Commentaar op conceptadvies Respirabel kristallijn silica

Comments on draft report Respirable crystalline silica

Dit document bevat de letterlijke weergave – in het Engels - van de commentaren van:

- NIOSH, *National Institute for Occupational Safety and Health* (commentaar van 5 reviewers)
- EOROSIL, *European Association of Silica Producers*
- Ceasar Consult, op verzoek van Koninklijke Metaalunie en Vereniging FME

This document contains the comments by:

- NIOSH, *National Institute for Occupational Safety and Health* (comments by 5 reviewers)
- EOROSIL, *European Association of Silica Producers*
- Koninklijke Metaalunie en Vereniging FME, by Ceasar Consult

Comments on DECOS draft document on Respirable Crystalline Silica

By: Eric J. Esswein, Industrial Hygienist
NIOSH/Western States Division
Denver, Colorado, USA

PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	The Committee's recommendations are sensible based on the evidence considered. The references cited are relevant and comprehensive. However, sensible does not always imply achievable in workplaces where respirable crystalline silica (RCS) aerosols are generated on a regular, ongoing basis and the effectiveness of controls may vary over time. The Committee's recommendation of a time-weighted average (TWA) of 0.38 µg/m^3 while highly protective and analytically achievable, is questionably achievable in workplaces where respirable crystalline silica (RCS) aerosols are generated on a routine basis especially workplaces where engineered stone is fabricated. Even with modern and highly efficient local exhaust ventilation systems, excellent housekeeping and worker training, such an exquisitely low concentration may be unrealistic. However, the proposed criterion of 36.3 µg/m^3 as a TWA may be more feasible in workplaces where RCS aerosols are generated and even in some workplaces where engineered stone is fabricated and the hierarchy of controls are effectively implemented including, engineering and administrative controls (housekeeping, policy and procedures and worker training), but even then personal protective equipment (respirators) may be required but would depend on ongoing confirmation of effectiveness of controls and frequent exposure assessments. In some cases the former proposed criterion of 0.38 µg/m^3 could approach or exceed ambient air concentrations in locations proximal to mining, quarrying, or other operations where RCS aerosols are generated.
Specific Comments	
Page 7, line 23	Move the word "cases" after the word "numerous" so the sentence reads: numerous cases of silicosis.
Page 8, lines 7, 25, and 36	Check spelling of the word "developing" and add the word "to" between the words "exposure and respirable." Check the spelling of the word "ischemic."
Page 9, line 6	Spell out the words for the abbreviation ANCA first time it is used.
Page 11, lines 26–28	Insert "as time-weighted averages" after the values for excess lung cancer risk. These values are based on a 40-year working period, which could also be added.

Page 17, line 10	Insert the word "respirable" after the word "of" to read respirable particles.
Page 19, Table 4b	Insert the words "in respirable dust" in remarks column for NIOSH method 7602. Similar comment for NIOSH method 7603.
Page 22, lines 8 and 11–19	Check spelling of word "desserts" and suggest revising it to "deserts." Consider including oil and gas extraction/hydraulic fracturing in work practices where exposures can occur. Reference is: Esswein EJ, Breitenstein M, Snawder J, Kiefer M, Sieber WK. Occupational exposures to respirable crystalline silica during hydraulic fracturing. J Occup Environ Hyg. 2013;10(7):347-56. doi: 10.1080/15459624.2013.788352. PMID: 23679563
Page 23, Table 5	Add oil and gas extraction, hydraulic fracturing to industry or activity list. Operations are sand transport and pneumatic handling; source material is quartz sand.
Page 25, line 13	The words "time-weighted average" (TWA) should be added after numerical values for silica exposures. This should be the case throughout the document.
Page 30, line 3	Suggest including the words: "source strength rate of emissions and controls if any are employed" after the word particles or integrate these into the paragraph. Source strengths of emissions are important for exposure and dose.
Page 31, line 7	Add the word "respirable" to crystalline silica particles.
Page 37, line 20	Revise spelling of possitive" to "positive."
Pages 53–54 Table 8a	Add the word "respirable" to the silica polymorphs.
Page 58, line 3	Suggest changing the word "eldest" to read "oldest."
Page 59, line 28	Revise spelling of word "respirabel" to "respirable."
Page 64, line 3	Add a space between the words literature and search.
Page 66, line 14	Revise spelling of the word "diatomaceous."
Page 68, line 9	Insert a space between the words therefore and less.
Page 69, lines 4 and 10	Revise the spelling of "quite" to read "quit." Should the phrase "smoking 20 cigarette packs per day" be better stated as "smoking a pack of 20 cigarettes per day."?
Page 78, section 9.7	Groups at extra risk also include workers with co-exposures to occupational carcinogens, diesel particulate matter, radon, asbestos, benzene, and polycyclic aromatic hydrocarbons.

Comments on DECOS draft document on Respirable Crystalline Silica

By: Aaron L. Sussell, Epidemiologist
NIOSH/Spokane Mining Research Division
Spokane, Washington, USA

PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	None.
Specific Comments	
Page 27, lines 3–11	Suggested revisions are in **bolded** text and strikethrough: "In recent years an overall decline in respirable crystalline silica levels was observed, some results of recent respirable crystalline silica measurements are shown in table 7. Despite the overall decline in respirable crystalline silica levels, Misra et al. (2023) [38] report an increase in mean exposure levels in American metal and non-metal mines for the years 2018 (geometric mean = 0.0459 mg/m^3) and 2019 (geometric mean = 0.0529 mg/m^3) compared to the overall mean exposure level (geometric mean = 0.0289 mg/m^3) for the period 2000 to 2019. The authors explained this increase in 2018 and 2019 by a **possible** change in sampling strategy, **with more focus on sampling** ~~where especially potential 'high risk'~~ **maximum risk workers or** occupations in ~~are selected for~~ **annual** sampling campaign**s** with fewer total measurements [38]."

Comments on DECOS draft document on Respirable Crystalline silica

By: Pius Joseph, Research Toxicologist
NIOSH/Health Effects Laboratory Division
Morgantown, West Virginia, USA

PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	Abbreviations used – the list (Annex B – Abbreviations, page 105) does not have all the abbreviations used in the report. Also, spell out the first place in the report where the abbreviation is used.
Specific Comments	
Page 6, line 25	State the rationale for evaluation of the respirable crystalline form – it is the toxic form.
Page 7, line 1	Change "widely" to "wide."
Page 7, line 15	The abbreviation, RCS, for Respirable Crystalline Silica is widely used in the literature. Suggest using the abbreviation throughout the document.
Page 7, lines 11–12	The second sentence is a confusing statement—silica is known for its prolonged retention in the lungs which is primarily responsible for its health effects. A statement reflecting this idea is more appropriate. The statement is also somewhat in contradiction to what has been described under section 5.1.1 Absorption, pages 30 and 31.
Page 7, lines 23–24	Revise the statement to indicate that accelerated silicosis has been reported in workers involved in manufacturing as well as fabrication of products using artificial stone. For example, the US does not manufacture artificial stone. The many cases of silicosis, including death, reported in the US were among workers engaged only in the fabrication of engineered stone countertops.
Page 7, line 32	Change "lung inflammation" to "persistent lung inflammation."
Page 9, line 6	Spell out ANCA.
Page 22, lines 13–19	Fracking or hydraulic fracturing is an occupation with significant, including excessive, exposure to RCS. Reference is Esswein et al. [2013]. Occupational exposures to respirable crystalline silica during hydraulic fracturing. J Occup Environ Hyg 10:347–56); it should be listed here. Also, include this information in Table 5 on page 23.
Page 25, lines 34–37	Include fracking and the relevant reference here, too.
Page 29, lines 5–7	Include relevant reference(s) to support the statement.
Page 29, line 13	Not sure how the "occurrence of other chemicals (e.g. resin)" results in the reported differences in the exposure to RCS. Other chemicals are likely to influence the health effects potentially resulting from exposure to RCS, originating from artificial stone products. Need to revise to clarify this point.

Page 18, lines 1–3 and page 30, lines 6–9	Which aerodynamic diameter of RCS (4 or 5 um) is correct for alveolar deposition?
Page 45, Section 6.5. Genotoxicity	Consider providing relevant citations in this section.
Page 48, Figure 1	Consider moving Figure 1 to page 46, prior to sub-section 7.1. where it is first mentioned.
Page 54, line 19	Eldest? Or earliest?
Page 58, line 3	Eldest? Or oldest?
Page 78, sub-section 9.7. Groups at extra risk	Gene polymorphism is another factor to consider here. There are reports regarding the role of specific gene polymorphisms on human susceptibility to silicosis.
Page 79, Section 10. Research needs	It is very well known that chest X-ray, the most employed technique to detect silicosis in the clinic, lacks the required sensitivity to detect all cases of the disease, especially those in the early stage. This has resulted in underreporting of silicosis cases (false negatives, as stated on page 58, lines 8-13 of this report). NIOSH has addressed this issue in your reference 11 (National Institute for Occupational Safety and Health (NIOSH). (2002). Hazard Review: Health Effects of Occupational Exposures to Respirable Crystalline Silica. US Department of Health and Human Services (NIOSH). Publication No. 2002-129; Available at: https://www.cdc.gov/niosh/docs/2002-129) and recommended the development of highly sensitive and practical approaches (non-invasive or minimally invasive biomarkers) for early detection of silicosis. This may also be considered as a research need.

Comments on DECOS draft document on Respirable Crystalline Silica: Evaluation of Health Hazards as Basis for an Occupational Exposure Limit

By: Chen Wang, Senior Service Fellow
NIOSH/Health Effects Laboratory Division
Cincinnati, Ohio, USA

PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	Need to update information of analytical methods in Tables 3 and 4a–4c in section 2.3.
Specific Comments	
Page 18, line 17	Remove "spectrometry" after "X-ray diffraction (XRD)" and all other places throughout the document.
Page 18, Table 3	Row 2 Add the following CEN methods: 1) "EN 13205-1:2014, Workplace exposure - Assessment of sampler performance for measurement of airborne particle concentrations - Part 1: General requirements" 2) "EN 13205-2:2014, Workplace exposure - Assessment of sampler performance for measurement of airborne particle concentrations - Part 2: Laboratory performance test based on determination of sampling efficiency"

Page 19, Table 4a	Row 2 1) Update OSHA Method ID-142 V4.0 reference: https://www.osha.gov/sites/default/files/methods/osha-id142.pdf 2) Update the measurement range and the reliable quantitation limit (RQL) from ID-142 method. Row 3 1) Add a reference for "MSHA Method P-2." Row 4 1) Remove method HSE MDHS 51/2; this method has been replaced by MDHS 101/2. Row 5 1) Update reference and corresponding range and LOD for the latest version HSE MDHS 101/2. https://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs101.pdf 2) This method is a direct-on-filter method, add a note to differentiate it from other re-deposition methods. Row 6 1) Update to the latest version ISO 24095:2021. 2) Also include two ISO methods: - ISO 16258-1:2015, "Workplace air Analysis of respirable crystalline silica by X-ray diffraction, Part 1: Direct-on-filter method" - ISO 16258-2:2015, "Workplace air Analysis of respirable crystalline silica by X-ray diffraction, Part 2: Method by indirect analysis"

