National Research Centre
for the Working Environment

Respirable quartz and other crystalline silica polymorphs:

Scientific basis for setting a health-based occupational exposure limit

(Respirabelt kvarts og andre former for krystallinsk silica:
Videnskabelig dokumentation for helbredsbaserede risikoestimater)

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Foreword

The Danish Working Environment Authority has asked the National Research Centre for the Working Environment (NFA) to reassess the documentation for the Danish occupational exposure limit (OEL) for respirable quartz. Quartz is the most abundant form of crystalline silica.

The US Occupational Safety and Health Administration (OSHA), evaluated respirable crystalline silica in 2016 (OSHA, 2016) and established dose-response relationship for crystalline silica-induced excess lung cancer risk, silicosis and kidney disease for health-based occupational exposure limits. In their final evaluation, OSHA did not differentiate between the different types of crystalline silica. The present report is based on an assessment of this recent risk assessment report of respirable crystalline silica by OSHA.

The present working group wishes to thank Chief Toxicologist Poul Bo Larsen, DHI, Denmark, for reviewing this assessment. Furthermore, we wish to thank documentalist Elizabeth Bengtsen and librarian Rikke Nilsson for performing the literature search, the retrieval of literature and reference management.

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Abbreviations

ANSES	The French Agency for Food, Environmental and Occupational Health & Safety
ATSDR	The Agency for Toxic Substances and Disease Registry
COPD	Chronic obstructive pulmonary disease
IARC	World Health Organization's International Agency for Research on Cancer
IHD	Ischaemic Heart Disease
ILO	International Labour Organisation
NEG	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NIOSH	The National Institute for Occupational Safety and Health
NFA	National Research Centre for the Working Environment
NOAEL	No Observed Adverse Effect Level
OEL	Occupational exposure limit
OSHA	US Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
REL	Recommended exposure limit
RR	Relative Risk
SCOEL	The Scientific Committee on Occupational Exposure Limits
SiO_2	Silica, silicon dioxide

Executive summary

In this report, a working group at the National Research Centre for the Working Environment (NFA) reviewed data relevant to risk assessment of respirable quartz. Quartz is the most abundant form of crystalline silica. The working group assessed human studies, toxicokinetics, animal studies, mechanisms of toxicity, previous evaluations of quartz/crystalline silica, scientific basis for setting an occupational exposure limit (OEL) and finally the present working group summarizes and suggests the same risk levels for the respirable crystalline silica polymorphs quartz, cristobalite, and tridymite. The focus of this report is on occupational exposure by inhalation.

Quartz is found in sands, soils and most rock types. Cristobalite and tridymite are examples of other types of crystalline silica. All three forms occur both in α- and β-forms. Occupational exposure to quartz occurs in many different sites, including 1) activities that involve the movement of earth, 2) disturbance of silica-containing products, and 3) handling or use of sand- and other silica-containing products in transportation, construction, railroad and mining industries (IARC, 2012).

The current Danish OEL for respirable quartz is 0.1 mg/m^3. A recent study of Danish demolition workers showed that the geometric mean value for respirable crystalline silica was 0.12 mg/m^3. The air concentrations ranged from below the limit of detection to 0.92 mg/m^3 (Kirkegaard et al., 2016). A recent Swedish study of respirable quartz exposure in industries in Southern Sweden showed that the median value and the geometric mean value for quartz were 0.01 and 0.02 mg/m^3, respectively. The highest measured concentration was 17 mg/m^3 (Hedmer, 2017). A detection level of 0.002 mg/m^3 was reported in the Swedish study (Hedmer, 2017). IARC states that "*it has been estimated that respirable crystalline silica levels in the low μg/m^3 range are common in ambient air*" (IARC, 1997).In 1997, the World Health Organization's International Agency for Research on Cancer (IARC) classified crystalline silica dust as a human carcinogen (Group 1) (IARC, 1997). This evaluation was further confirmed when IARC reassessed crystalline silica in 2012 (IARC, 2012). IARC concluded that there is sufficient evidence in humans that crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

In the present report, endpoints were evaluated based on reported adverse effects of quartz exposure in reports and in the scientific literature. Especially the recent report by US Occupational Safety and Health Administration (OSHA) on crystalline silica (OSHA, 2016) including the background documents for this report (OSHA, 2010, 2013) were used as basis for the present report. OSHA evaluated several adverse health effects for crystalline silica. OSHA did not provide specific evaluations for each of the different crystalline silica polymorphs because they concluded that both epidemiological and experimental evidence show that quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency. The current working group agrees with this view and therefore decided to include all epidemiological studies of crystalline silica in the current evaluation. OSHA estimates that at their final permissible exposure limit of 50 μg/m^3 respirable crystalline silica as an 8-hour time-weighted average, the excess lung cancer mortality risk with 45 years of occupational exposure is 5 to 23 deaths per 1000 workers,

the silicosis morbidity is 20 to 170 per 1000 workers, the silicosis and non-malignant lung disease mortality is 7 to 44 per 1000 workers, and the renal disease mortality is 32 per 1000 workers. Overall, the present working group regards the OSHA report (OSHA, 2016) as a thorough evaluation of the available scientific evidence for the toxicity of respirable crystalline silica and the scientific evidence for dose-dependent induction of cancer, silicosis and renal disease.

The OSHA concluded that for autoimmune diseases, no quantitative exposure-response data are available for a quantitative risk assessment (OSHA, 2016). The present working group identified a very recent Danish cohort study on occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases with more than 3 million workers including approximately 17 000 cases (Boudigaard et al., 2021). The present working group considers that this is an important study showing an exposure-dependent association between exposure to respirable crystalline silica and autoimmune rheumatic diseases. However, since no mathematical relationship between exposure to respirable crystalline silica and autoimmune rheumatic diseases is presented, the present working group does not consider it possible to perform a quantitative risk analysis for this endpoint.

The OSHA report did not include cardiovascular effects as an endpoint. However, a recent criteria document on occupational chemical exposures and cardiovascular disease from Nordic Expert Group (NEG) concludes that there is strong evidence for an association between exposure to crystalline silica and cardiovascular disease, and we have therefore chosen to consider this endpoint as well (NEG, 2020). However, the present working group does not consider cardiovascular disease as one of the critical effects of crystalline silica exposure because cancer and silicosis may occur at lower exposure levels.

Based on the evaluation, the present working group regards lung cancer and silicosis as the critical effects.

The mechanism of action of crystalline silica-induced lung cancer is not clear, but primary genotoxicity caused by particle surface reactivity cannot be excluded, and therefore, the current working group decided to use a non-threshold approach. This is in line with the mathematical equations used for the risk calculations by OSHA. For silicosis, no threshold could be established in epidemiological studies.

The scientific literature on the health effects of quartz is enormous and therefore the present working group chose to focus the evaluation on the studies that OSHA considered appropriate for their final risk assessment. However, to ensure that the most recent literature also was assessed, a literature search was performed to identify studies published since the publication of the OSHA report. For the critical effects selected by the present working group, OSHA based their final risk assessment on 5 lung cancer mortality studies, 2 silicosis and non-malignant lung disease mortality studies, and 5 silicosis morbidity studies. By our own literature search, one additional study on lung cancer was identified that was considered relevant for inclusion in the final risk

assessment. The current working group notes that the OSHA risk estimates for lung cancer, silicosis and renal disease were of similar magnitude.

The current working group notes that there is evidence that occupational exposure to crystalline silica causes silicosis morbidity and mortality to the same extent or more potently as the exposure causes lung cancer. However, the present working group is of the opinion that the risk estimates for lung cancer mortality are better determined than the risk estimates for silicosis morbidity.

The current working group is of the opinion that the available quantitative epidemiological data for the dose-response relationship with lung cancer are more extensive, more transparent and comparable than the available data for silicosis and renal disease. The current working group therefore decided to use the quantitative epidemiological data for lung cancer as the most adequate and reliable basis for the risk assessment of crystalline silica.

All the quantitative studies on lung cancer risk provided models for the dose-response relationship between cumulative exposure to crystalline silica and lung cancer. The models varied between the studies (linear, log-linear, and linear spline models were used). Log-linear models were frequently used, and the present working group chose to base the risk estimation of cancer risk on the individual studies with log-linear equations. This approach made it possible to base the calculations of lung cancer risk on four studies which all used log-linear models. In summary, three of the five OSHA key studies (Attfield & Costello, 2004; Hughes et al., 2001; Miller & MacCalman, 2010) and one additional study identified in our own literature search (Liu et al., 2013) used log-linear model. These studies represent almost 60,000 workers and include approximately 1,600 deaths. The present working group suggests to calculate an un-weighed mean β based on these four studies for the risk calculations, using the same approach as for the previous evaluation of Cr(VI) by the present working group (NFA, 2019). Thus, the equation for the log-linear relationship between relative risk (RR) and cumulative exposure (E, mg/m^3*years) is:

$$RR = \exp(0.107 * E)$$

Based on this equation, the expected excess lung cancer risk based on an un-weighed mean β based on four epidemiological studies is 1:1,000 at 4 $\mu g/m^3$, 1:10,000 at 0.4 $\mu g/m^3$ and 1: 100,000 at 0.04 $\mu g/m^3$ respirable crystalline silica.

