with the DNA. As also stated in the report, we follow the precautionary approach recommend by ECHA: "It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice. For mutagens/carcinogens, it should be stressed that the Carcinogens and Mutagens Directive (2004/37/EC) requires that occupational exposures are avoided/minimised as far as technically feasible. As REACH does not overrule the Carcinogens and Mutagens Directive, the approach to

controlling workplace exposure should therefore comply with this minimisation requirement."(ECHA, 2012).

We have inserted the following paragraph:

"The present working group notes that crystalline silica exposure induces inflammation and generation of reactive oxygen species. Reactive oxygen species are both generated at the surface of crystalline particle surface and by inflammatory particles exposed to crystalline silica. This means that crystalline silica exposure may induce both primary and secondary genotoxicity".

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.

Response: We are pleased to note that the Quality Committee agrees with this decision.

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).

Response: We agree that this is a good suggestion: The type of crystalline silica and the type of exposure measurement is now included in the revised Table 9. By a mistake, we wrote that only one study stated that the exposure was "essentially" pure quartz (Hughes et al. 2001). Actually, two studies reported that the exposure was "essentially/mainly" pure quartz (Hughes et al, 2001; Miller and MacCalman, 2001). This has been corrected in the revised report and does not affect the conclusions.

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.

Response: We agree that the Rice et al study is a high quality study and note that the risk estimates obtained by linear modelling results in similar excess cancer risk as obtained by using the unweighted mean β in the log linear model.

We chose to calculate an un-weighed mean β because it is difficult to decide which parameter that would be the most relevant for the calculation of a weighed mean. Other factors than the number of participants such as the quality (e.g. confounder control, exposure assessment method, follow-up period

of the study may be relevant for such a calculation). In addition, this is the previously used method[2,3].
Therefore, we find it most transparent to calculate an un-weighed mean.

The corresponding risk estimates for the Rice study are added to the table below

Studies	Model	Exposure unit	Excess risk			
			1:100	1:1000	1:10,000	1:100,000
			Concentration of silica in µg/m³			
Log-linear						
Attfield and Castello, 2004	Log-linear: RR=exp(0.19*E)	mg/m³ years	21.32	2.32	0.23	0.02
Hughes et al., 2001	Log-linear: RR=exp(0.13*E)	mg/m³ years	31.17	3.39	0.34	0.03
Miller and MacCalman, 2009	Log-linear: RR=exp(0.0524*E)	mg/m³ years	77.32	8.40	0.85	0.08
Liu et al., 2013	Log-linear: RR= exp(0.055*E)	mg/m³ years*	73.67	8.00	0.81	0.08
NRCWE calculation of log-linear studies with a mean β	Log-linear: RR= exp(0.107*E)	mg/m³ years*	**37.87**	**4.11**	**0.41**	**0.04**
Linear						
Rice et al., 2001	Linear: RR= 1 + 0.1441 * E	mg/m³ years	30.84	3.08	0.31	0.03

*We have added the following sentence to the report: "The present working group notes there is
consistency between the risk estimates of the selected studies and the Rice et al study despite the fact
that Rice et al, 2001 is based on linear modeling and the un-weighed calculation is based on log-linear
studies."*

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
1:1000 at 4 µg/m³, 1:10,000 at 0.4 µg/m³ and 1:100,000 at 0.04 µg/m³ RCS.

[2]Saber et al. Diesel exhaust particles: Scientific basis for setting a health-based occupational
limit. København: Det Nationale Forskningscenter for Arbejdsmiljø 2018.

[3]Saber et al. Chromium (VI) compounds: Assessment of SCOEL/REC/386. København: Det Nationale
Forskningscenter for Arbejdsmiljø 2019.

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.

Response: We are pleased to note that the Quality Committee agrees with the suggested risk levels.

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.

Response: This is a highly relevant remark. IARC notes that "it has been estimated that respirable crystalline silica levels in the low µg/m³ range are common in ambient air" (IARC, 1997) and this information has been included in the Executive summary, conclusion and the paragraph on human exposure.