Pages 19–20, Table 4b	Rows 1&2 1) Update the reference, measurement range and LOD for the latest version NIOSH 7602 and 7603 methods from 5th Ed. NMAM https://www.cdc.gov/niosh/nmam/pdf/7602.pdf https://www.cdc.gov/niosh/nmam/pdf/7603.pdf Row 3 1) Add a reference to the latest version MSHA method P-7, update method's measurement range and LOD. https://arlweb.msha.gov/Techsupp/pshtcweb/MSHA%20P7.pdf Rows 4&5 1) Remove method HSD MDHS 37 and 38. They have been replaced by MDHS 101/2. Row 6 1) Update reference and corresponding measurement range and LOD for the latest version HSE MDHS 101/2. https://www.hse.gov.uk/pubns/mdhs/pdfs/mdhs101.pdf 2) This method is a direct-on-filter method, add a note to differentiate it from other re-deposition methods. Row 7: 1) Update to the latest version ISO 24095:2021.
Page 20, Table 4c	Update the NIOSH method 7601 reference https://www.cdc.gov/niosh/docs/2003-154/pdfs/7601.pdf

Comments on DECOS draft document on Respirable Crystalline Silica

By: Faye L. Rice, Health Scientist (Policy)
NIOSH/Division of Science Integration
Cincinnati, Ohio, USA

PAGE NUMBER, LINE NUMBER	COMMENT
General Comments	-Congratulations to the authors of this extensive draft document. Respirable crystalline silica is a very large topic with many health effects to consider. -Abbreviations list (Annex B) is incomplete. Many epidemiological abbreviations are missing. -The reference list contains references with missing author names, often the second author. Suggest checking entire list. -Artificial stone: suggest conducting a search for "engineered stone" and/or "countertop" in the NIOSHTIC-2 database and adding references to your draft as needed. There are 30 entries with the term "engineered stone" in NIOSHTIC-2 now: https://www2a.cdc.gov/nioshtic-2/advsearch2.asp -When cumulative exposure is mentioned, the exposure should be mentioned, too. It could be respirable dust or respirable crystalline silica or respirable quartz, for example.
Specific Comments	
Page 6, line 16	Change "protecting" to "protect."
Page 6, line 29	Change "temperature" to "temperatures."
Page 7, line 1	Change "widely" to "wide."
Page 7, line 7	Change "composes" to "present" for clarity.
Page 9, line 14	Change "oesophageal" to "oesophagus."
Page 9, line 36	The sentence "One pooled analysis…" is incomplete.
Page 11, line 23	Change "have set" to "have recommended or set."
Page 12, line 3	The word "both" seems to be misplaced.
Pages 13–14 and Annex A	The literature search strategy did not appear to include "autoimmune" as a search term. Two epidemiologic studies published after 2019 from my own small database: -Blanco-Pérez et al. [2022]. Prevalence and clinical impact of systemic autoimmune rheumatic disease in patients with silicosis. Arch Bronconeumol 2021 Vol. 57 Issue 9 Pages 571–576 DOI: 10.1016/j.arbr.2021.06.003 -F. Mehri, E. Jenabi, S. Bashirian, F. G. Shahna and S. Khazaei [2020]. The association between occupational exposure to silica and risk of developing rheumatoid arthritis: a meta-analysis. Saf Health Work Vol. 11 Issue 2 Pages 136–142, PMCID: PMC7303526 DOI: 10.1016/j.shaw.2020.02.001

Page 15, line 3	Check that crystalline silica is actually **a metal oxide** as stated here and provide a reference.
Page 15, lines 19–23	Please provide supporting references for the statements in this paragraph.
Page 16, line 1	Provide references for the information presented in Table 1. Insert "forms of" after "common" in the Table's title.
Page 17, line 7	Provide references for the information presented in Table 2.
Page 21, line 4	Suggest adding "crystalline silica-containing" before the word "sand" because there are other types of sands. Line 8 needs no change because it says "Crystalline silica sand…".
Page 21, lines 8 and 9	Reference needed for silica content and impurities percentages.
Page 21, lines 18 and 19	Reference needed for content of silica in artificial stone.
Page 25, lines 33 and 34	This sentence is important—reported exposure levels still exceed limits. Suggest adding "recommended" before or after "legislated."
Page 26, line 4	Change "impression on" to "impression of."
Page 27, Table 6 footnote	Check spelling of "arithematic." Page 38, line 5 has "arithmetic."
Page 28, Table 7	Check the units reported by reference 33 (European Industrial Minerals Association). An erratum was issued in Occupational and Environmental Medicine to correct the unit reported in one sentence from milligram to microgram. Link: https://doi.org/10.1136/oemed-2019-106074corr1
Page 28, section 4.2	For your information, Australia has become the first country to ban engineered stone because of silicosis risk. See this December 2023 news article in British Medical Journal (BMJ): *BMJ* 2023; 383 doi: https://doi.org/10.1136/bmj.p2954
Page 30, line 11	Change "het mucoscilliary" to "the mucociliary."
Page 32, line 1	Replace the comma after "well" with a semicolon or a period.
Page 32, line 4	Change "thusfar" to "thus far."

Page 33, lines 8–11	This paragraph discusses reasons for "differences in toxic potential." The Health and Safety Executive (HSE) published two hazard assessment documents about respirable crystalline silica: Phase 1 (EH 75-4) reviewed the factors relating to the fibrogenic potency and Phase 2 (EH 75-5) covered carcinogenicity. Please consider including them. Free downloads are available: Phase 1 document (fibrogenic potency and silicosis): https://www.hse.gov.uk/pubns/priced/eh75-4.pdf Phase 2 document (carcinogenicity): https://www.hse.gov.uk/pubns/priced/eh75-5.pdf This reviewer wrote a short review of the above documents that was published in The Annals of Occupational Hygiene: Rice FL [2004]. Ann Occup Hyg 48(4):379–380, https://doi.org/10.1093/annhyg/meh026 The HSE documents could also be cited in Section 7.1 (surface and structural factors).
Page 34, line 7	Change "prosessing" to "processing."
Page 34, line 8	Change "overal" to "overall."
Page 34, line 31	The word "monotonic" could be restated as "monotonically."
Page 34, lines 35–37	Change "report" to "reported" and "is" to "was." The phrase about the reference category could be written as a separate sentence or placed in parentheses to improve readability.
Page 35, lines 26–34	A possible additional reference for the silicotuberculosis section: Rajavel S, P. Raghav, M. K. Gupta and V. Muralidhar [2020]. Silico-tuberculosis, silicosis and other respiratory morbidities among sandstone mine workers in Rajasthan- a cross-sectional study. PLoS One Vol. 15 Issue 4 Pages e0230574 Accession Number: 32298271 PMCID: PMC7162522 DOI: 10.1371/journal.pone.0230574
Page 36, line 8	Define the abbreviation "HIV."
Page 36, line 11	Reference needed for sentence about lung cancer being "the most diagnosed malignant disease worldwide."
Page 37, line 16	Insert a comma after "exposure."
Page 38, lines 4, 15, 18, and 33	"Average exposure levels:" state what substance was measured. Define "SIR" the first time it is used. Line 18: the phrase "chronic lower levels" is unclear; if it means a period of time, please indicate. Line 33: change "appears" to "appear."

Page 39, line 21	Change “was” to “were.”
Page 39, lines 31–37	Define heterogeneity measure “I^2.” Some percentages are reported with commas instead of decimal points.
Page 40, line 21	Indicate what exposure was measured in “cumulative exposure…”.
Page 41, lines 15–18	Define the abbreviation BMI. Change “seamingly” to “seemingly” and replace the comma after “healthy worker effect” with a semi-colon or make it a separate sentence.
Page 41, lines 22–35	Change present tense verbs to past tense, define I^2, and state what substance was measured for cumulative exposure.
Page 42, lines 14–17	The paragraph states that “strong evidence” was based on “more than ten studies” but that “the classification” was based primarily on one study. Please clarify.
Page 43, lines 16–34	The study descriptions in the rheumatoid arthritis section do not provide information about specific jobs or occupations. If known, it would be helpful to include occupational information as well as the “exposure” mentioned in cumulative exposure.
Page 44, line 12	Change “affect” to “affects.”
Page 44, lines 21–32	A study and a letter for your information: -Seaton A [2020]. Silica dust and sarcoidosis. Occup Med (Lond) 70(2): 139 Accession Number: 32311042 DOI: 10.1093/occmed/kqaa016- this reference is a letter written in response to the following study: - E. Jonsson, B. Jarvholm and M. Andersson [2019]. Silica dust and sarcoidosis in Swedish construction workers. Occup Med (Lond) Accession Number: 31504840 DOI: 10.1093/occmed/kqz118
Page 48, figure 1	Figure 1 is a color illustration. Please clarify the source of the illustration (i.e., an original design or borrowed from another source.)
Page 49, lines 22–26	Please provide a reference for this statement about the pathogenesis of acute and accelerated silicosis. Is “oxygen-free radicals” the correct phrase to use?
Page 50, line 8	Change “Subcommittees” to “Subcommittee’s.”
Page 51, lines 1–10	This paragraph about COPD mechanisms has no references except one at the end that was published in 2003.
Page 54, lines 5–7	Footnote 1 about the OSHA permissible exposure limit (PEL) is confusing because it seems to include the former PEL at the end. Suggest checking the punctuation at least.

Page 54, Table 8b	Row 4 cites the NIOSH hazard review document (reference 11). In that document, the NIOSH recommended exposure limit (REL) is not stated as an 8-hour time-weighted average as presented in Table 8b's heading. (See reference 11, Table A–1.) Annex C of the draft document has the correct information about the NIOSH REL, taken from the hazard review document, reference 11.
Page 55, lines 12–14	The NIOSH hazard review document (reference 11) did not use the phrase "human carcinogen." NIOSH used the phrase "potential occupational carcinogen" and NIOSH made the statement **before** the IARC 1997 and ATS statement. Please revise the sentences to reflect reference 11's information. Suggest deleting lines 13 and 14 about "based on the extensive evaluations" by IARC 1997 and ATS. Your Table C2 in Annex C (page 116) has the language from the NIOSH hazard review.
Page 55, line 23	"…their evaluation report" (OSHA) is mentioned and reference 8 is cited. A little more information needs to be added to reference 8. It appears that you may be citing the OSHA 2016 crystalline silica final rule, not an evaluation report.
Page 56, line 1	Change "programme" to "program."
Page 61, lines 22–23	Change "absense" to "absence" and "developing" to "developing."
Page 62, line 29	"Criterium" does not seem to be the correct word. Maybe "criteria" if plural.
Page 63, line 3	Change "literaturesearch" to "literature search."
Page 66, lines 7 and 14	Suggest inserting "and" before "the exposure-response trends…". Fix spelling of diatomaceous.
Page 68, lines 9 and 30	Change "thereforeless" to two separate words. Change "subjects" to "subject's."
Page 69, lines 22–23	Change "for the control of" to "to control for the effects of…".
Page 70, lines 11–25	These paragraphs have incomplete sentences and could benefit from editing for grammar and punctuation.
Page 71, lines 31–33	The sentence about the IARC conclusion being based mainly on the pooled study may be an overstatement. This reviewer suggests a review of the sentence; perhaps include a direct quotation from IARC monograph 100C.

Page 77, line 17	Reference 157 is cited as the source for occupational exposure limits in some European countries. Recommend adding more information to reference 157 to enable readers to retrieve it. Is it here? https://nepsi.eu/wp-content/uploads/2022/10/oel_full_table_september_2020_europe.pdf
Page 79, all lines	This reviewer suggests consulting the research needs chapter (6) of reference 11 (NIOSH Hazard Review, Publication 2002-129) for more research need ideas.
Page 83, line 7 (References)	The second author's name (Sussell AL) is missing from Reference 38 (first author Misra S).
Page 88, line 1	Author names appear to be missing from reference 103.
Annexes	Not closely reviewed by this reviewer.