In comparison, OSHA estimates that at their final permissible exposure limit of 50 $\mu g/m^3$ respirable crystalline silica as an 8-hour time-weighted average, the excess risk lung cancer mortality risk associated with 45 years of occupational exposure is 5 to 23 deaths per 1,000 workers, the silicosis morbidity is 20 to 170 per 1,000 workers, the silicosis and non-malignant lung disease mortality is 7 to 44 per 1,000 workers and the renal disease mortality is 32 per 1,000 workers. Based on four epidemiological studies with almost 60,000 participants, the current working group estimates that occupational exposure to 38 $\mu g/m^3$ crystalline silica for 45 years will cause 10 excess lung cancer cases per 1,000

exposed. At 50 μg/m^3, this would correspond to 13 excess lung cancer cases per 1,000 exposed, and is therefore very similar to the risk estimates by OSHA.

The present working group concludes that there is evidence that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency, whereas the carcinogenic potency of silica dust may be modified depending on age and level and type of impurities. However, the information is insufficient to conclude to what extent these factors affect the toxicity. The present working group therefore recommends to adapt the same OEL for crystalline silica polymorphs quartz, cristobalite, and tridymite.

Dansk sammenfatning

Ved fastsættelse af grænseværdier i arbejdsmiljøet indgår en række hensyn. Det drejer sig om helbredsrisikoen, men også tekniske og samfundsmæssige hensyn.

I NFA's arbejde med grænseværdidokumentation anvendes risikoestimater, som er et teoretisk mål for hvor mange, der ved dagligt udsættelse for stoffet ved grænseværdien efter et helt arbejdsliv (typisk efter 40-45 år) vil blive syge. I disse beregninger er der ikke taget hensyn til personlige værnemidler eller andre kendte foranstaltninger til beskyttelse mod eksponering.

NFA udarbejder dokumentation for helbredsbaserede grænseværdier. Der tages udgangspunkt i publiceret systematisk litteraturgennemgang af epidemiologiske studier, dyrestudier og cellestudier af sammenhængen mellem udsættelse og risiko for forskellige helbredsudfald og de biologiske virkningsmekanismer. På baggrund af dette videnskabelige arbejde beregnes risikoestimaterne.

Dokumentation for helbredsbaserede grænseværdier vil sammen med de tekniske og samfundsmæssige betragtninger ligge til grund for forhandlinger mellem arbejdsmarkedets parter om endelig fastsættelse af grænseværdierne.

I denne rapport vurderer en arbejdsgruppe ved det Nationale Forskningscenter for Arbejdsmiljø (NFA) data, der er relevante for risikovurdering af respirabel kvarts. Kvarts er den hyppigst forekommende form af krystallinsk silica. Arbejdsgruppen vurderede humane studier, toksikokinetik, dyreforsøg, toksicitetsmekanismer, tidligere evalueringer af kvarts/krystallinsk silica og videnskabeligt grundlag for fastsættelse af en erhvervsmæssig eksponeringsgrænseværdi (OEL). Den nuværende arbejdsgruppe foreslår de samme risikoniveauer for respirabel krystallinsk silica polymorfe kvarts, cristobalit og tridymit. I denne rapport fokuseres på erhvervsmæssig eksponering ved indånding.

Kvarts findes i sand, jord og de fleste stenarter. Cristobalite og tridymite er eksempler på andre typer af krystallinsk silica. Alle tre former forekommer både i α- og β-former. Erhvervsmæssig eksponering for kvarts forekommer i mange erhverv, herunder i forbindelse med 1) aktiviteter, der involverer flytning af jord som fx ved minedrift, landbrug, byggeri og stenbrud, 2) nedbrydning af silicaholdige produkter som fx nedrivning af murværk og beton og 3) håndtering eller brug af sand- og andre silicaholdige produkter under transport, konstruktion, jernbane- og minedrift (IARC, 2012).

Den nuværende danske grænseværdi i arbejdsmiljøet for respirabel kvarts er 0,1 mg/m^3. En nyere undersøgelse af danske nedrivningsarbejdere viste, at den geometriske middelværdi for respirabel krystallinsk silica var 0,12 mg/m^3. Luftkoncentrationerne varierede fra under detektionsniveau til 0,92 mg/m^3 (Kirkegaard et al., 2016). En nyere svensk undersøgelse af respirabel kvartseksponering i industrier i det sydlige Sverige viste, at medianværdien og den geometriske middelværdi for kvarts var henholdsvis 0,01 og 0,02 mg/m^3. Den højeste målte koncentration var 17 mg/m^3. Detektionsgrænsen var 0,002 mg/m^3 i den svenske undersøgelse (Hedmer, 2017). IARC skriver, at " *it has been*

estimated that respirable crystalline silica levels in the low μg/m³ range are common in ambient air " (IARC, 1997).

I 1997 klassificerede Verdenssundhedsorganisationens Internationale Agentur for Kræftforskning (IARC) krystallinsk silicastøv som kræftfremkaldende for mennesker (gruppe 1) (IARC, 1997). Denne evaluering blev yderligere bekræftet, da IARC revurderede krystallinsk silica i 2012 (IARC, 2012). IARC konkluderede, at der hos mennesker er tilstrækkelig dokumentation for, at krystallinsk silica i form af kvarts eller cristobalitstøv forårsager lungekræft.

I denne rapport blev toksikologiske endepunkter evalueret på baggrund af rapporterede helbredseffekter af kvartseksponering i rapporter og i den videnskabelige litteratur. Den nyere rapport fra OSHA om krystallinsk silica (OSHA, 2016), sammen med baggrundsdokumenter til denne rapport (OSHA, 2010, 2013), dannede især grundlag for indeværende rapport. OSHA vurderede flere forskellige skadelige helbredseffekter for krystallinsk silica. OSHA har ikke udarbejdet særskilte evalueringer for hver af de forskellige krystallinske silica-former, fordi de konkluderede, at både epidemiologisk og eksperimentel dokumentation viser, at kvarts, cristobalit og tridymit har sammenlignelig toksicitet og kræftfremkaldende potens. Den nuværende arbejdsgruppe er enig i denne opfattelse og besluttede derfor at medtage alle epidemiologiske undersøgelser af krystallinsk silica i nærværende evaluering. OSHA estimerer, at ved den endelige tilladte eksponeringsgrænse på 50 μg/m³ respirabel krystallinsk silica som et 8-timers tidsvægtet gennemsnit er den overskydende risiko for lungekræftdødelighed efter 45 års arbejdsmæssig eksponering 5 til 23 dødsfald pr. 1.000 arbejdere, silicosesygdom er 20 til 170 per 1.000 arbejdere, silikose og den ikke-maligne lungesygdomsdødelighed er 7 til 44 pr. 1.000 arbejdere, og nyresygdomsdødeligheden er 32 pr. 1.000 arbejdere. Samlet set betragter den nuværende arbejdsgruppe OSHA-rapporten (OSHA, 2016) som en grundig evaluering af de tilgængelige videnskabelige data for toksiciteten af respirabel krystallinsk silica og den videnskabelige evidens for dosisafhængig induktion af kræft, silikose og nyresygdom.

OSHA konkluderede, at der ikke findes tilgængelige dosis-respons data, som kan anvendes til kvantitativ risikovurdering for autoimmune sygdomme (OSHA, 2016). Den nuværende arbejdsgruppe identificerede et helt nyt dansk kohortestudie om erhvervsmæssig eksponering for respirabel krystallinsk silica og risiko for autoimmune reumatiske sygdomme hos mere end 3 millioner arbejdere, herunder ca. 17.000 sygdomstilfælde (Boudigaard et al., 2021). Den nuværende arbejdsgruppe mener, at dette er en vigtig undersøgelse, der viser en eksponeringsafhængig sammenhæng mellem eksponering for respirabel krystallinsk silica og autoimmune reumatiske sygdomme. Da der imidlertid ikke angives nogen matematisk sammenhæng mellem eksponering for respirabel krystallinsk silica og autoimmune reumatiske sygdomme, anser den nuværende arbejdsgruppe det ikke for muligt at udføre en kvantitativ risikoanalyse for dette endepunkt.

OSHA behandlede ikke hjerte-kar-sygdom som endepunkt. Imidlertid konkludede et nyligt kriteriedokument om erhvervsmæssig kemisk eksponering og hjerte-kar-sygdom fra Nordisk Ekspert Gruppe (NEG), at der er stærk evidens for en sammenhæng mellem

eksponering for krystallinsk silica og hjerte-kar-sygdomme, og den nuværende arbejdsgruppe har derfor valgt at inkludere dette endepunkt i evalueringen af helbredseffekter af krystallinsk silica (NEG, 2020). Imidlertid betragter den nuværende arbejdsgruppe ikke hjerte-kar-sygdomme som en af de kritiske effekter af eksponering for krystallinsk silica, fordi kræft og silikose kan forekomme ved lavere eksponeringsniveauer.

Den nuværende arbejdsgruppe betragter derfor lungekræft og silikose som de kritiske effekter.

Virkningsmekanismen for krystallinsk silica-induceret lungekræft er ikke entydigt klarlagt, men primær genotoksicitet forårsaget af partikeloverfladeaktivitet kan ikke udelukkes, og derfor besluttede den nuværende arbejdsgruppe at anvende en ikke-tærskel tilgang. Dette er på linje med OSHA, idet OSHA bruger matematiske modeller, der forudsætter en ikke-tærskel effekt. For silicose kunne der ikke etableres nogen tærskel for effekt i epidemiologiske undersøgelser.

Den videnskabelige litteratur om sundhedseffekter af kvarts er enorm, og derfor valgte den nuværende arbejdsgruppe at fokusere evalueringen på de undersøgelser, som OSHA valgte at inkludere i deres endelige risikovurdering. For at sikre, at den nyeste litteratur også blev vurderet, blev der foretaget en litteratursøgning for at identificere undersøgelser, der er offentliggjort efter OSHA-rapporten. OSHA baserede deres helbredsbaserede risikoestimater for lungekræft og silikose på 5 lungekræftdødelighedsundersøgelser, 2 silikose- og ikke-maligne dødelighedsundersøgelser i lungesygdomme og 5 undersøgelser af silikosesygdom. Ved vores egen litteratursøgning blev der identificeret yderligere én undersøgelse af lungekræft, der blev anset for relevant for inkludering i den endelige risikovurdering. Den nuværende arbejdsgruppe bemærker, at OSHA's helbredsestimerede risikoestimater for lungekræft, silikose og nyresygdom var i samme størrelsesorden.

Den nuværende arbejdsgruppe bemærker, at der er evidens for, at erhvervsmæssig eksponering for krystallinsk silica forårsager silikose sygelighed og -dødelighed i samme eller større omfang som eksponeringen forårsager lungekræft.

Den nuværende arbejdsgruppe er af den opfattelse, at de tilgængelige kvantitative epidemiologiske data for dosis-respons-forholdet for lungekræft er mere omfattende, mere gennemsigtige og sammenlignelige end de tilgængelige data for silikose og nyresygdom. Den nuværende arbejdsgruppe besluttede derfor at bruge de kvantitative epidemiologiske data for lungekræft som det mest passende og pålidelige grundlag til risikovurderingen af krystallinsk silica.

Alle de kvantitative undersøgelser af lungekræftrisiko angav matematiske modeller for dosis-respons-forholdet mellem kumulativ eksponering for krystallinsk silica og lungekræft. Typen af matematiske modeller varierede mellem studierne (lineære, log-lineære og lineære spline-modeller blev brugt). Log-lineære modeller ((ln RR = β*E) blev ofte brugt, og den nuværende arbejdsgruppe valgte at basere risikovurderingen af kræftrisiko på de individuelle studier med log-lineære ligninger. Denne tilgang gjorde

det muligt at basere beregningerne af lungekræftrisiko på fire undersøgelser, som alle brugte log-lineære modeller.

Sammenfattende brugte tre af de fem OSHA-nøgleundersøgelser (Attfield & Costello, 2004; Hughes et al., 2001; Miller & MacCalman, 2010) og en yderligere undersøgelse identificeret i vores egen litteratursøgning (Liu et al., 2013) log-lineære modeller. Disse undersøgelser repræsenterer næsten 60.000 arbejdere og inkluderer cirka 1.600 dødsfald. Arbejdsgruppen foreslår at beregne et ikke-vægtet gennemsnit af hældningskoefficienten β baseret på disse fire undersøgelser til risikoberegningerne, og dermed bruge den samme tilgang som ved den tidligere evaluering af Cr (VI) foretaget af den nuværende arbejdsgruppe (NFA, 2019). Ligningen for det log-lineære forhold mellem relativ risiko (RR) og kumulativ eksponering (E, mg/m^3 * år) er således:

RR = eksp (0,107 * E)

Baseret på denne ligning er den forventede overskydende lungekræftrisiko baseret på et ikke-vægtet gennemsnit β baseret på fire epidemiologiske studier 1:1.000 ved 4 μg/m^3, 1:10.000 ved 0,4 μg/m^3 og 1:100.000 ved 0,04 μg/m^3 respirabel krystallinsk silica.

Til sammenligning estimerer OSHA, at ved deres tilladte grænseværdi på 50 μg/m^3 respirabel krystallinsk silica som et 8-timers tidsvægtet gennemsnit er den overskydende lungekræftdødelighed for eksponering over et 45 års arbejdsliv 5 til 23 dødsfald pr. 1.000 arbejdere, silikosesygdom er 20 til 170 pr. 1.000 arbejdere, silikose og den ikke-maligne lungesygdomsdødelighed er 7 til 44 pr. 1.000 arbejdere, og nyresygdødeligheden er 32 pr. 1.000 arbejdere. Baseret på fire epidemiologiske undersøgelser med næsten 60.000 deltagere estimerer den nuværende arbejdsgruppe, at erhvervsmæssig eksponering for 38 μg/m^3 krystallinsk silica i 45 år vil medføre 10 overskydende lungekræfttilfælde pr. 1.000 udsatte. Ved 50 μg/m^3 svarer dette til 13 overskydende lungekræfttilfælde pr. 1.000 eksponerede og ligger derfor indenfor OSHA's risikoestimat på 5-23 ekstra dødsfald forårsaget af lungekræft.

Den nuværende arbejdsgruppe konkluderer, at der er evidens for, at de krystallinske silica-polymorfe kvarts, cristobalit og tridymit har sammenlignelig toksicitet og kræftfremkaldende potens, mens den kræftfremkaldende effekt af silicastøv kan modificeres afhængigt af alder og niveau og typen af urenheder. Den tilgængelige evidens er imidlertid utilstrækkelig til at kunne konkludere, i hvilket omfang disse faktorer påvirker toksiciteten. Den nuværende arbejdsgruppe anbefaler derfor at anvende den samme grænseværdi i arbejdsmiljøet for alle tre former for krystallinsk silica.

Introduction

Quartz and other types of crystalline silica

The chemical formula of quartz is SiO_2 (silica, silicon dioxide). Silica exists in crystalline and amorphous forms. α-quartz is the most abundant form of silica and is found in sands, soils and most rock types (IARC, 1997). The term quartz is often used in place of the general term crystalline silica (NIOSH, 2002). Other types of crystalline silica are: β-quartz, α-tridymite, β-tridymite, α-cristobalite, β-cristobalite. The silica polymorphs may be converted into other forms by heating (IARC, 1997).

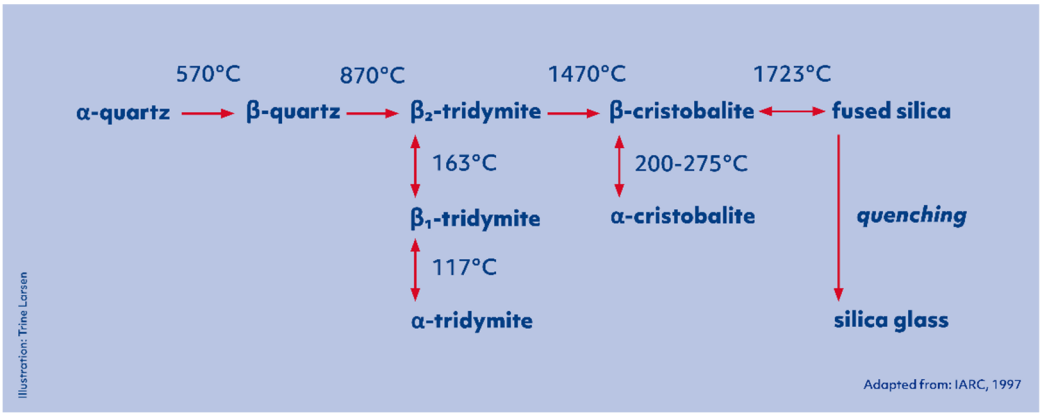

Figure 1. Interconversion from one silica polymorph to another due to heating or cooling (as schematized in (IARC, 1997)).

Selected physical and physical and chemical properties for different forms of crystalline silica are listed in Table 1.

Table 1. Selected physical and chemical properties for different forms of crystalline silica*.

Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties

Name	CAS No.	Basic Formula	Classification	Synonyms	Properties
Silica	7631-86-9	SiO_2	α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite		Structure: crystalline, amorphous, cryptocrystalline Molecular weight: 60.1 Solubility: poorly soluble in water at 20 °C and most acids; increases with temperature and pH Reactivity: reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol
Crystalline Silica					
Cristobalite	14464-46-1		α-cristobalite, β-cristobalite		
Quartz	14808-60-7		α-quartz, β-quartz	α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Solubility: 6–11 μg/cm³ (6–11 ppm) at room temperature; slightly soluble in body fluids Thermodynamic properties: melts to a glass; coefficient of expansion by heat—lowest of any known substance
Tripoli	1317-95-9				
Tridymite	15468-32-3		α-tridymite, β1-tridymite, β2-tridymite		

*The table is from (IARC, 2012).

The current Danish OEL is 0.1 mg/m^3 for respirable quartz and the Danish OEL for total quartz is 0.3 mg/m^3. These and other current Danish OELs for other types of crystalline silica are presented in Table 2.

Table 2. Current Danish OELs for respirable and total quartz, cristobalite and tridymite*.

Cas-nr.	Type of crystalline silica	mg/m^3	Note
14808-60-7	Quartz, respirable	0.1	K**
	Quartz, total	0.3	
14464-46-1	Cristobalite, respirable	0.05	K**
	Cristobalite, total	0.15	
15468-32-3	Tridymite, respirable	0.05	K**
	Tridymite, total	0.15	

*Table based on information in (AT, 2020).
**K: Considered to be carcinogenic by the Danish Working Environment Authorities: Carcinogenic substances are substances that are considered to be carcinogenic and covered by the regulation/directive/executive order on measures to prevent the risk of cancer when working with substances and materials.