European Association of Silica Producers A.I.S.B.L.
Member of IMA-Europe

Comments on the Dutch Expert Committee on Occupational Safety's reliance on Ge et al. (2020) in their public draft report "Respirable crystalline silica: Evaluation of health hazards as basis for an occupational exposure limit"

Collaboration of the Dutch Expert Committee on Occupational Safety DECOS), a Committee of the Health Council of the Netherlands, and the Nordic Expert Group (NEG) for Criteria Documentation of Health Risks from Chemicals, Version 9, last meeting 8 December 2023

Background and Summary Conclusions

We understand that Expert Committee (members from DECOS and NEG) intends to submit the Draft Report to the Subcommittee on Occupational Exposure Limits of the Social and Economic Council (SER-GSW) of the Netherlands, and are inviting comments from employers' organisations, trade unions, and other interested parties which will be considered in finalizing the advisory report. We appreciate this opportunity to comment, and on behalf of EUROSIL, we submit the following comments addressing the fundamental question of whether the associations between exposure to respirable crystalline silica and silicosis and lung cancer scientifically are well established.

Based on our own epidemiological research on workers in the German Porcelain Industry (performed on behalf of EUROSIL and the German Verwaltungs-Berufsgenossenschaft) including a 15-year update of this cohort (to be published later this year), we believe that the relationship between exposure to relatively high concentrations of respirable crystalline clearly demonstrates an exposure threshold for silicosis risk. Among the same cohort, even with additional follow-up of 15 years and a total of 284 lung cancer deaths, we see no excess risk at any level of exposure. The updated study results are summarized below, but not yet published. Thus, if respirable crystalline silica causes lung cancers, it likely does so at exposure levels greater than those historically sustained in the German Porcelain Industry that clearly were associated with increased silicosis risk.

Other publications present results consistent with these. However, because the Expert Committee relied heavily on the pooled analysis by Ge et al. (2020), we will focus on what that study reports. We commend the committee on their comments on the strengths of Ge et al. (2020) and largely agree that Ge et al. (2020) is one of the studies better suited to address the exposure-response relationship between cumulative silica exposure and risk of lung cancer, primarily due to the large number of lung cancer cases and the quality of the information on smoking history. We do have some reservations about the validity of the attempts to quantify historical occupational exposures to multiple carcinogens using occupational history and job-exposure matrices. One primary reason for this is that the authors pointed out that the majority of the variance in the respirable crystalline silica exposures modelling was not explainable (Peters et al. 2011). Also, as with any case-control study or group of case-control studies relying on recalled and self-reported occupational histories and exposures may be subject to reporting and other biases. We also note that the results presented in Ge et al. (2020) extend well beyond those captured and reiterated in the draft report, specifically, for example, their analyses reflecting different exposure-response relationships among non or never smokers compared with groups of smokers (even controlling for smoking).

As discussed below, we believe that the most reliable results presented in Ge et al. (2020) were those specifically for non-smokers, which showed no clear association between respirable crystalline silica exposure at lower concentrations, in contrast with analyses among groups including smokers and where a parameter for smoking was included in analytical models.

We believe that the risks seen in those analyses likely reflect residual (i.e., partially uncontrolled) confounding – a phenomenon unlikely in statistical analyses of the subset of never smokers. It is well established that cigarette smoking remains the strongest common cause of lung cancers, and that small risks seen after adjustment for smoking may reflect its residual confounding effects. Other studies, as discussed below, also appear to support our interpretation that moderate to low levels of occupational crystalline silica exposure are unlikely to cause lung cancers, although exposures in the higher ranges of this distribution clearly do increase the risk of silicosis.

Assessment of the stronger epidemiological studies

As noted throughout the draft report and ultimately identified as one of the strongest studies, Ge et al. (2020) is a pooled case-control study, known as the SYNERGY Project, of 14 separate population- or hospital-based case-control studies conducted in Europe and Canada. The pooling of these case-control studies results is likely the largest number of lung cancer cases (n=16,901) evaluated in any study. Further, Ge et al. (2020) is one of multiple publications on lung cancer from the SYNERGY Project (28 publications listed on their website as of 19 March 2024: https://synergy.iarc.who.int/publications/). At least two new publications of the SYNERGY Project appear to address silica: Ohlander et al. (2024) and Olsson et al. (2024), and to be up-to-date, these should be considered before the draft advisory report is finalized.

The draft report, with respect to Ge et al. (2020), refers multiple times specifically to the "increased odds ratio of 1.15 (95% CI 1.04-1.27) for lung cancer at very low exposure levels (exposure category >0 - <0.39 mg/m3-years) of respirable quartz" (see pp. 36, 58, 62, 66). While the statement is correct, this odds ratio is reported from Table 2 of Ge et al. (2020) from initial analysis and was the result of an unconditional logistic regression model with multiple adjustment factors including study, age group, sex, smoking (pack-years, time since quitting smoking) and list A jobs. Although we agree with the approach and the adjustment factors used, we believe Ge et al. (2020) offers more informative and reliable results later in the publication, as the initial overall estimate (OR=1.15) does not provide a basis for evaluating – and could be the result of – residual confounding from cigarette smoking. Residual confounding reflects confounding that could not be eliminated because of imperfect or incomplete data on the confounding factor. Several other studies provide evidence of small risks likely resulting from residual confounding (e.g., Blair et al. 2007; Lipworth et al. 2009; Siew et al 2012; Blakely et al. 2013; Lukic et al. 2016; Guertin et al 2016; Vieira et al 2016; Chang et al. 2020; Zhu et al. 2021).

It is well known that cigarette smoking is an extremely strong cause of lung cancer, with studies where exposures were well characterized (such as using amount of tar inhaled) reporting relative risks approaching 100 (see Zang and Wynder 1992). As demonstrated in an earlier publication of the SYNERGY Project, Pesch et al. (2012) reported odds ratios greater than twenty for current smoking in men and even seven-fold higher in former smokers for lung cancer compared to never smokers. When an outcome (lung cancer) is so strongly related to a causal factor (e.g., smoking), the potential for residual confounding is great, and must carefully be considered, as illustrated with a few examples below:

- Neuberger and Field (2003) wrote: "To examine the influence of occupation independent of smoking, we reviewed the literature on occupational lung cancer in nonsmokers. We found that most individual studies and summaries of occupational lung cancer are based on data having a heavy preponderance of male smokers. Relatively little data are available concerning females and nonsmokers. Specific dose-response information is often lacking.

Although many studies have been adjusted for smoking, there remains a significant potential for residual confounding because of the overwhelming importance of smoking in the etiology of this disease."

- Lukic et al. (2016) used the results from never smokers to evaluate possible residual confounding from smoking. This study on Norwegian women evaluated the risk of lung cancer by different levels of coffee consumption. The study reported a significantly increased risk of lung cancer in those with heavy coffee consumption (more than 7 cups a day) compared to one or less cups of coffee per day (HR = 2.01, 95 % CI 1.47-2.75, p trend < 0.001). The authors noted "This was most likely caused by residual confounding due to smoking, as no statistically significant association was observed in never smokers (>5 vs. ≤1 cup/day HR = 1.42, 95 % CI 0.44-4.57, p trend = 0.30)." The authors concluded that "Residual confounding due to smoking may have contributed to the positive association between high coffee consumption and the risk of lung cancer."

Ge et al. (2020) did not evaluate the potential for residual confounding of smoking; however, the study does report results for silica and lung cancer specifically among never smokers. The use of a never smoking population, assuming no substantial misclassification due to inclusion of smokers, provides an opportunity to avoid the result of direct and residual confounding in evaluating the risk of lung cancer from exposure to respirable crystalline silica. The detailed analyses of lung cancer among never smokers in Ge et al. (2020) inform the effect of crystalline silica on risk of lung cancer in the absence of smoking. This point only tangentially is mentioned in the draft report: "Furthermore, increasing cumulative respirable quartz exposure was associated with increasing lung cancer risk (p-trend <0.01) even in the absence of silicosis (p-trend <0.01) and in current, former, and never smokers (p-trend <0.01)" (p. 66). Much clearer results are presented by Ge et al. (2020). The size of the never-smoker groups (including 248 lung cancer cases in individuals also with silica exposure) provides the best opportunity in the literature to isolate the effect of silica on lung cancer without the complications due to confounding (and residual confounding) by cigarette smoking. The odds ratio for ever-silica exposure among never smokers is not increased (see Table 6; OR=1.02, 95% CI: 0.87-1.19), and we believe that the exposure-response results from Table 5 of Ge et al. (2020) are more informative (reproduced below). We further note these findings are captured in the draft report in Table D1e (p. 129) in the confounding and interaction column, but perhaps not fully appreciated as the interpretation we propose appears not to have been considered.

Table 5. Lung Cancer Risks Associated with Cumulative Occupational Silica Exposure by Smoking Status

	Never-Smokers			Former Smokers			Current Smokers		
Cumulative exposure (mg/m^3-years)	Cases (*n*)	OR*	95% CI	Cases (*n*)	OR†	95% CI	Cases (*n*)	OR‡	95% CI
Never	1,121	1.0	Referent	3,696	1.0	Referent	7,161	1.0	Referent
>0–0.39	60	1.17	0.85–1.57	366	1.07	0.92–1.25	687	1.19	1.03–1.39
0.4–1.09	59	1.07	0.78–1.43	433	1.37	1.18–1.59	729	1.33	1.15–1.55
1.1–2.39	60	1.02	0.75–1.36	441	1.35	1.16–1.57	730	1.29	1.11–1.50
≥2.4	69	1.40	1.03–1.86	496	1.47	1.27–1.70	793	1.39	1.20–1.62
Test for trend, *P* value		<0.01			<0.01			<0.01	
P value excluding never exposed		0.02			<0.01			0.07	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
*OR adjusted for sex, study, age group, and list A jobs.
†OR adjusted for sex, study, age group, list A jobs, pack-years, and time since quitting smoking.
‡OR adjusted for sex, study, age group, list A jobs, and pack-years.

The draft report is therefore incorrect in stating that "the stratified analyses showed that regardless of smoking status, increasing cumulative silica exposure was associated with increasing risk of lung

cancer" (p. 69, l. 13-15). While risk is elevated (OR = 1.40., 95% CI: 1.03-1.86) in the highest crystalline silica cumulative exposure category (i.e., $\geq$ 2.4 mg/m^3-years), no other exposure category indicates any increased risk. Therefore, the Expert Committee's statement appears to be an oversimplification of these results for never smokers. The statistical test for trend here also is significant, however, it only indicates that at least one of the higher exposure categories (in this case the highest) is statistically different from the other categories; it is not an indication of any dose-response relationship, i.e., a monotonically increasing risk of lung cancer with increasing exposure to silica. The proper interpretation of the results among never smokers is that only the group with highest cumulative exposure to silica demonstrated an increased risk of lung cancer. **Therefore, the draft report's statement on p. 62 that "the pooled analysis by Ge et al. (2020), shows that increased risk of lung cancer is associated with the lowest exposure levels to respirable quartz" is not supported by the best available data within Ge et al. (2020), that of the never smokers.**

The reported finding in Ge et al. (2020) of no clear association between low levels of respirable crystalline silica exposure and lung cancer risk among never smokers is consistent with a number of occupational cohort studies evaluating the relationship between silica and lung cancer that have that failed to observe statistically significant effects either overall (Chen et al. 2012; Cherry et al. 2008; Cocco et al. 2001; Gallagher et al. 2015; Graber et al. 2014; Mundt et al. 2011; Preller et al. 2010) or have only found statistically significant risks in the higher exposure categories (Hnizdo et al. 1997; Steenland et al. 2001).

For example, in our German Porcelain Workers Study (Birk et al. 2009; Mundt et al. 2011), a cohort of about 18,000 porcelain workers was followed and clinically examined regarding signs of silicosis by the statutory accidence insurance surveillance program between 1985 and 1987 and with a minimum duration of exposure of six months. Eligible workers were followed for mortality and silicosis incidence until December 31st, 2005. The study included a comprehensive exposure assessment (Birk et al. 2010) and re-reading of all x-rays for any employee with at least one radiograph originally scored 1/0 or higher (Mundt et al. 2011). Smoking status was available for more than two thirds of the cohort. No increase in lung cancer mortality, based on 90 cases compared to the German general population, nor any exposure-response relationship between lung cancer mortality and estimated cumulative crystalline silica exposure was observed. On the other hand, respirable crystalline silica exposure of more than 4 mg/m^3-years (cumulative) or more than 0.15 mg/m^3 (average) were strongly associated with silicosis incidence risk, but unrelated to lung cancer risks. Smoking clearly remained a strong risk factor for lung cancer regardless of crystalline silica exposure level.

An update of this study *(publication in prep*aration), extending follow-up of the cohort an additional 15 years through December 31st, 2020, identified three times as many lung cancer deaths (n= 284) as the original study. Neither among men (SMR = 0.90; 95% CI = 0.78-1.04, n= 194) nor among women (SMR = 0.98; 95% CI = 0.80-1.21, n= 90) was any increased occurrence of lung cancer mortality observed compared to the general German population. However, smoking was strongly predictive of lung cancer risk. Furthermore, no exposure-response relationship with increasing cumulative exposure to crystalline silica was observed for lung cancer deaths (see Table below); however, incident cases of silicosis (i.e., those classified upon re-reading of radiographs as ILO 1/1 or higher), confirming the results of the original study. For the silicosis cases, a strong exposure threshold for risk was reported.

Table: Update of the Porcelain Worker Study: Lung cancer hazard ratios (HRs) and 95% confidence intervals (95% CI) by categories of cumulative exposure (mg/m^3-years) stratified by sex and controlling for age and smoking (from publication in preparation)

	Men		Women	
Cumulative exposure, all cut-points	n[†]	HR (95% CI)	n[†]	HR (95% CI)
≤0.5	45	Reference	27	Reference
>0.5-1.0	25	0.8 (0.5-1.3)	22	1.0 (0.6-1.8)
>1.0-1.5	18	0.8 (0.5-1.4)	7	0.5 (0.2-1.2)
>1.5-3.0	35	0.9 (0.6-1.5)	16	0.7 (0.4-1.4)
>3-4	13	1.2 (0.7-2.3)	8	1.1 (0.5-2.6)
>4-5	10	1.2 (0.6-2.4)	4	0.8 (0.3-2.2)
>5-6	14	1.5 (0.8-2.8)	2	0.5 (0.1-2.0)
>6	34	1.0 (0.6-1.6)	4	0.6 (0.2-1.7)

[†]Number of observed deaths

The results reported by Ge et al. (2020) for never smokers also are consistent with a potential threshold risk for lung cancer from cumulative silica exposure. This concept has also been considered in the scientific literature. For example, in a population registry-based study in Finland and incorporating silica exposure based on the FINNJEM job-exposure matrix (Kauppinen et al. 2014), Pukkala et al. (2005) reported:

> We observed an increase in the risk ratio of lung cancer with increasing silica exposure, and the incorporation of sufficient lag time also produced a higher risk ratio. These findings can be interpreted as signs of causality. Our results also suggest a threshold in that the excess was mainly attributable to workers in occupations with an estimated cumulative exposure exceeding 10 mg/m^3-years or threshold exposure of at least 0.2 mg/m^3. In a pooled exposure–response analysis of 10 silica-exposed cohorts the relative risk of lung cancer was observed to increase when cumulative exposure exceeded 9 mg/m^3-years (20). In this case our average exposure estimates give a risk coefficient similar to the individual level estimates of the pooled analysis. Overall, our results concerning increased lung cancer risk among workers exposed to silica dust are consistent with the IARC evaluation, which stated in 1997 that occupational exposure to crystalline silica is carcinogenic to humans (8). (Pukkala et al. 2005, p. 106)

Although we feel the results among never smokers in Ge et al. (2020) are the most informative, we caution that there are uncertainties in the results. For example, the upper limit of silica exposure for Ge et al. (2020) is not defined and the estimated exposure levels are unclear. Further, even the results for never smokers may be subject to confounding by smoking if the never smoking category contains current or former smokers who have been misclassified in the original studies and contribute to the increased risk among the most highly exposed group. Given the definitions used and as noted on p. 69 of the draft report, “Former smokers were defined as persons who had smoked for at least 1 year but quit [sic] smoking at least 2 years before the date of the interview. Subjects who had smoked for less than 1 year were considered occasional smokers and were treated as never smokers in the analyses.”

Histologic types of lung cancers

Risks factors for various histological types of lung cancers vary in the strength of causal associations. The risks of squamous cell and small cell lung cancers from cigarette smoking are usually much higher than for adenocarcinoma of the lung. As demonstrated in an earlier publication of the SYNERGY Project, Pesch et al. (2012) reported odds ratios greater than 45 among current smokers for both squamous cell and small cell lung cancers. Even the odds ratios for former smokers are above 10. In contrast, the odds ratios for adenocarcinoma are 10.1 among current and 4.2 higher in former smokers (see Table 1 reproduced below).

Table 1. Relative risk of lung cancer and major subtypes by smoking status

				All histologies		Squamous cell cancer		Small cell lung cancer		Adenocarcinoma	
Studies	Gender	Smoking cigarettes	Controls	Cases	OR[1] (95% CI)	Cases	OR[1] (95% CI)	Cases	OR[1] (95% CI)	Cases	OR[1] (95% CI)
All	Men	Never	2,83	220	1.0	51	1.0	22	1.0	99	1.0
		Former	5,647	3,496	7.5 (6.5–8.7)	1,585	14.7 (11.0–9.6)	460	10.1 (6.5–15.5)	862	4.2 (3.4–5.2)
		Current	3,829	6,784	23.6 (20.4–27.2)	3,038	45.6 (34.3–60.6)	1,249	45.7 (29.9–70.0)	1,398	10.8 (8.7–13.3)
		Other tobacco	399	153	5.9 (4.6–7.4)	73	12.6 (8.6–18.4)	29	9.6 (5.4–17.0)	25	2.0 (1.3–3.2)
		Total	12,758	10,651		4,747		1,760		2,384	

Taking these findings into consideration when evaluating the results for histologic type of lung cancer in Table 7 of Ge et al. (2020) may be informative (reproduced below). Ge et al. (2020) report no statistically significant excess by histologic type of lung cancer in the never-smoker and ever-silica exposure group, however, the point estimates for the two types of lung cancer most closely linked to smoking (squamous cell OR =1.22 and small cell OR =1.49) are slightly elevated, while the adenocarcinoma point estimate is not (OR=1.01). This could indicate some misclassification of smokers into the never smoker category, thereby introducing confounding that could not be controlled, as this group was assumed not to have any influence from smoking. Simply put, because of the extremely strong causal association between smoking and both squamous and small cell lung cancers (and demonstrated in Table 1 of Ge et al. (2020), it is for these types of lung cancer that the greatest potential for confounding and residual confounding exists. Although not performed in Ge et al. (2020), other studies have used sensitivity analyses to investigate whether residual confounding effects of smoking may be an issue in a result for never smokers (e.g., Freudenheim et al. 2005).

Similarly, the increased odds ratios for the ever-smoker and ever silica exposure groups compared to the ever-smoker and never silica exposure groups might also be consistent with heavier smokers in the ever silica group (and especially those most highly exposed) compared to the never silica group resulting in residual confounding in the point estimates. This appears to be a possibility as the ever silica group had a higher percentage of smokers with greater than 19 pack-years (80.7%) than the never silica group (76.4%) (see Table 1 in Ge et al. 2020).

Table 7. Interactions between Occupational Silica Exposure and Smoking for Major Lung Cancer Subtypes

	Adenocarcinoma			Squamous Cell Carcinoma			Small Cell Carcinoma		
Exposure Status	Cases (*n*)	OR*	95% CI	Cases (*n*)	OR*	95% CI	Cases (*n*)	OR*	95% CI
Never-smoker and never silica	589	1.0	Referent	195	1.0	Referent	82	1.0	Referent
Never-smoker and ever silica	111	1.01	0.81–1.24	62	1.22	0.90–1.62	29	1.49	0.96–2.27
Ever-smoker and never silica	3,094	3.90	3.52–4.32	4,057	11.0	9.47–12.8	1,779	13.6	10.9–17.3
Ever-smoker and ever silica	958	4.61	4.06–5.23	2,189	16.1	13.7–18.9	840	19.2	15.3–24.7
P value multiplicative interaction		0.17			0.23			0.80	
RERI		0.70	0.26–1.15		4.86	3.63–6.09		5.13	3.03–7.23

For definition of abbreviations, see Table 6.
*OR adjusted for sex, study, age group, and list A jobs.

Exposure Assessment

Additionally, and as noted above, Ge et al. (2000) is a pooled case-control study, and therefore (as with many case-control studies) the accuracy and validity of historical RCS exposure estimation likely varies, especially in situations where the ultimate quantification of potential respirable crystalline silica relied or was based on individual case (and control) rumination, recollection and reporting, which can vary by case or control status. The quantitative exposure modelling of respirable crystalline silica (RCS) exposure in the SYNERGY study is reported in Peters et al. (2011). In discussing the variance of the estimates of RCS exposure, the authors noted:

> Although part of the variance could be attributed to job titles and regions, most of the variance remained unexplained. The residual variance can be partitioned in between-factory variability, variability between different jobs within the same ISCO code, between-worker differences in average exposure within the same job and temporal (day-to-day) variability in exposure concentrations. We were not able to incorporate these correlation structures, since it was unknown for most measurements whether they came from the same worker or even factory. (Peters et al. 2011; p. 3267, emphasis added)

One of the most recently SYNERGY publications (Ohlander et al. 2024) may provide additional insights as to the potential for and magnitude of exposure misclassification and warrants further consideration by the Expert Committee. Specifically, these authors conclude:

> The established exposure–response relationship between occupational silica exposure and lung cancer was marginally influenced by varying the dimensions of SYN-JEM. Optimized modelling of exposure–response relationships will be obtained when incorporating all relevant dimensions, namely prior rating, job, time, and region. Quantitative job-specific estimates appeared to be the most prominent dimension for this general population JEM. (Ohlander et al. 2024)

Concluding comments

We recommend that similar evaluation of the exposure assessment methods be considered for each of the case-control studies included in the pooled analysis.

In summary, we agree that there is an established association and threshold dose-response relationship between respirable crystalline silica exposure and risk of silicosis. This finding in part validates our exposure assessment as it allowed us to predict and quantify silicosis risk. However, we do not agree that the epidemiological evidence is clear regarding lung cancer risk, at least in settings where exposures clearly increased the risk of silicosis but not the risk of lung cancer. In our study of about 18,000 porcelain workers and 280 lung cancer deaths, we demonstrated strong associations between smoking and lung cancer (HR = 17.9, 95% CI, 7.3-43.7 among men and HR = 6.1, 95% CI 3.4-10.9 among women) but did not identify any relationship between respirable crystalline silica exposure and lung cancer mortality.