The present report

The present report is primarily based on a critical evaluation of a recent report by the US Occupational Safety and Health Administration (OSHA) on occupational exposure to respirable crystalline silica (OSHA, 2016). In their report, OSHA presents risk estimates for the following endpoints: lung cancer mortality, silicosis and non-malignant lung disease mortality, renal disease mortality, and silicosis morbidity.

The current working group has focused on epidemiological studies and will only briefly mention other types of studies.

Human studies

Human exposure

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

In 2016, the Swedish Occupational and Environmental Medicine South (AMM Syd) carried out a collaborative project with the occupational health service in the Southern Swedish healthcare region concerning quartz measurements in Southern Sweden

(Skåne, Blekinge, Kronoberg og Södra Halland) (Hedmer, 2017). Person-borne measurements in the inhalation zone were performed in different industries (construction, concrete, stone, brewery and metal foundry). In total, 28 person-borne measurements of respirable quartz dust were performed. In addition 20 measurements of respirable inorganic dust were performed. The measured quartz levels varied between <0.002 (the level of detection for the used technique) and 17 mg/m^3, and the corresponding values for inorganic dust varied between 0.1 and 64 mg/ m^3. The median value and the geometric mean value for quartz were 0.01 and 0.02 mg/m^3, respectively. The corresponding values for respirable inorganic dust were 0.4 and 0.8 mg/m^3, respectively. Hedmer notes that the highest values were uncertain due to loose dust on the filter. The reported quartz levels in the dust varied between 0.9–27% with a median value of 2.5%. While doing quartz work, 21% of the workers used some form of respiratory protection (Hedmer, 2017).

The World Health Organization's International Agency for Research on Cancer (IARC) summarized occupational crystalline silica exposure data (IARC, 2012):

"*Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations (IARC, 1997)*" (IARC, 2012). IARC mentions the following main industries and activities: 1) activities that involve the movement of earth, 2) disturbance of silica-containing products, and 3) handling or use of sand- and other silica-containing products.

IARC (2012) refers to the previous IARC monography regarding exposure levels in main occupations with crystalline quarts exposure: "*Respirable quartz levels exceeding 0.1 mg/m^3 are most frequently found in metal, non-metal and coal mines and mills; in granite quarrying and processing, crushed stone and related industries; in foundries; in the ceramics industry; in construction and in sandblasting operations. Cristobalite is formed from quartz or any other form of silica at high temperatures (> 1400 ^{o}C) and from some amorphous silicas (e.g. diatomaceous earth) at somewhat lower temperatures (800 ^{o}C). Cristobalite exposure is notably associated with the use and calcination of diatomaceous earth as well as refractory material installation and repair operations. Few data exist on non-occupational exposures to crystalline silica. It has been estimated that respirable crystalline silica levels in the low μg/m^3 range are common in ambient air. Exposure may also occur during the use of a variety of consumer or hobby products*"(IARC, 1997).

The present working group notes that a recent study of Danish demolition workers showed that the geometric mean value for respirable crystalline silica was 0.12 mg/m^3 [<0.01 (no detectable crystalline silica) to 0.92 mg/m^3] (Kirkegaard et al., 2016). The highest measured concentration was 0.92 mg/m^3. The geometric mean of the Danish respirable crystalline silica meaurements were approximately 6-fold higher than the measurements of respirable quartz exposure in industries in Southern Sweden . The highest measured concentration was 17 mg/m^3 in the Swedish study. The present working group furthermore notes that a detection level of 0.002 mg/m^3 was reported in a Swedish study (Hedmer, 2017). The present working group also notes that IARC states

that "*it has been estimated that respirable crystalline silica levels in the low μg/m³ range are common in ambient air*" (IARC, 1997).

Epidemiological studies

Based on their literature review of adverse health effects related to inhalation of respirable crystalline silica, OSHA concludes: "*OSHA finds that employees exposed to respirable crystalline silica at the preceding Permissible Exposure Limits* (PELs) [The US preceding PEL was 100 μg/m³ when the OSHA report is written] *are at an increased risk of lung cancer mortality and silicosis mortality and morbidity. Occupational exposures to respirable crystalline silica also result in increased risk of death from other nonmalignant respiratory diseases including chronic obstructive pulmonary disease (COPD), and from kidney disease.*" (OSHA, 2016).

The current working group notes that OSHA concludes that there is increased risk of lung cancer mortality and silicosis mortality and morbidity at 0.1 mg/m³, the current Danish OEL for crystalline quartz (which is similar to the preceding US PELs).

The present chapter presents an overview and some background information of silicosis and quartz-induced lung cancer based on epidemiological studies. The individual studies will be described in more detail in the chapter on *Scientific basis for setting an occupational exposure limit*.

Lung cancer

IARC

In 1997, IARC classified crystalline silica dust as a human carcinogen (Group 1) (IARC, 1997). This evaluation was further confirmed when IARC reassessed crystalline silica in 2009 (IARC, 2012): "*There is sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung. There is sufficient evidence in experimental animals for the carcinogenicity of quartz dust.*" and "*Crystalline silica in the form of quartz or cristobalite dust is carcinogenic to humans*" (IARC, 2012).

IARC further concludes: "*Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk*" and "*The strongest evidence supporting the carcinogenicity of crystalline silica in the lungs comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure-response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusio*ns" (IARC, 2012).

OSHA

Regarding the dose-response relationship for cancer, OSHA has focused on a pooled exposure-response analysis performed by Steenland et al. (Steenland et al., 2001) and

later reanalyzed by Steenland and Bartell (Steenland & Bartell, 2004), and in addition, four more recent studies by Rice et al. (Rice et al., 2001), Attfield and Costello (Attfield & Costello, 2004), Hughes et al. (Hughes et al., 2001), Miller and MacCalman (Miller & MacCalman, 2010) which form the basis for the cancer risk assessments performed by OSHA.

NFA literature search

The OSHA report (OSHA, 2016) is based on a background document from 2010 (OSHA, 2010) and a supplementary report from (OSHA, 2013). To be able to identify dose-response studies or meta-analyses of epidemiological studies published during the last decade, the current working group performed a literature search in MEDLINE restricted to the time-period between 01.01.2010 and 31.12.2019. A detailed description of the literature search is included in appendix A. In brief, we combined search terms for "quartz" and "exposure" and ("meta-analysis" or "dose-response").

The literature search resulted in 367 publications. Based on a screening of titles, 16 publications were chosen for a further abstract screening. Reading of abstracts resulted in 4 publications that were considered possible useful for quantitative risk assessment on lung cancer (Gamble, 2011; Liu et al., 2013; Poinen-Rughooputh et al., 2016; Sogl et al., 2012). Below, these manuscripts are briefly described.

Liu et al., 2013

Liu et al. analyzed a cohort (1960-2003) of 34,018 Chinese workers with exposure to quartz (and without known exposure to any carcinogenic confounders). The cohort included 546 lung cancer deaths (mean follow-up was 34.5 years). At lower silica levels, the authors found a clear exposure-response trend between cumulative silica exposure and lung cancer, while this trend was decreasing at high exposure levels. A model with continuous logged cumulative silica exposure gave the best fit (β=0.055 with a 15-year lag and 0.065 with a 25-year lag) (Liu et al., 2013). The present working group finds that this study is relevant to include in our risk assessment due to the following strengths of the study: 1) large cohort, 2) long follow-up period, 3) exclusion of persons with possible confounding carcinogenic exposure (tin and cupper miners), and 4) adjustment for smoking (time-dependent variable).

Sogl et al., 2012

The cohort analyzed by Sogl et al includes 58 677 German uranium miners for which there were information on occupational exposure to crystalline silica and possible confounding exposure to radon and arsenic. The cohort included 2,995 lung cancer deaths in the follow-up period from 1946-2003. The study found a positive exposure response relationship between high cumulative exposure to silica and lung cancer. The best fit of the data were found to be a piecewise spline function with a knot at 10 mg/m^3 years. Even though the authors adjust for radon exposure in their analysis, the present working group decided not to include this study in our risk assessment because as the authors state themselves: "Owing to *the relatively high correlation of radon and dust over time and the fact that radon is a stronger risk factor than silica, it cannot be ruled out that the adjustment for radon including the three effect modifiers* [age, time and exposure rate] *may have led to some over adjustment*"(Sogl et al., 2012).

Poinen-Rughooputh et al., 2016
Poinen-Rughooputh has provided a recent meta-analysis of studies on lung cancer and occupational crystalline silica exposure in the epidemiological literature in the period from January 1982 to April 2016. Overall, a positive exposure-response relation was found between silica exposure (cumulative) and risk of lung cancer. An increased risk of lung cancer was both found in persons with (SMR: 2.32 (95% CI: 1.92-2.81)) and without silicosis (SMR=1.78 (95% CI: 1.07-2.96). Since the meta-analysis did not report estimates of quantitative dose-response relationship, the present working group has not used the study for our risk assessment (Poinen-Rughooputh et al., 2016).