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08 April 2024

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RISICOBEOORDELING VAN CHEMISCHE STOFFEN
CHEMICAL SUBSTANCES RISK ASSESSMENT

Koninklijke Metaalunie en Vereniging FME
p/a Zilverstraat 69
2718 RP Zoetermeer

Date 7 April 2024
from: dr. J.G.M. van Rooij (PhD)
Your reference: Your email message dated 18 March 2024
Contact person: Mr. K. Halm (FME)
Our reference: project number 2024.005 (proposal dated 2024-02-16)
Concerns: Review draft report of Health Council of the Netherlands: Respirabel Crystalline Silica (December 2023)

Dear Mr. K. Halm,

Thank you for sending us the draft Health Council report on Respirable Crystalline Silica (Dec 2023).

You are asking me to respond to this draft Health Council report, based on my knowledge of toxicology and occupational hygiene.

My response can be found in the attachment. If you have any questions or comments, please contact me by phone or email.

Yours sincerely,

dr. J.G.M. van Rooij (PhD)
toxicologist / occupational hygienist

Review of draft report of the Health Council of the Netherlands:

Respirabel Crystalline Silica - Evaluation of health hazards as basis for an occupational exposure limit. The Hague, public draft, 15 December 2023

Place, Date:	Nijmegen The Netherlands, April 7, 2024.
By:	dr. J.G.M. van Rooij (PhD), toxicologist / occupational hygienist at Caesar Consult
On behalf of:	Koninklijke Metaalunie en Vereniging FME

1. Introduction

In December 2023, the *Dutch Expert Committee on Occupational Safety* (DECOS) of the Health Council published a draft advice for a limit value for respirable crystalline silica (Public draft, dated December 15, 2023)[1]. The advice was drawn up in collaboration with the *Nordic Expert Group* for Criteria Documentation of Health Risk from Chemicals (NEG).

DECOS and NEG come to the conclusion that:

- the target risk level for respirable crystalline silica in the workplace corresponds to 0.00038 mg/m^3 (4 additional cases of lung cancer per 100,000 employees for 40 years of exposure; 'low risk level'),
- the prohibitive risk level for respirable crystalline silica in the workplace corresponds to 0.0363 mg/m^3 (4 additional cases of lung cancer per 1,000 employees for 40 years of exposure; 'high-risk level').

This concerns 8-hour time-weighted average concentrations (8-hour TWA). These so-called *health-based calculated occupational cancer risk values* (HBC-OCRVs) apply to quartz as well as cristobalite and tridymite because these polymorphic silica are, according to DECOS and NEG, comparable in terms of toxicity and carcinogenic potential. DECOS and NEG follow the so-called risk-based approach in the derivation assuming that there is no safe threshold value for respirable crystalline silica (RCS).

These proposed target and prohibition risk levels are considerably stricter than the current Dutch legal limit value for respirable crystalline silica dust of 0.075 mg/m^3 (8-hour TWA), and also lower than the EU binding occupational exposure limit value of 0.1 mg/m^3 (8 -hour TWA).

While a threshold effect is currently assumed in The Netherlands and the EU, but also in the United States (ACGIH, 2010), DECOS and NEG assume that there is no safe threshold value for silica.

This advice may have major consequences for the metal sector, especially if quartz is to be regarded as a carcinogen without a safe threshold value (a so-called *direct-acting genotoxic carcinogen*). In that case, in accordance with Dutch Occupational Health and Safety Regulations, the aim must be to achieve 'zero exposure' in all companies where possible quartz exposure occurs, regardless of the level of exposure and regardless of the costs.

Koninklijke Metaalunie and Vereniging FME have asked dr. J.G.M. van Rooij, toxicologist/occupational hygienist at Caesar Consult in The Netherlands, to carry out a review of the draft Health Council report.

[1] Health Council of the Netherlands: Respirable Crystalline Silica - Evaluation of health hazards as basis for an occupational exposure limit. Den Haag, public draft, 15 December 2023.

2. Aim

Critical assessment of the findings and conclusions of the DECOS committee of the Health Council of the Netherlands and the NEG committee in their draft report entitled: *Respirable Crystalline Silica - Evaluation of health hazards as a basis for an occupational exposure limit* (The Hague, Public draft, December 2023).

3. Approach

In this review special attention is given to the Committees' working methods, the inventory and processing of the current and available toxicological and epidemiological data, the selection of the critical effect(s) and the key-study/studies, the quality of the selected key-study/studies, and the interpretation of the selected research data.
In this review the instructions of the Health Council for submitting comments were followed.[2]

4. Expertise

The review was conducted by dr. J.G.M. van Rooij (PhD). He is a EUROTOX registered toxicologist and senior occupational hygienist at Caesar Consult, The Netherlands.

5. Results of the review

Studying the Health Council report shows that DECOS and NEG make a number of assumptions, choices and conclusions that have a major influence on the evaluation and the recommended limit value for respirable crystalline silica (RCS), but which are insufficiently substantiated with scientific data.

The results of the review in broad terms is presented in § 5.1. Detailed comments and suggestions are presented in § 5.2.

5.1 Main findings (review in broad terms)

5.1.1 The working method of DECOS/NEG deviates from the Health Council's own guidelines

The Health Council has published guidelines for recommending classifications and health-based occupational exposure limits:

- *Guidance for recommending classifications and health-based occupational exposure limits*. Health Council of the Netherlands, The Hague**,** 2021.
- *Guideline for the classification of carcinogenic substances*. Subcommittee on the Classification of Carcinogenic Substances of DECOS, Health Council of the Netherlands, The Hague, 2023.

According to these guidance's the evaluation of the available toxicological studies is an essential part of the process/working procedure of deriving of a health-based occupational exposure limit. In the *Guidance for recommending classifications and health-based occupational exposure limits* (2021), it is stated on page 11:

> *"Information on the toxicity of substances is derived from a variety of research methods, including epidemiological studies, laboratory studies with humans, animal (in vivo) experiments, cellular and tissue (in vitro or ex vivo) studies, and computational methodologies and disciplines."*

[2] Health Council of the Netherlands: Instructions for submitting comments on the draft advisory report Respirable Crystalline Silica (The Hague NL, December 15, 2023)

According to this guidance, information on the toxicity should not only be derived from epidemiological studies but also from toxicological studies, such as controlled human exposure studies, animal experiments, in vitro and ex vivo test systems and computational (in silico) toxicology (see also § 3.1.1 of this guidance on p13 -15).

The focus in the draft report on RCS is almost exclusively on health effects and epidemiological studies.

In the *Guidance for recommending classifications and health-based occupational exposure limits* (2021), it is stated on page 35 that:

> "*a risk-based approach is applicable to: direct-acting genotoxic carcinogens and respiratory allergens for which the threshold is too low to measure*."

In the *Guideline for the classification of carcinogenic substances (2023),* it is explained in more detail how to determine the genotoxic mode of action (see appendix 1 of this review report for test systems that are available for identifying a carcinogen's mode of action). The genotoxic mode of action determines the type of occupational exposure limit DECOS should derive and determines the approach DECOS should follow.

A risk-based approach resulting in a HBR-OCRV should only be derived for carcinogens that act by a direct genotoxic mechanism. For carcinogens that act by an indirect genotoxic mechanism or for non-genotoxic carcinogens a HBR-OEL should be derived based on a threshold-based approach (see appendix 1 for a more detailed description of the different types of carcinogens) .

There is convincing evidence that RCS does not directly interact with DNA. This means that, according the Health Council's own guidance's, a HBR-OEL should be derived based on a threshold-based approach. Instead DECOS/NEG uses a risk-based approach resulting in a HBR-OCRV.

In conclusion, the evaluation of RCS by DECOS/NEG as described in the draft report of December 2023 deviates from the Health Council's own guidelines with regard to the following parts/steps:

a) DECOS/NEG do not provide a thorough evaluation of the available toxicological studies on RCS.
b) DECOS/NEG use the wrong approach (Risk-based approach instead of Threshold-based approach)

5.1.2 DECOS/NEG do not provide a thorough evaluation of toxicological studies on RCS.

The author(s) of the draft advice has (have) made little effort to delve into the available toxicological studies on RCS. The focus in the Health Council's draft report is almost exclusively on health effects and epidemiological studies.

As a result, highly relevant toxicological relevant information is not included in the assessment. This is illustrated, for example, by the review that Borm et al. published in 2018 on the mode of action of RCS-induced genotoxicity (see also appendix 2). They conclude the following:

> "*In conclusion, the different modes of action of RCS-induced genotoxicity have been evaluated in a series of independent, adequate studies since 2011. Earlier conclusions on the role of inflammation driven by quartz surface in genotoxic and carcinogenic effects after inhalation are confirmed and findings support a practical threshold. Whereas classic in vitro genotoxicity studies confirm an earlier no-observed effect level (NOEL) in cell cultures of 60-70 µg/cm2, transformation frequency in SHE cells suggests a lower threshold around 5 µg/cm2. Both levels are only achieved in vivo at doses (2–4 mg) beyond in vivo doses (> 200 µg) that cause persistent inflammation and tissue remodelling in the rat lung."*

An other consequence of not evaluating the available toxicological studies on RCS is that the choice of the critical health effect is only based on available epidemiological data and not on toxicological data. DECOS/NEG state in their draft-report on RCS:

> *"For the critical effect, both lung cancer and silicosis have been reported to occur at low exposure levels. However, the committees are of the opinion that the available epidemiological data for a quantitative dose-response relationship with lung cancer are more extensive, and generally of higher quality (concerning exposure and health assessment) than the available data for silicosis (e.g., diagnosis by using chest radiographs may have let to underreporting of silicosis). The committees therefore decided on lung cancer as the most critical effect and basis for the risk analysis."*

By not taking toxicological information into account, it cannot be ruled out that DECOS/NEG assumes the wrong critical health effect of RCS.

5.1.3 DECOS/NEG use the wrong approach (risk-based instead of threshold-based)

For the derivation of an exposure limit value for a carcinogen there are two approaches that can be used according to guidance's of the Health Council of the Netherlands: the so-called *Risk-based approach* or the *Threshold-based approach*. Which approach to choose depends on the mode of action of the carcinogen.

For carcinogens or its metabolites that interact directly with DNA ('act by a direct genotoxic mechanism') a risk-based approach resulting in a HBR-OCRV should be applied. For this kind of carcinogens it is assumed that one molecule can transform a cell in a cancer cell, a so-called one-hit (stochastic) occasion. In order to derive an occupational limit value for this kind of carcinogens one has to accept a certain risk level (e.g. 4 additional cases of lung cancer per 1,000 employees for 40 years of exposure; so called 'prohibition risk level').

For all other carcinogens (indirect genotoxic mechanism or non-genotoxic carcinogens) a threshold-based approach should be used for the derivation of a health-based recommended occupational limit value. This approach starts with the search of dosis-response relationships/curves based on toxicological and/or epidemiological data and the identification of a *no-observed-adverse-effect-level* (NOAEL).

The key-question here is whether RCS or its metabolite is a carcinogen that interacts directly with DNA.

DECOS/NEG consider RCS as a direct acting genotoxic carcinogen as stated on page 50, line 7 -19:

> "*The Subcommittee has come to that conclusion because, according to the Subcommittees guideline, direct-acting genotoxic carcinogens include substances that (either in their unchanged form or as reactive metabolites) interact directly with DNA to induce genotoxic effects [141]. According to the currently available scientific literature there is no evidence that crystalline silica particles can enter the nucleus themselves [142, 143]. Although the Subcommittee notes that the available data on intracellular translocation of crystalline silica particles are limited. Reactive oxygen species (ROS), however, which can be generated both at the surface of crystalline silica particles and through inflammatory responses caused by respirable crystalline silica, can enter the nucleus themselves and interact with DNA. The Subcommittee considers genotoxic carcinogens that generate ROS also as direct genotoxic carcinogens, given the genotoxicity of the produced ROS [141]. As a result, a direct genotoxic mechanism involving particle-generated ROS cannot be excluded."*

First of all, it is good to note that DECOS/NEG also recognize that '*according to the currently available scientific literature there is no evidence that crystalline silica particles can enter the nucleus themselves'*.

This means that a direct interaction between RSC and DNA (that is located in the nucleus!) is very unlikely or even not possible.

Second, DECOS/NEG are correct in stating that the Subcommittee (on the Classification of Carcinogenic Substances of DECOS) may consider genotoxic carcinogens that generate ROS also as direct genotoxic carcinogen given the genotoxicity of the ROS that is produced.

But what DECOS/NEG fail to mention, is that the Subcommittee only draws that conclusion if there are no data available from experimental studies that demonstrate the existence of a threshold (see also Annex A of the *Guideline for the classification of carcinogenic substances* (2023)). However, for ROS these experimental data are available, as shown in the review article of Borm et al. published in 2018 on the mode of action of RCS-induced genotoxicity (see also § 5.2.1 and appendix 2).

What DECOS/NEG also fail to mention, is that the Subcommittee states that ROS indeed can be formed on the surface of crystalline silica particles, but that there is no evidence that these ROS contribute to the observed genotoxic effects (see annex F of the draft report on RCS, page 146, line 3 – 6).

The review article of Borm et al. show that RSC should be assessed as a carcinogen that does NOT act by a direct genotoxic mechanism, with the result that a threshold-based approach should be used instead of a risk-based approach for the derivation of a health-based recommended occupational limit value (HBR-OEL).

Regarding the approach that was used, DECOS/NEG also state that they have chosen the *precautionary approach*. In doing so they seem to legitimize the choice for a risk-based approach (see page 10, line 8 – 13):

> "*Regarding the approach, although the carcinogenic potential of respirable crystalline silica primarily results from indirect mechanisms, a direct genotoxic mechanism, because of particle-generated ROS, cannot be excluded. Therefore, the committees take a precautionary approach and decided on a non-threshold (or risk-based) approach for risk calculations using a life table analysis to estimate the excess risk of lung cancer*."

But the suggestion that a risk-based approach is always more cautious than a threshold-based approach for indirect or non-genotoxic carcinogens is not correct. This depends on, among other things, on the NOAEL and the extrapolation factors that are used in relation to the carcinogenic potency when assuming that it is a direct acting carcinogen.

5.1.4 Recommendations based on review in broad terms

Based on this review in broad terms it is recommended:

1. to include a chapter in the report that provides a thorough evaluation of the available toxicological studies,
2. to re-assess the critical health effect of RCS based on a comprehensive evaluation of both toxicological and epidemiological data,
3. to re-assess the mode of action,
4. to derive a HBR-OEL for RCS based on a threshold based approach, and
5. to update the report accordingly.

Page 1 to 152 of the draft report on RCS
Based on the review in broad terms, it is concluded that DECOS/NEG (i) use a working method that deviates from the Health Council's own guidelines, (ii) do not provide a thorough evaluation of the available toxicological studies on RCS, and (iii) use the wrong approach (risk-based instead of threshold-based) by assuming that RCS is a direct acting genotoxic carcinogen. Recommendations are made in order to improve the evaluation. The publications that I have based my comments on are included in § 5.1.1, § 5.1.2 and § 5.1.3.
DECOS/NEG are kindly requested to adopt the recommendations and to thoroughly revise and update the draft evaluation report on RCS.

5.2 Detailed comments and suggestions

If DECOS/NEG is open to the main findings and conclusion as stated in § 5.1, the recommendations will result in a thorough revision of the draft report on RCS, 15 December 2023. In that case I look forward to receiving the amended draft version for a detailed review.

In the event that DECOS/NEG rejects the comments and recommendations in § 5.1, I still have some detailed comments and suggestions that may be useful for DECOS/NEG to consider.

But it is emphasized that providing detailed comments does not mean that I agree with the main findings and conclusions presented in the draft report on RCS, dated December 2023.

Executive Summary

Page 6 – 10:
DECOS/NEG are kindly requested to adjust the executive summary based on the changes and corrections made in the main body of the report (see below).

1. Scope

Page 10, line 4 -7:
The formal request of the Minister of SZW for an advise on RCS is not presented. That the Minister has submitted a request for an advice on RCS is remarkable given the busy work program of DECOS and the fact that we already have a European limit value (BOEL) for RCS of which the implementation and enforcement is well underway.

DECOS/NEG are kindly requested to include the letter from the Minister of SZW with the formal request for advice on RCS in the appendix.

Page 12, line 21 – 24*:*
It is stated that *'The first part of this advisory report provides an overview of the toxicity of respirable crystalline silica'*.
This is not correct. The focus in the draft report on RCS is almost exclusively on health effects and epidemiological studies. A comprehensive evaluation of the available toxicological studies (e.g. laboratory studies with humans, animal (in vivo) experiments, cellular and tissue (in vitro or ex vivo) studies and computational methodologies) on RCS has not been carried out.

DECOS/NEG are kindly requested to include a comprehensive evaluation of the available toxicological studies on RCS in the report. If DECOS/NEG decides not to add an chapter with available toxicological information, DECOS/NEG are kindly requested to indicate why they decide not to do so.

2. Identity, properties and monitoring

Page 18, line 1
It is indicated that '*The respirable fraction consists of particles that usually have a aerodynamic diameter of less than 4 µm. Most particles, larger than 5 µm may not reach the alveolar region but will be deposited in the upper airways*"

DECOS/NEG are kindly requested to check this information. As far as I know, the respirable fraction is defined as the fraction that consists of particles with 50% aerodynamic separation diameter of 4.25 µm (see also EN 481). This means that respirable dust particles usually have an aerodynamic diameter of less than 10 µm.

Page 18 , § 2.31 Workplace sampling and analytical methods
DECOS/NEG provide a comprehensive overview of the available methods for sampling RCS in the workplace atmosphere and the available analytical methods for quantifying RCS in these samples.

DECOS/NEG do not address differences between these sampling and analytical methods and the possible consequences for the exposure characterization in the epidemiological studies that are used by DECOS/NEC in deriving a HBC-OCRV.

DECOS/NEG are kindly requested to evaluate differences between the sampling and analytical methods for RCS and to evaluate the possible consequences for the exposure characterization in the epidemiological studies that are used in deriving the HBC-OCRV.

3. Sources and uses

No comments or suggestions

4. Exposure

Page 27, table 6, line 12-14
In the table 6 it is indicated that in USA North America, sand industry, in the period 1947 – 1955, the GM (geometric mean) of RCS exposure ranges from 0.083 – 96.6 mg/m^3.
The value of 96.6 mg/m^3 seems unrealistic high and is probably a type error.
DECOS/NEG are kindly requested to check the presented mean concentrations in table 6.

5. Kinetics and biomonitoring

Page 30, line 6-11 and line 28 - 31
DECOS/NEG state '*that it is generally considered that respirable particles (the mass fraction of inhaled particles that can reach the unciliated airways), like crystalline silica, consists of particles with an aerodynamic diameter below 4 µm which can reach the alveolar region of the lungs. Most particles larger*

than 5 µm will not reach the alveolar region but will be deposited in the upper airways (extra thoracic, tracheobronchial region)'.

DECOS/NEG are kindly requested to check this information. As stated above, the respirable fraction is defined as the fraction that consists of particles with a 50% aerodynamic separation diameter of 4.25 µm (see also EN 481). This means that respirable dust particles usually have an aerodynamic diameter of less than 10 µm.

6. Health effects

Page 35, line 1 to 10
't Mannetje et al. (2002) conducted a pooled analysis among six cohorts of silica exposed workers. This pooled dataset included 170 deaths with silicosis (n=150) or pneumoconiosis (n=20). 't Mannetje et al. calculated that for a RSC exposure of 0.05 mg/m^3 during 45 years of exposure the estimated life time risk of death due to silicosis was 6 per 1000 workers.

DECOS/NEG are kindly requested to calculate from the data presented by 't Mannetje et al, the estimated life time risk of death due to silicosis of RSC exposure during 40 years of exposure that corresponds with a life-time risk of 4 death per 1000 workers.
Is it correct that this value is 0.0375 mg/m^3 and about 2 times lower than the current Dutch legal limit value for respirable crystalline silica dust of 0.075 mg/m^3 (8-hour TWA)?
And is it correct that this calculated life time risk value of death due to silicosis of 0.0375 mg/m^3 is almost equal to prohibitive risk level of lung cancer that is calculated by DECOS/NEG (0.0363 mg/m^3).
Do DECOS/NEG support the conclusion that, based on these calculations, occupational exposure to respirable crystalline silica causes silicosis morbidity and mortality as well as lung cancer to approximately the same extent?

Page 45, line 20 -27
DECOS/NEG state in § 6.5 Genotoxicity: "*For a summary on genotoxicity of respirable crystalline silica see Annex F, the report of the Subcommittee on the Classification of Carcinogenic Substances. In short, the Subcommittee concludes that it is undisputable that exposure to respirable crystalline silica may cause tumors and that a genotoxic mechanism of action is involved. The carcinogenic potential of respirable crystalline silica results primarily from genotoxicity by indirect mechanisms, related to damage of lung cells with consequently inflammation and a tumor-promoting inflammatory microenvironment. Involvement of a direct mechanism involving particle-generated ROS, however, cannot be excluded*."

But what DECOS/NEG fail to mention, is that the Subcommittee states that ROS indeed can be formed on the surface of crystalline silica particles, but that there is "no evidence that these ROS contribute to the observed genotoxic effects" (see annex F of the draft report on RCS, page 146, line 3 – 6).

DECOS/NEG are kindly requested to add to *§ 6.5 Genotoxicity*, that there is no evidence whatsoever that these particle-generated ROS contribute to the observed genotoxic effects.

7. Mechanism of toxicity

Page 50, line 1 - 6
DECOS/NEG state: '*The report of the evaluation by the Subcommittee can be found in Annex F of this advisory report. In short, respirable crystalline silica may cause lung tumors and the carcinogenic potential results primarily from genotoxicity by indirect mechanisms, related to damage of*

lung cells with inflammation and a tumor-promoting inflammatory microenvironment as a result. Involvement of a direct mechanism involving particle-generated ROS, however, cannot be excluded.''

But what DECOS/NEG fail to mention, is that the Subcommittee states that ROS indeed can be formed on the surface of crystalline silica particles, but that there is 'no evidence that these ROS contribute to the observed genotoxic effects' (see annex F of the draft report on RCS, page 146, line 3 – 6).

DECOS/NEG are kindly requested to add that there is no evidence whatsoever that these particle-generated ROS contribute to the observed genotoxic effects.

8. Existing guidelines, standards and evaluation

No comments or suggestions. Excellent overview.

9. Hazard assessment

Page 60, line 14 – 19
DECOS/NEG state: '' For lung cancer the Subcommittee on the Classification of Carcinogenic Substances has concluded that the carcinogenic mechanism of respirable crystalline silica results primarily from genotoxicity by an indirect mechanism, related to damage of lung cells resulting in inflammation and a tumor-promoting inflammatory microenvironment. Although, a direct genotoxic mechanism involving particle-generated ROS cannot be excluded (see also Annex F or section 7.3.2)."

But what DECOS/NEG fail to mention, is that the Subcommittee states that ROS indeed can be formed on the surface of crystalline silica particles, but that there is 'no evidence that these ROS contribute to the observed genotoxic effects' (see annex F of the draft report on RCS, page 146, line 3 – 6).