Gamble, 2011
This review is a critical appraisal against the IARC classification and against the pooled analysis by Steenland et al (Steenland et al., 2001). Gamble argues that other studies should have been included in the IARC and Steenland analyses, which were evaluated as appropriate by IARC and OSHA. OSHA also evaluated the Gamble study in their supplemental literature review of epidemiological studies on lung cancer associated with exposure to respirable crystalline silica, and concluded as follows: "*The main reason for the discordant conclusion regarding associations between crystalline silica exposure and lung cancer reached by OSHA and Gamble were (1) different opinions regarding the reliability and usefulness of individual studies in the data set and (2) different methods for assessing weight of evidence. In the background document on respirable crystalline silica, OSHA thoroughly evaluated the strengths and limitations of each study; the Agency stands by its interpretations of study reliability. In weighing the evidence, OSHA considered only the best designed studies, and believes that approach is more appropriate than simply summing up the number of positive and negative studies. Based on substantial evidence of an effect in the best designed studies, OSHA maintains that the weight of the evidence supports an association between exposure to respirable crystalline silica and lung cancer*"(OSHA, 2013). The present working group agrees with IARC and OSHA and notes that the author declared financial support from the stone industry (Gamble, 2011). The review is not further considered in the present evaluation.

By the literature search covering the period since the publication of the OSHA background documents, the present working group identified one study on lung cancer that was considered relevant for the risk assessment (Liu et al., 2013).

The present working group notes that there is strong and convincing evidence of a causal association between exposures to crystalline silica and lung cancer, and that there is a clear exposure-response relationship.

Silicosis

Silicosis is named after its causal agent, silica, and is a biomarker of exposure to crystalline silica at high concentrations. Silicosis is characterized by fibrotic nodules in the lung ('t Mannetje et al., 2002a). In order to diagnose silicosis, the following three requisites are necessary (OSHA, 2010): 1) Silica exposure, 2) chest radiographic abnormalities consistent with silicosis, and 3) lack of other diseases that could look like silicosis. The abnormalities resemble opacities on chest radiographic. Based on the profusion of opacities, silicosis is classified into four major categories of which each is

further classified in three subcategories according to a standard by the International Labour Organization (ILO)(1980)(as described in (OSHA, 2010)). This results in a 12-point scale as shown in Table 3. The four major categories and their subcategories represent a continuum of increasing concentration of opacities compared to a standard radiograph. Thus, the extremities are major category 0 defined by having no opacities or a concentration of opacities less than category 1/0, and major category 3 with the highest level of profusion of opacities. The ILO classification was updated in 2011 thereby extending the applicability of the classification to digital radiographic images of the chest (ILO, 2011).

Table 3. 12-point scale for the classification of silicosis on the basis of an evaluation of the profusion of opacities[1].

Major category	Subcategory		
Category 0	0/-	0/0	0/1
Category 1	1/0	1/1	1/2
Category 2	2/1	2/2	2/3
Category 3	3/1	3/2	3/+

[1]The categories are defined as described by ILO (ILO, 2011): "*Category 0 refers to the absence of small opacities or the presence of small opacities that are less profuse than category 1. Classification of a radiograph using the 12-subcategory scale is performed as follows. The appropriate category is chosen by comparing a subject radiograph with standard radiographs that define the levels of profusion characteristic of the centrally placed subcategories (0/0, 1/1, 2/2, 3/3) within these categories. The category is recorded by writing the corresponding symbol followed by an oblique stroke, i.e. 0/ , 1/ , 2/ , 3/. If no alternative category was seriously considered, the radiograph is classified into the central subcategory, i.e. 0/0, 1/1, 2/2, 3/3. For example, a radiograph that shows profusion which is considered to be similar to that shown on a subcategory 2/2 standard radiograph, i.e. neither category 1 nor 3 was seriously considered as an alternative, would be classified as 2/2. However, subcategory 2/1 refers to a radiograph with profusion of small opacities judged to be similar in appearance to that depicted on a subcategory 2/2 standard radiograph, but category 1 was seriously considered as an alternative before deciding to classify it as category 2. The standard radiographs provide examples of appearances classifiable as subcategory 0/0. Subcategory 0/0 refers to radiographs where there are no small opacities, or if a few are thought to be present, they are not sufficiently definite or numerous for category 1 to have been seriously considered as an alternative. Subcategory 0/1 is used for radiographs classified as category 0 after having seriously considered category 1 as an alternative. Subcategory 1/0 is used for radiographs classified as category 1 after having seriously considered category 0 as an alternative. If the absence of small opacities is particularly obvious, then the radiograph is classified as subcategory 0/−. A radiograph showing profusion much greater than that depicted on a subcategory 3/3 standard radiograph is classified as subcategory 3/+*".

The sensitivity of the radiological evaluation of silicosis was evaluated by comparing the radiological and pathological diagnosis of silicosis on 557 gold miners (Hnizdo et al., 1993). The study showed that a large proportion of those that were evaluated as having silicosis based on pathological examination at autopsy were not diagnosed radiologically approximately 3 years before autopsy.

OSHA concludes:"*Chest radiography is not the most sensitive tool used to diagnose or detect silicosis*" and "*The low sensitivity seen for radiographic evaluation suggests that risk estimates derived from radiographic evidence likely understate the true risk of developing fibrotic lesions as a result of exposure to crystalline silica*" (OSHA, 2010).

The present working group notes that this indicates that there may be a relatively large group of false negative when using radiological evaluation for the examination of silicosis thereby underestimating the risk of silicosis.

NFA literature search

The OSHA report (OSHA, 2016) is based on a background document from 2010 (OSHA, 2010) and a supplementary report from (OSHA, 2013). To be able to identify dose-response studies regarding silicosis or meta-analyses of epidemiological studies published during the last decade we performed a literature search in MEDLINE restricted to the time-period between 01.01.2010 and 31.12.2019. A detailed description of the literature search is included in appendix A. In brief, we combined search terms for "quartz" and "exposure" and ("meta-analysis" or "dose-response").

Our literature search resulted in 367 publications. Based on a screening of titles, 16 publications were chosen for a further abstract screening. Reading of abstracts resulted in selection of one publication that were considered possible useful for quantitative risk assessment of silicosis (Leso et al., 2019). The study is briefly described below.

Leso et al., 2019

Leso et al. has provided a recent systematic review of studies of silicosis and exposure to artificial stone (Leso et al., 2019). Artificial stone is produced by mixing of finely crushed rocks with polymeric resin. The silica content is approximately 90%. Artificial stone is a material that is used for manufacturing of kitchen and bathroom countertops. The authors concluded that "*the characteristics of artificial stone associated silicosis were comparable to those that were reported for the disease in traditional silica exposure settings, some critical issues emerged concerning the general lack of suitable strategies for assessing/managing silica risks in these innovative occupational fields*".

The present working group notes that the review by Leso et al. (Leso et al., 2019) illustrates that exposure to crystalline silica may occur in new occupational settings. No calculations of risks are performed by Leso et al. and therefore the manuscript is not discussed further in the present report.

Renal disease

For renal disease mortality, OSHA has based its risk estimates on a large combined cohort of three cohorts consisting in total of 13,382 workers including 51 kidney deaths (Steenland et al., 2002a). The combined cohort was based on studies of: 1) gold miners, 2) industrial sand workers, and 3) granite workers. OSHA concludes: "*Although these estimates are based on only 50 renal disease deaths in the pooled cohort, and are therefore less robust than risk estimates for other health effects discussed in this assessment, OSHA believes that the risk estimates for renal disease are credible given the large size of the pooled cohort study and quality of underlying exposure and job history information*".

Although this is a large combined cohort with exposure assessment for about 95% of the study subjects (OSHA, 2010), the present working group does not consider renal disease mortality in the final risk assessment because of the low number of deaths, potentially leading to less certain risk estimates.

Autoimmune diseases

OSHA concluded that the reviewed epidemiological studies suggested an association between respirable silica exposure and autoimmune diseases, including rheumatoid arthritis, scleroderma and systemic lupus erythematosus. However, OSHA further concluded that for autoimmune diseases, no quantitative exposure-response data are available for a quantitative risk assessment (OSHA, 2016). The present working group identified a very recent Danish cohort study on occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases with more than 3 million workers including approximately 17,000 cases (Boudigaard et al., 2021). When comparing men and women exposed to high levels of respirable crystalline silica with non-exposed, the incidence rate ratio for autoimmune rheumatic diseases increased with increasing cumulative exposure of 1.07 (1.05-1.09) and 1.04 (0.99-1.10) per 50 μg/m^3-years for men and women, respectively. The present working group considers this to be an important study showing an exposure-dependent association between exposure to respirable crystalline silica and autoimmune rheumatic diseases. However, since no mathematical model for the relationship between exposure to respirable crystalline silica and autoimmune rheumatic diseases is presented, the present working group does not consider that it is possible to perform a quantitative risk analysis for this endpoint and therefore this endpoint is not discussed further in the present report.

Cardiovascular disease

The OSHA report does not assess cardiovascular effects as an endpoint. However, a recent criteria document on occupational chemical exposures and cardiovascular disease concludes that there is strong evidence for an association between exposure to crystalline silica and cardiovascular disease, (NEG, 2020) and therefore the current working group chose to consider this endpoint as well. For respirable crystalline silica, the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) concludes that "*exposure at 0.01–0.02 mg/m^3 for 40 years, estimated from cumulative exposure data, was associated with IHD [ischaemic heart disease]*".

In one of the reported studies in the NEG report, it was found that cumulative exposure of 0.56-0.87 mg/m^3 –years led to an increased risk of mortality due to ischemic heart disease (HR 1.52, 95% CI 1.02-2.27). Converted to a 40 years working life this corresponds to exposure to 0.01-0.02 mg/m^3 respirable crystalline silica. When the cohort was divided so that only participants with lifetime highest respirable crystalline silica exposure ≤0.05 mg/m^3 were studied, workers exposed to more than 0.67 mg/m^3 –years had an increased risk of ischemic heart disease (HR 1.89, 95% CI 1.07-3.35) (NEG, 2020). Considering that crystalline silica is a human carcinogen, the present working group does not consider cardiovascular disease as one of the critical effects of crystalline silica exposure because cancer may occur at lower exposure levels.

In conclusion, based on epidemiological studies, the present working group considers lung cancer and silicosis as the critical effects following occupational exposure to crystalline silica.

Animal studies

IARC has evaluated the carcinogenicity of crystalline silica in experimental animals, and summarizes:

"*Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black (Mauderly et al., 1994).*

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induces lymphomas were observed in only a single experiment" (IARC, 2012).

Based on the above, IARC concludes that "*there is sufficient evidence in experimental animals for the carcinogenicity of quartz dust*" and that "*there is limited evidence in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust*" (IARC, 2012). The experimental studies that form the background for these conclusions are described in detail by IARC in their latest evaluations of silica (IARC, 1997, 2012) and will not be further described in the present report.
The present working group notes that most of the referred studies in the IARC monography are studies in rats. However, some studies are in hamsters and mice as well. IARC report the following inhalation studies: mouse (1 study, no significant increase in lung tumours), rat (4 studies, significant increase in lung tumours in all studies) and hamster (1 study, no significant increase in lung tumours).) In general, hamsters and mice are more resistant than rats to the induction of lung cancer following exposure to particles. Furthermore, the present working group notes that only a few animal experiments with tridymite and cristobalite dust have been performed. In a single experiment, tridymite and cristobalite induced lymphomas.

Toxicokinetics

Toxicokinetics has been summarized by IARC as follows:
"*Crystalline silica deposited in the lungs causes epithelial and macrophage injury and activation. Crystalline silica translocates to the interstitium and the regional lymph nodes. Crystalline silica results in inflammatory cell recruitment in a dose-dependent manner. Neutrophil recruitment is florid in rats exposed to high concentrations of quartz; marked, persistent inflammation occurs accompanied by proliferative responses of the epithelium and interstitial cells. In humans, a large fraction of crystalline silica persists in the lungs, culminating in the development of chronic silicosis, emphysema, obstructive airways disease and lymph node fibrosis in some studies. In-vitro studies have shown that crystalline silica can stimulate release of cytokines and growth factors from macrophages and epithelial cells; evidence exists that these events occur in vivo and contribute to disease. Crystalline silica stimulates release of reactive oxygen and nitrogen intermediates from a variety of cell types in vitro. Oxidative stress is detectable in the lungs of rats following exposure to quartz*"(IARC, 1997).

The Agency for Toxic Substances and Disease Registry (ATSDR) recently summarized the toxicokinetics of silica (ATSDR, 2019):

"Absorption:
o Respiratory tract: Absorption of silica compounds from the respiratory tract is the most studied absorption pathway.

- *No quantitative estimates of absorption of silica compounds from the respiratory tract are available. However, detection of silica in the urine of exposed workers indicates that c-silica [crystalline silica] undergoes absorption following inhalation exposure.*
- *Respiratory particles of silica are cleared from the pulmonary region primarily by lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow.*
- *Due to limited solubility, dissolution of c-silica [crystalline silica], followed by absorption from the respiratory tract is not a predominant pathway for absorption. Dissolution of a-silica [amorphous (or noncrystalline)] compounds may be a more important absorption pathway for a-silica [amorphous (or noncrystalline)].*
- *Inhaled c-silica [crystalline silica] compounds may be retained within the lungs for years after cessation of exposure*

o Gastrointestinal tract: Limited information from animal studies indicates that absorption of silica compounds following oral exposure is negligible.

o Dermal: No studies examining dermal absorption of silica compounds were identified, although it is anticipated that absorption through the skin would be negligible.

Distribution: *Studies in humans and animals show that inhaled c-silica is distributed to the kidneys, lymph nodes, blood, liver, and spleen. No information on distribution of silica compounds following oral or dermal exposure was identified.*

Metabolism: *Absorbed silica compounds do not undergo metabolism.*

Excretion: *Silica has been detected in urine of workers exposed to c-silica [crystalline silica]. Ingested silica compounds are excreted in the feces. No information on excretion of silica compounds following dermal exposure was identified*" (ATSDR, 2019).

The current working group concludes that inhalation exposure is the most relevant exposure route. Uptake through the skin and the gastrointestinal tract is considered negligible. Crystalline silica has limited solubility and accumulates in the lung following inhalation, leading to long-term accumulation in the lung.

Mechanisms of toxicity

Cancer

IARC proposes three mechanisms for the carcinogenicity of crystalline silica in rats: 1) inflammation-induced carcinogenicity, 2) extracellular generation of free radicals by crystalline silica resulting in depletion of antioxidants and cell injury followed by epithelial cell proliferation, and 3) direct, primary genotoxicity caused by generation of free radicals by crystalline silica particles taken up by epithelial cells (IARC, 2012). IARC considers "*the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust*" (IARC, 2012).

OSHA concludes:"*A review of epidemiologic studies has also attempted to answer the question of whether silicosis is a necessary precursor to lung cancer in silica-exposed individuals. Checkoway and Franzblau (2000) reviewed 17 studies of lung cancer mortality among silicotics. They concluded that the question of whether silicosis is required for elevated lung cancer risk in silica-exposed individuals cannot be answered from currently available epidemiologic literature, and that risk assessments should consider silicosis and lung cancer in silica-exposed individuals as separate entities whose cause/effect relations are not necessarily linked"* (OSHA, 2013).

A similar conclusion is reached in a recent report by HSE Workplace Health Expert Committee: "…*indicates that RCS [respirable crystalline silica] is a cause of lung cancer, suggests that lung cancer can occur in the absence of radiologically evident silicosis but, as yet, the evidence is insufficient to distinguish in humans whether the cancer is secondary to the inflammatory reaction to silica retained in the lungs or from a direct genotoxic effect of silica*" (WHEC, 2017).

Similarly, the very recent conclusions by The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) and ATSDR were in line with the above: "*Although having silicosis increases a person's risk of developing cancer, the available studies confirm the existence of a significant risk even without silicosis*"(ANSES, 2019) and "*results of a cohort study of over 30,000 workers in China indicate that exposure to c-silica [crystalline silica] is associated with lung cancer in the absence of silicosis (Liu et al. 2013)*" (ATSDR, 2019), respectively.

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

Since a non-threshold mechanism of carcinogenicity cannot be excluded, the present working group considers the mechanism of action to be a non-threshold mechanism of action in the hazard assessment of carcinogenicity. This precautionary approach is based on the recommendation from ECHA REACH R8 (ECHA, 2012) in which it is stated that:

"*It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice. For mutagens/carcinogens, it should be stressed that the Carcinogens and Mutagens Directive (2004/37/EC) requires that occupational exposures are avoided/minimised as far as technically feasible. As REACH does not overrule the Carcinogens and Mutagens Directive, the approach to controlling workplace exposure should therefore comply with this minimisation requirement.*"

Silicosis

OSHA has summarized:
"*Silicosis is an irreversible, progressive disease induced by the inflammatory effects of respirable crystalline silica in the lung, leading to lung damage and scarring and, in some cases, progressing to complications resulting in disability and death. Exposure to respirable crystalline silica is the only known cause of silicosis. Three types of silicosis have been described: An acute form following intense exposure to respirable dust of high crystalline silica content for a relatively short period (i.e., a few months or years); an accelerated form, resulting from about 5 to 15 years of heavy exposure to respirable dusts of high crystalline silica content; and, most commonly, a chronic form that typically follows less intense exposure of more than 20 years (Becklake, 1994, Document ID 0294; Balaan and Banks, 1992, 0289). In both the accelerated and chronic forms of the disease, lung inflammation leads to the formation of excess connective tissue, or fibrosis, in the lung. The hallmark of the chronic form of silicosis is the silicotic islet or nodule, one of the few agent-specific lesions in pathology (Balaan and Banks,1992, Document ID 0289). As the disease progresses, these nodules, or fibrotic lesions, increase in density and can develop into large fibrotic masses, resulting in progressive massive fibrosis (PMF). Once established, the fibrotic process of chronic silicosis is thought to be irreversible (Becklake, 1994, Document ID 0294). There is no specific treatment for silicosis (Davis, 1996,Document ID 0998; Banks, 2005, 0291)*" (OSHA, 2016).

SCOEL has concluded that it is not possible to identify a threshold for silicosis. On that background SCOEL concludes that*: "any reduction of exposure will reduce the risk of silicosis" (SCOEL*, 2003). This conclusion is backed up by the recent assessment by ATSDR: "…*a no-observed-adverse-effect level (NOAEL) for silicosis has not been defined, with silicosis and death due to silicosis observed for the lowest estimated cumulative exposure ranges reported*" (ATSDR, 2019).