DECOS/NEG are kindly requested to add that there is no evidence whatsoever that these particle-generated ROS contribute to the observed genotoxic effects.

Page 61, line 34 – 35, line 1 – 4.
DECOS/NEG state: "*Epidemiological studies, generally, show that silicosis is particularly associated with higher exposure levels to respirable crystalline silica. This is demonstrated in the pooled analysis by 't Mannetje et al (2002), in which the increased risk of silicosis was particularly high for cumulative exposure to respirable crystalline silica of more than 28.10 mg/m3-year (RR=63.63 (95% CI 19.87-203.8) (see also Annex D for a more 3 detailed study summary) [64]."*

This statement is not in line with the simple calculation of the estimated life time risk of death due to silicosis from the data provided by 't Mannetje et al. (2002) in my comment related to page 35, line 1 -10. The calculated life time risk value of death due to silicosis of 0,0375 mg/m^3 (40 years exposure, 4 deaths per 1000 workers) is almost equal to prohibitive risk level of lung cancer that is calculated by DECOS/NEG (0.0363 mg/m^3).
In addition, the following is stated on page 62, line 16-19 in the DECOS/NEG report: '*The NFA (2021) noted that, based on the evaluation by OSHA, there is evidence that occupational exposure to respirable crystalline silica causes silicosis morbidity and mortality as well as lung cancer to approximately the same extent*.'

DECOS/NEG are kindly requested to add to § 9.1.3. *Conclusion on the critical effect,* that occupational exposure to respirable crystalline silica causes silicosis morbidity and mortality as well as lung cancer to approximately the same extent. In other words, silicosis and lung cancer are both critical effects of RCS exposure.

Page 62, line 22-31
DECOS/NEG state: "*After considering the scientific evidence outlined in this advisory report, the committees decided, in line with the NFA, for lung cancer as the critical effect. The committees are of the opinion that, compared with the available evidence for silicosis, the available quantitative data for the exposure-response relationship with lung cancer generally has a higher quality, due to extensive exposure data and a good registration of lung cancer mortality*."

But Ge et al. (2020) state that their estimates of silica exposure may be affected by exposure misclassification and less accurate than some industrial cohort–based studies, particularly those with detailed work history and extensive historical silica measurements.

DECOS/NEG are kindly requested to clarify why the exposure data used in the lung cancer studies have a higher quality than the exposure data used in, for example, the silicosis study by 't Mannetje et al. (2002). DECOS/NEG are also kindly requested to clarify why the registration of lung cancer mortality is better than the registration of silicosis mortality and pneumoconiosis used by 't Mannetje et al. (2001).

Page 67, line 12 -14.
DECOS/NEG conclude from the key-study of Ge et al. (2020): '*Furthermore, increasing cumulative respirable quartz exposure was associated with increasing lung cancer risk (p-trend <0.01) even in the absence of silicotics (p-trend <0.01) and in current, former, and never smokers (p-trend <0.01).*'

The presented lung cancer Odds Ratios associated with cumulative silica exposure in subjects without silicosis that are presented in table 3 of the publication of Ge et al. (2020) appear to be stable rather than increasing with exposure (ORs: 1.22 -> 1.50 -> 1.48 -> 1.42; see also appendix 3).
My conclusion based on the information presented in table 3 of Ge et al (2020) is that an increase in silica exposure in subjects without silicosis is NOT associated with an increasing lung cancer risk.

I am not the only one with this view. ACGIH (2010) concluded in their TLV documentation document on RCS:

> *There is little support for the hypothesis that occupational silica exposure is a direct-acting initiator, while at the same time, there is compelling evidence that many forms of pulmonary fibrosis constitute a major risks for human lung cancer. Available data do not prove that the fibrosis associated with silicosis lead directly to lung cancer among silica-exposed workers. However, the implications from this assessment are that reductions of workers' exposures sufficient to eliminate silicosis will likely prevent the excess of lung cancer observed among silica-exposed individuals.*

The presented lung cancer Odds Ratios associated with cumulative silica exposure in never smokers in table 5 (see also appendix 3) also appear to be stable rather than increasing with exposure. The ORs in the 3 lower silica exposure groups of never smokers are stable and hardly increased (ORs: 1.17 -> 1.07 -> 1.02) and statistically not different from the non-exposed group. Only the group of never smokers with the highest cumulative exposure has an elevated lung cancer risk (OR of 1.40; 95% CI: 1.03 – 1.86).
My conclusion based on the information presented in table 5 of Ge et al (2020) is that an increase in silica exposure in never smokers is NOT associated with an increasing lung cancer risk. I would rather conclude that there appears to be a threshold value in never smokers for cumulative silica exposure below which there is no increased risk of lung cancer (threshold value: 2.39 mg/m^3-years).

Based on the results presented in table 5 one might even conclude that smoking (former or current smoking) has such a strong and dominant effect that it greatly complicates any conclusion about the contribution of silica exposure to the risk of lung cancer.

DECOS/NEG are kindly requested to visualize the alleged trends in silica exposure versus lung cancer risk (ORs, including the 95% C.I.!) in (i) subjects without silicosis and (ii) in never smokers, through graphs. Does the DECOS/NEG agree with the above described conclusions based on the information in table 3 and 5 in the publication of Ge et al. (2020): an increase in silica exposure in subjects without silicosis is NOT associated with an increasing lung cancer risk, and an increase in silica exposure up to 2.39 mg/m^3-years in never smokers is NOT associated with an increasing lung cancer risk? If not, please provide arguments why DECOS/NEG disagree.

Page 69, line 10 - 15.
DECOS/NEG state: "*Ge et al. (2020) have performed stratified analyses for smoking status (never, former, or current smoker) and investigated interactions between respirable crystalline silica exposure and smoking on risks of overall lung cancer and lung cancer subtypes. The stratified analyses showed that regardless of smoking status, increasing cumulative silica exposure was associated with increasing risk of lung cancer*".

Ge et al. (2020) have summarized the results of their stratified analyses in table 5 (see also appendix 3). In this table lung cancer Odds Ratios associated with cumulative silica exposure in never smokers, former smokers and current smokers are presented. When I look at the mentioned number of lung cancer cases in the 3 lowest exposure groups, I wonder whether these are not lung cancer cases caused by passive smoking. It is noted that about 5% of lung cancer cases are caused by passive smoking. I can imagine that silica exposed workers in for example construction, are more exposed to passive smoke than others, because they generally drink coffee or have lunch in a very mall break room (in Dutch 'schaftkeet').

Another issue that is not addressed in the study of Ge et al. 2020, that was selected by DECOS/NEG as key-study, is the possible role of background (non-occupational) exposure to RCS. Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar (see also IARC Monographs, volume 100 C Arsenic Metals, Fibres and Dusts, 1997). This background exposure cannot simply be ignored. It is noted that in de group of 'Never Exposed to Silica' studied by Ge et al. (2020), there were 13 lung cancer cases with reported silicosis and 5 control subjects with reported silicosis (see also table 1 in the publication of Ge et al., 2020).

DECOS/NEG are kindly requested to analyze the possible confounding effect of variables like passive smoking and background RCS exposure on the exposure-response relationship described in the selected key-publication of Ge et al. (2020) and the calculated cancer risk estimates by DECOS/NEG.

Page 72, line 21 – 33.
DECOS/NEG conclude on the suitability of the available epidemiological studies on lung cancer: '*Considering the two pooled analyses by Steenland et al. (2001) and Ge et al. (2020) [93], the committees prefer the pooled analysis conducted by Ge et al. (2020) as the key study. The committees are of the opinion that the study by Ge et al. (2020) is very well conducted.'*

That DECOS is of the opinion that the study of Ge et al. (2020) is '*very well conducted*' is not a surprise. Many authors of this publication have a close connection to members of the DECOS committee and/or were members of the DECOS committee in the past (see also appendix 3).

The DECOS/NEG prefer the pooled analysis of the population based case-control studies conducted by Ge et al. (2020) over the pooled analyses of industrial based cohort studies by Steenland et al. (2001). This does not mean that industrial cohort studies are less useful. Most important is the quality of the studies selected for the pooled analyses. It is noted that the NFA (2021), that used a selection of four industrial based cohort studies for the risk calculations in deriving HBC-OCRV for RCS, arrives at slightly higher but

quite comparable results as DECOS/NEG that used the pooled analyses of population based case-control studies (see § 9.4.2: 1:1,000 at 0.004 mg/m^3).

DECOS/NEG are kindly requested to clarify that risk calculations by NFA based on a selection of four industrial based cohort studies arrives at quite comparable results as DECOS/NEG that used the pooled analyses of population based case-control studies conducted by Ge et al. (2020).

Page 73, line 1 – 19
The DECOS/NEG describe why they choose to use a risk-based approach instead of a threshold-based report. The risk-based approach is chosen because it cannot be excluded that a direct genotoxic mechanism is involved due to particle-generated ROS (see also Annex F). Therefore, the committees take a precautionary approach and decided on a non-threshold (or risk-based) approach for risk calculations to estimate the excess risk of lung cancer.

Again, it is highly uncertain that a direct genotoxic mechanism plays a role, because there is no evidence whatsoever that the assumed particle-generated ROS contribute to the observed genotoxic effects.
Also the suggestion that a risk-based approach is always more cautious for indirect or non-genotoxic carcinogens than a threshold-based approach, is not correct. This depends on, among other things, on the NOAEL and the extrapolation factors that are used in relation to the carcinogenic potency when assuming that it is a direct acting carcinogen.

DECOS/NEG are kindly requested to clarify that the choice for using the risk-based approach instead of a threshold-based approach has no solid scientific basis.

Page 75, line 15 – 27
DECOS/NEG presents in table 9:

- the calculated target risk level or low-risk level of 4 extra lung cancer deaths per 100,000 workers, for 40 years of occupational exposure: 0.00038 mg/m^3.
- the calculated prohibition risk level or high-risk level of 4 extra lung cancer deaths per 1,000 workers, for 40 years of occupational exposure: 0.0363 mg/m^3.

In the publication of Ge et al. (2020) it is stated: "*Lung cancer ELRs were 0.22%, 0.45%, and 0.96% for workers exposed to 0.025, 0.05, and 0.1 mg/m^3 of silica, respectively*." This means that, according to Ge et al. (2020) a long cancer ELR of 4 per 1000 (0,4%) is equivalent to a RCS exposure of about 0.044 mg/m^3 instead of 0.0363 mg/m^3.

The target risk level is by definition exactly a factor of 100 lower than the prohibition risk level.

DECOS/NEG are kindly requested to clarify the difference between the estimated prohibition risk level by Ge et al. (0.044 mg/m^3) and the estimated risk level by DECOS/NEFG (0.0363 mg/m^3).
DECOS/NEG are kindly requested to adjust the reported risk levels in such a way that they differ from each other by exactly a factor of 100.