Based on the above, the present working group notes that the only known cause of silicosis is exposure to respirable crystalline silica. Silicosis exists in three forms: 1) an acute form, 2) an accelerated form, and 3) a chronic form that are all caused by an inflammatory reaction towards respirable crystalline silica in the lungs. With regard to the accelerated and the chronic forms, the pulmonary inflammation results in the formation of excess connective tissue, or fibrosis, in the lung. The chronic form of silicosis is the most common form. There is no cure for silicosis. Furthermore, SCOEL and ATSDR have concluded that it is not possible to identify a threshold for silicosis. In line with this, the current working group will regard silicosis as having no threshold.

Particle characteristics

OSHA has evaluated different physical factors that may affect the toxicity of crystalline silica (OSHA, 2016). Among these, OSHA compared the evidence of toxicity of different polymorphs of crystalline silica. OSHA refers that in some animal studies, cristobalite and tridymite have been found to be more toxic than quartz. However, OSHA further refers that several reviews of animal studies performed by others conclude that cristobalite and tridymite are not more toxic than quartz, and that this is backed up by epidemiological studies that do not show different toxicity of cristobalite and quartz. OSHA preliminary concludes: "*..based on epidemiologic and experimental evidence, that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency*"(OSHA, 2010). In addition, OSHA discusses the toxicity of freshly fractured silica to that of aged silica in animal studies. OSHA concludes that "*these studies have demonstrated that although freshly fractured silica is more toxic than aged silica, aged silica still retains significant toxicity*"(OSHA, 2016). Finally, OSHA discusses the effect of surface impurities: Metal surface impurities, particularly metals, have been shown to either increase or decrease silica toxicity. Eg. "*Aluminium as well as other metal ions are thought to modify silanol groups on the silica surface, thus decreasing the membranolytic and cytotoxic potency and resulting in enhanced particle clearance from the lung before damage can take place*"(OSHA, 2016).

IARC (IARC, 2012) has similar considerations as OSHA (OSHA, 2016): "*Physicochemical features – polymorph characteristics, associated contaminants – may account for the differences found in human and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called "variability of quartz hazard" have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle"* and concludes that "*the pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron)*"(IARC, 2012).

OSHA concludes: "*that while there was considerable evidence that several environmental influences can modify surface activity to either enhance or diminish the toxicity of silica, the available information was insufficient to determine in any quantitative way how these influences may affect disease risk to workers in any particular workplace setting*" (OSHA, 2016).

The present working group is of the opinion that the toxicity of silica dust may depend on the type of silica polymorph and/or impurities. In a recent publication, the importance of surface silanols in the interaction between silica particles and biological systems (biomolecules, membranes, cell systems, animal models) is highlighted (Pavan et al., 2019): "*It also has become clear that silanol configuration, and eventually biological responses, can be affected by impurities within the crystal structure, or coatings covering the particle surface*"(Pavan et al., 2019). The present working group agrees with the conclusion in this recent publication and the conclusion by OSHA (OSHA, 2016) that the available information shows that surface properties may be modified by external factors

and affect the toxicity. However, the information is insufficient to conclude to what extent these factors affect the toxicity.

The present working group concludes that it is evidenced that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency, whereas the carcinogenic potency of silica dust may be modified depending on age and level and type of impurities. However, the information is insufficient to conclude to what extent these factors affect the toxicity. The present working group therefore recommends to adapt the same occupational exposure limit for crystalline silica polymorphs quartz, cristobalite, and tridymite.

Previous evaluations of quartz/crystalline silica

OSHA (2016)

The US Occupational Safety and Health Administration (OSHA) evaluated respirable crystalline silica in 2016 (OSHA, 2016) and established dose-response relationship for crystalline silica-induced excess lung cancer risk, silicosis and other endpoints for health-based occupational exposure limits. In their final evaluation, OSHA did not differentiate between the different types of crystalline silica. OSHA's final quantitative mortality risk estimates for excess mortality for lung cancer and non-malignant respiratory disease (including silicosis) and risk estimates for silicosis morbidity are presented in Table 4.

Table 4. OSHA risk estimates at different concentrations of respirable crystalline silica (OSHA, 2016).

Health endpoint	Risk associated with 45 years of occupational exposure (per 1,000 workers)				
	Respirable crystalline silica exposure (µg/m^3)				
	25	50	100	250	500
Lung cancer mortality (lifetime risk)	3-21	5-23	11-54	24-231	32-657
Silicosis and non-malignant lung disease mortality (lifetime risk)	4-22	7-44	11-85	17-192	22-329
Renal disease mortality (lifetime risk)	25	32	39	52	63
Silicosis morbidity (cumulative risk)	5-40	20-170	60-773	300-1000	634-1000

The risk estimates in Table 4 are based on the OSHA key studies (listed in Table 5) and show the range of risk associated with 45 years of occupational exposure (per 1,000 workers) estimated in the different studies. The calculations are performed as explained briefly in the Table 5 legend. The calculations are described in detail in the chapter *Scientific basis for setting an occupational exposure limit* in the present assessment.

Table 5. OSHA's summary of lifetime or cumulative risk estimates for crystalline silica (as presented in the OSHA report (OSHA, 2016)).

Table VI-1. Summary of Lifetime or Cumulative Risk Estimates for Crystalline Silica*					
Health Endpoint (Source)	Risk Associated with 45 Years of Occupational Exposure (per 1,000 Workers)				
	Respirable Crystalline Silica Exposure ($\mu g/m^3$)				
	25	50	100	250	500
Lung Cancer Mortality (Lifetime Risk)					
Pooled Analysis, ToxaChemica, Inc (2004)[a,b]	10-21	16-23	20-26	24-30	32-33
Diatomaceous Earth Worker study (Rice et al., 2001)[a,c]	8	15	30	72	137
U.S. Granite Worker study (Attfield and Costello, 2004)[a,d]	10	22	54	231	657
North American Industrial Sand Worker study (Hughes et al., 2001)[a,e]	7	14	33	120	407
British Coal Miner study (Miller and MacCalman, 2009)[a,f]	3	5	11	33	86
Silicosis and Non-Malignant Lung Disease Mortality (Lifetime Risk)					
Pooled Analysis (ToxaChemica, Inc., 2004) (silicosis)[g]	4	7	11	17	22
Diatomaceous Earth Worker study (Park et al., 2002) (NMRD)[h]	22	44	85	192	329
Renal Disease Mortality (Lifetime Risk)					
Pooled Cohort study (Steenland et al., 2002a)[i]	25	32	39	52	63
Silicosis Morbidity (Cumulative Risk)					
Chest x-ray category of 2/1 or greater (Buchanan et al., 2003)[j]	21	55	301	994	1,000
Silicosis mortality and/or x-ray of 1/1 or greater (Steenland and Brown, 1995b)[k]	31	75	440	601	634
Chest x-ray category of 1/1 or greater (Hnizdo and Sluis-Cremer, 1993)[l]	6	127	773	995	1,000
Chest x-ray category of 1or greater (Chen et al., 2001)[m]	40	170	590	1,000	1,000
Chest x-ray category of 1or greater (Chen et al., 2005)[n]					
Tin miners	40	100	400	950	1,000
Tungsten miners	5	20	120	750	1,000
Pottery workers	5	20	60	300	700

* The numbers in these tables represent central estimates based on the given underlying study. Although they account for data uncertainty, they do not always account for model uncertainty. Furthermore, the strength of the evidence available for each of the health effects listed varies. For instance, we are less certain about the causality determination for renal mortality than for lung cancer mortality and silicosis mortality and morbidity. See accompanying text for a discussion of the uncertainties around these risk estimates, which vary in kind and magnitude.

[a] Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death. Background all-cause and lung cancer mortality rates are 2011 rates for all males (National Center for Health Statistics, accessed at http://wonder.cdc.gov/ucd-icd10.html). Background lung cancer mortality rate is based on ICD-10 categories C-33-C34, malignant neoplasms of trachea, bronchus, lung. Exposure to crystalline

Table 5. OSHA's summary of lifetime or cumulative risk estimates for crystalline silica (as presented in the OSHA report* (OSHA, 2016)(continued).