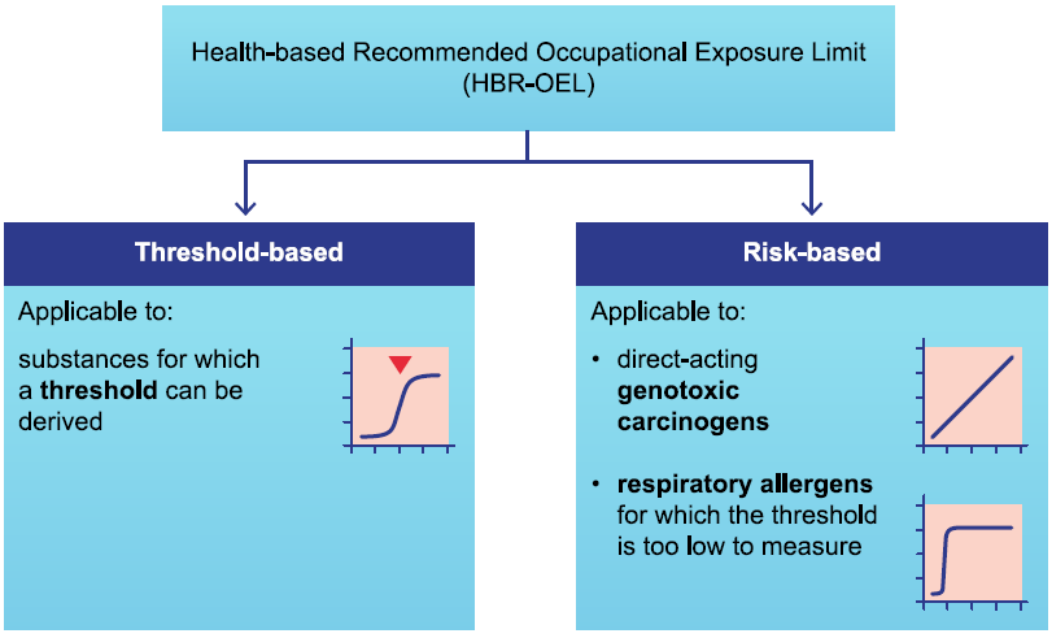
10. Research needs

no comments

Appendix 1. Choice for Threshold-based approach or Risk-based approach for derivation of health-based recommended occupational exposure limit (HBR-OEL)

Source: Health Council of the Netherlands (2021)
Guidance for recommending classifications and health-based occupational exposure limits. The Hague**, 2021**

HBR-OELs are derived using either a threshold approach or a risk-based approach, depending on the substance's critical effect



Source: Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety (2023)
Guideline for the classification of carcinogenic substances. Health Council of the Netherlands, The Hague, 2023

Page 18…

4.2 Proposed categorisation based on genotoxic mode of action

In view of the above, the Committee uses the following categorisation based on mode of action:

Mode of action	Limit value based on
Genotoxic - direct	HBR-OCRV
Genotoxic - indirect	HBR-OEL
Non-genotoxic	HBR-OEL

Page 18, 19 and 20:

Carcinogens that act by a direct genotoxic mechanism
This group includes substances that (either in their unchanged form or as reactive metabolites) interact directly with DNA, causing damage (adducts, single- and double-strand breaks). If this damage is not repaired quickly or adequately, gene mutations and chromosome abnormalities can occur at sites that are associated with carcinogenesis.

Carcinogens that act by an indirect genotoxic mechanism
These include substances that do not interact directly with DNA, but which can ultimately damage DNA indirectly.

Non-genotoxic carcinogens
These carcinogens are capable of promoting various phases of the cancer process without damaging DNA, either directly or indirectly. Such substances are known as tumor promoters.

There is a wide range of test systems for identifying a carcinogen's mode of action. Table 4 contains a list of measurable endpoints and of the carcinogenic modes of action that may be associated with them.

Table 4 Indicators of carcinogenic mode of action

Endpoint	Mechanism(s)	Genotoxic - Direct	Genotoxic - Indirect	Non-genotoxic
DNA-adducts	• direct interaction with DNA	+	–	–
	• inhibition of DNA-repair enzymes	–	+	–
DNA-breaks	• direct interaction with DNA	+	–	–
	• replication of damaged DNA	+	–	–
	• inhibition of DNA-repair enzymes	–	+	–
Gene mutations (mutations, deletions, amplifications, breaks, translocations)	• replication of damaged (alkylation) DNA	+	–	–
	• inhibition of DNA-repair enzymes	–	+	–
Structural chromosome aberrations (translocations, deletions, sister chromatid exchanges)	• replication of damaged DNA (alkylation, intercalation, cross-links)	+	–	–
	• inhibition of DNA-repair enzymes	–	+	–
	• inhibition of topoisomerases	–	+	–
Numerical chromosome aberrations (aneuploidy, polyploidy; micronuclei)	• replication of damaged DNA (alkylation, intercalation, cross-links)	+	+	–
	• inhibition of topoisomerases	–	+	–
	• disturbance of spindle apparatus	–	+	–
Changed gene expression[a]	• epigenetic: DNA hypo- of hyper-methylation of cytosine	–	–	+
	• epigenetic: disturbance of (de)acetylation of histones	–	–	+
	• disturbance of receptor-directed regulation of gene transcription	–	–	+
Changes in normal cell proliferation and differentiation, and cell transformation	• disturbance of hormone equilibrium	–	–	+
	• immune suppression	–	–	+
	• cytotoxicity and chronic irritation	–	–	+
	• disturbed activity of growth factors and signaling factors	–	–	+
	• disturbed receptor mediated regulation of cell division	–	–	+
	• disturbed intracellular communication (via *gap junctions*)	–	–	+

[a] Gene mutations, structural and numerical chromosome aberrations can result ultimately in changed gene expression and cell proliferation and differentiation, and cell transformation.

Appendix 2. Review of genotoxicity of respirable crystalline Silica

Source : P. Borm et al. (2018) An updated review of the genotoxicity of respirable crystalline silica. Part Fibre Toxicol 2018, p 15-23, 2018

Part Fibre Toxicol. 2018; 15: 23.
Published online 2018 May 21. doi: 10.1186/s12989-018-0259-z
PMCID: PMC5963024
PMID: 29783987

An updated review of the genotoxicity of respirable crystalline silica

Paul J. A. Borm,[*1] Paul Fowler,[2] and David Kirkland[3]

Journal Article

Associated Data

▸ Data Availability Statement

Abstract

Go to: ▸

Human exposure to (certain forms of) crystalline silica (CS) potentially results in adverse effects on human health. Since 1997 IARC has classified CS as a Group 1 carcinogen [1], which was confirmed in a later review in 2012 [2]. The genotoxic potential and mode of genotoxic action of CS was not conclusive in either of the IARC reviews, although a proposal for mode of actions was made in an extensive review of the genotoxicity of CS by Borm, Tran and Donaldson in 2011 [3]. The present study identified 141 new papers from search strings related to genotoxicity of respirable CS (RCS) since 2011 and, of these, 17 relevant publications with genotoxicity data were included in this detailed review.

Studies on in vitro genotoxic endpoints primarily included micronucleus (MN) frequency and % fragmented DNA as measured in the comet assay, and were mostly negative, apart from two studies using primary or cultured macrophages. In vivo studies confirmed the role of persistent inflammation due to quartz surface toxicity leading to anti-oxidant responses in mice and rats, but DNA damage was only seen in rats. The role of surface characteristics was strengthened by in vitro and in vivo studies using aluminium or hydrophobic treatment to quench the silanol groups on the CS surface.

In conclusion, the different modes of action of RCS-induced genotoxicity have been evaluated in a series of independent, adequate studies since 2011. Earlier conclusions on the role of inflammation driven by quartz surface in genotoxic and carcinogenic effects after inhalation are confirmed and findings support a practical threshold. Whereas classic in vitro genotoxicity studies confirm an earlier no-observed effect level (NOEL) in cell cultures of 60-70 μg/cm^2, transformation frequency in SHE cells suggests a lower threshold around 5 μg/cm^2. Both levels are only achieved in vivo at doses (2–4 mg) beyond in vivo doses (> 200 μg) that cause persistent inflammation and tissue remodelling in the rat lung.

Keywords: Crystalline silica, Quartz, Nanoparticles, Genotoxicity, Risk assessment

Appendix 3. Lung cancer risk associated with Cumulative Occupational Silica exposure in subjects without silicosis and by smoking status .

Source : Ge, Peters, Olsson, et al. (2020)
Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks - A Pooled Analysis of Case–Control Studies. Am J Respir Crit Care Med Vol 202, Issue 3, pp 412–421, Aug 1, 2020

ORIGINAL ARTICLE

Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks

A Pooled Analysis of Case–Control Studies

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Abstract

Rationale: Millions of workers around the world are exposed to respirable crystalline silica. Although silica is a confirmed human lung carcinogen, little is known regarding the cancer risks associated with low levels of exposure and risks by cancer subtype. However, little is known regarding the disease risks associated with low levels of exposure and risks by cancer subtype.

Objectives: We aimed to address current knowledge gaps in lung cancer risks associated with low levels of occupational silica exposure and the joint effects of smoking and silica exposure on lung cancer risks.

Methods: Subjects from 14 case–control studies from Europe and Canada with detailed smoking and occupational histories were pooled. A quantitative job-exposure matrix was used to estimate silica exposure by occupation, time period, and geographical region. Logistic regression models were used to estimate exposure–disease associations and the joint effects of silica exposure and smoking on risk of lung cancer. Stratified analyses by smoking history and cancer subtypes were also performed.

Measurements and Main Results: Our study included 16,901 cases and 20,965 control subjects. Lung cancer odds ratios ranged from 1.15 (95% confidence interval, 1.04–1.27) to 1.45 (95% confidence interval, 1.31–1.60) for groups with the lowest and highest cumulative exposure, respectively. Increasing cumulative silica exposure was associated (P trend < 0.01) with increasing lung cancer risks in nonsilicotics and in current, former, and never-smokers. Increasing exposure was also associated (P trend ≤ 0.01) with increasing risks of lung adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. Supermultiplicative interaction of silica exposure and smoking was observed on overall lung cancer risks; superadditive effects were observed in risks of lung cancer and all three included subtypes.

Conclusions: Silica exposure is associated with lung cancer at low exposure levels. An exposure–response relationship was robust and present regardless of smoking, silicosis status, and cancer subtype.

Keywords: lung cancer; crystalline silica; occupational exposure

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Table 3. Lung Cancer Odds Ratios Associated with Cumulative Occupational Silica Exposure in Subjects without Silicosis

Cumulative Silica Exposure (mg/m^3-*years*)	Cases (*n*)	OR*	95% CI
Never	6,091	1.0	Referent
>0–0.39	665	1.22	1.07–1.40
0.4–1.09	720	1.50	1.31–1.71
1.1–2.39	757	1.48	1.30–1.69
⩾2.4	740	1.42	1.25–1.63
Test for trend, *P* value		<0.01	
P value excluding never exposed		<0.01	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
*OR adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), and list A jobs.

Table 5. Lung Cancer Risks Associated with Cumulative Occupational Silica Exposure by Smoking Status

	Never-Smokers			Former Smokers			Current Smokers		
Cumulative exposure (*mg/m³-years*)	**Cases (*n*)**	**OR***	**95% CI**	**Cases (*n*)**	**OR†**	**95% CI**	**Cases (*n*)**	**OR‡**	**95% CI**
Never	1,121	1.0	Referent	3,696	1.0	Referent	7,161	1.0	Referent
>0–0.39	60	1.17	0.85–1.57	366	1.07	0.92–1.25	687	1.19	1.03–1.39
0.4–1.09	59	1.07	0.78–1.43	433	1.37	1.18–1.59	729	1.33	1.15–1.55
1.1–2.39	60	1.02	0.75–1.36	441	1.35	1.16–1.57	730	1.29	1.11–1.50
⩾2.4	69	1.40	1.03–1.86	496	1.47	1.27–1.70	793	1.39	1.20–1.62
Test for trend, *P* value		<0.01			<0.01			<0.01	
P value excluding never exposed		0.02			<0.01			0.07	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
*OR adjusted for sex, study, age group, and list A jobs.
†OR adjusted for sex, study, age group, list A jobs, pack-years, and time since quitting smoking.
‡OR adjusted for sex, study, age group, list A jobs, and pack-years.