silica is assumed to occur at ages 20 through 65.
[b] Range based on three models (log-linear, linear, and linear spline, see Table II-2 of Document ID 1711, p. 290).
[c] Based on the linear relative risk model with exposures lagged 10 years, RR = 1 + (0.1441*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-yrs.
[d] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.19*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-yrs.
[e] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.13*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-yrs.
[f] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.0524*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-yrs.
[g] Estimates derived from rate ratios based on the categorical model after accounting for exposure measurement uncertainty, from Table 7 of ToxaChemica, Inc. (2004, Document ID 0469). Absolute risk calculated as 1 – exp(-∑time*rate), where rate is the rate ratio for a given cumulative exposure times a base rate of 4.7E-5.
[h] Estimated by OSHA based on the Park et al. (2002, Document ID 0405) linear relative rate model, RR = 1 + (0.5469*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-yrs. Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death. Background all-cause and non-malignant lung disease mortality rates are 2011 rates for all males (National Center for Health Statistics, accessed at http://wonder.cdc.gov/ucd-icd10.html). Non-malignant lung disease mortality rates reflect those for ICD-10 disease codes J40-J47 (chronic lower respiratory diseases) and J60-J66 (pneumoconioses and chemical effects). Exposure to crystalline silica is assumed to begin at age 20 through age 65.
[i] Estimated by OSHA based on the Steenland et al. (2002a, Document ID 0448) log-linear model with log cumulative exposure, RR = exp(0.269(lnE)) where E is cumulative respirable crystalline silica exposure in mg/m^3-days. Lifetime risks through age 85 were calculated from a life table that accounts for competing causes of death. Background all-cause and end-stage renal disease (ESRD) are 1998 rates for all males (National Center for Health Statistics, 2005, Document ID 1105). Background ESRD mortality rates reflect those for ICD-9 disease codes 580-589. Exposure to crystalline silica is assumed to begin at age 20 through age 65 with 250 days per year of exposure.
[j] Estimated by OSHA from the equation $Prob(2/1+) = exp(-4.83 + 0.443*cum.\ quartz_{<2.0\ mg/m^3})/ (1+exp(-(-4.83 + 0.443*cum.\ quartz_{<2.0\ mg/m^3}))$, where "cum. quartz" is cumulative respirable silica exposure in $g\text{-}hm^3$, with one year of work = 2000 hours (250 days per year x 8 hours per day). Exposure to crystalline silica is assumed to begin at age 20 through age 65. Age of cohort at follow-up was between 50 and 74 years.
[k] Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death. Background all-cause mortality rates are 2011 rates for all males (National Center for Health Statistics, accessed at http://wonder.cdc.gov/ucd-icd10.html). Silicosis rate is age- and calendar-time-adjusted, from Table 2 of Steenland et al. (1995b, Document ID 0451). Exposure to crystalline silica is assumed to begin at age 20 through age 65, with no exposure lag.
[l] Estimated by OSHA from the equation $CR = 1 – \{1/[1 + exp(2.439/.2199)*CDE^{1/.2199}]\}$, where CR is cumulative risk and CDE is cumulative respirable dust exposure in mg/m^3-yrs; assumed quartz content of respirable dust is 30 percent. Assumed 45 years of exposure. Mean age of cohort at onset was 55.9 years (range 38-74).
[m] Estimated by OSHA from the equation $CR = 1\text{-}exp(-(0.0076*E)^{2.23})$ where E is cumulative exposure to total dust. Respirable crystalline silica reported by Chen et al. (2001, Document ID 0332) to be 3.6 percent of total dust. Assumed 45 years of exposure. Mean age at onset was 48.3 years.
[n] Estimated from Figure 2B in Chen et al. (2005, Document ID 0985) showing cumulative risk vs. cumulative exposure to respirable crystalline silica. Mean age at onset was 47.9, 41.8, and 52.5 years for tin, tungsten, and pottery workers, respectively.

OSHA's final recommendation is as follows: "*Even though OSHA's risk assessment indicates that a significant risk also exists at the revised action level of 25 µg/m³, the Agency is not adopting a PEL [*permissible exposure limit*] below the revised 50 µg/m³ limit because OSHA must also consider the technological and economic feasibility of the standard in determining exposure limits"*(OSHA, 2016).

ATSDR (2019)

The Agency for Toxic Substances and Disease Registry's (ATSDR) toxicological profile identifies and reviews the key literature that describes silica's toxicological properties (ATSDR, 2019). Regarding silicosis and lung cancer of inhaled crystalline silica ATSDR concludes:

Silicosis:
"*Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis. However, a no-observed-adverse-effect level (NOAEL) for silicosis has not been defined, with silicosis and death due to silicosis observed for the lowest estimated cumulative exposure ranges reported. For the lowest estimated cumulative exposure range reported in the available literature (0–0.2 mg/m³-year), silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). At the estimated cumulative exposure range of 0.1–1.23 mg/m³-year, death due to silicosis was observed in 2,857 of 74,040 mining and pottery workers in China (Chen et al. 2012). In other occupational studies, cumulative exposure levels associated with silicosis and silicosis-related death are higher*"

Lung cancer:
"*Numerous epidemiological studies have evaluated associations between silica exposure and lung cancer. Compared to other occupational lung carcinogens, such as asbestos, the reported association between c-silica* [crystalline silica] *exposure and lung cancer is low, requiring large study populations to achieve adequate power to detect and quantify any such association. Results of pooled- and meta-analyses, which provide the strongest support for the carcinogenicity of c-silica* [crystalline silica] *in the lung, show increased risks of lung cancer in c-silica* [crystalline silica] *workers, with risks exhibiting dependence upon cumulative exposure (Finkelstein 2000; Lacasse et al. 2009; Steenland 2005; Steenland et al. 2001a). Results of a cohort study of over 30,000 workers in China indicate that exposure to c-silica* [crystalline silica] *is associated with lung cancer in the absence of silicosis (Liu et al. 2013). Smoking, as in all studies of potential lung carcinogens, could be a confounding factor in studies examining the relationship between c-silica* [crystalline silica] *exposure and lung cancer (Hessel et al. 2000). However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking (Steenland et al. 2001a).*

The Department of Health and Human Services classified c-silica [crystalline silica] *(respirable size) as a Group 1 (definite) human lung carcinogen. The International Agency for Research on Cancer (IARC 2012) and NIOSH (2002) also have classified c-silica* [crystalline silica] *(respirable size) as a Group 1 (definite) human lung carcinogen. IARC (1997, 2012) acknowledged that some occupational exposure studies did not show an association between c-silica* [crystalline silica] *exposure and lung cancer, possibly due to the characteristics of c-silica* [crystalline silica] *in different occupational settings or other factors affecting its carcinogenic potential; in addition, other confounding factors and biases may have influenced study results (e.g., errors in estimating c-silica* [crystalline silica] *exposure levels, absence [or presence and severity] of silicosis, adequate control of confounding from smoking, and unaccounted occupational co-exposures that may have contributed to lung cancer risk). NIOSH (2002) also concluded that c-silica* [crystalline silica] *(respirable size) is a human carcinogen*".

ANSES (2019)

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) evaluated health risks for workers in France exposed to crystalline silica (ANSES, 2019). The report is in French. However, a summary of the report is given in English:
"*Crystalline silica exposure in various industries*
In France, nearly 365,000 workers could potentially breathe in this mineral, mainly from quartz. ANSES estimates that 23,000 to 30,000 workers could be exposed to levels exceeding the occupational exposure limit (OEL) of 0.1 mg.m^{-3} currently in force in France, and more than 60,000 workers to levels exceeding the lowest international OEL of 0.025 mg.m^{-3}. More than two thirds of exposures at these levels are in the construction sector, followed by non-metallic mineral products manufacturing, metallurgy and mining.

High health risks for workers exposed to crystalline silica in France
Since the International Agency for Research on Cancer (IARC) classified crystalline silica as a human carcinogen in 1997, all studies published since then have confirmed its connection to lung

cancer development. Although having silicosis increases a person's risk of developing cancer, the available studies confirm the existence of a significant risk even without silicosis.
While this causal link is well established, the expert appraisal underlines the importance of revising the current medical definition of silicosis to include early forms.
In addition to silicosis and lung cancer, the ANSES expert appraisal found a significant link between exposure to crystalline silica and the risk of developing an autoimmune disease such as systemic scleroderma, systemic lupus erythematosus or rheumatoid arthritis. Similarly, exposure to crystalline silica increases the risk of developing non-malignant respiratory diseases other than silicosis, such as chronic obstructive pulmonary disease (COPD), emphysema or tuberculosis.
Studies have shown an association between exposure to crystalline silica and the risk of kidney disease and idiopathic interstitial pneumonia in the form of idiopathic pulmonary fibrosis (IPF), but data are currently insufficient to ascertain the exact relationship between them.
Taking into account both the health effects and the data on exposure in France, the ANSES expert appraisal has concluded that there is an especially high health risk for workers exposed to crystalline silica at levels equal to or above the OEL of 0.1 mg.m^{-3} currently in force in France.

Recommendations for enhanced exposure prevention and medical surveillance
ANSES recommends a series of measures in terms of preventing and controlling occupational exposure, ensuring medical surveillance and recognising occupational diseases.
With regard to prevention, ANSES recalls the need to apply the prevention measures as set out in Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. According to Annex I of this Directive, "work involving exposure to respirable crystalline silica dust generated by a work process" is considered to be a carcinogenic process. Accordingly, ANSES recommends rapidly transposing this condition into French law. It also recommends revising the OELs for crystalline silica, considered to be insufficiently protective, without distinguishing between its different forms.
In terms of medical surveillance, ANSES recommends changes in the diagnosis and screening processes for certain diseases (silicosis, tuberculosis, kidney diseases, etc.) for subjects currently or previously exposed to crystalline silica in their work environment.
Finally, ANSES recommends revising the occupational disease tables related to crystalline silica. Additionally, the Agency recommends conducting studies to improve knowledge of the prevalence of exposure, metrology and the health effects" (ANSES, 2019).

Swedish Criteria Group for Occupational Standards (2014)

In 2014, the Swedish Criteria Group for Occupational Standards concluded (Swedish Criteria Group for Occupational Standards, 2014):
"*The critical effects of occupational exposure to quartz dust are silicosis and lung cancer. Increased risk of silicosis (radiological changes corresponding to ILOclassification ≥1/0 or ≥1/1), increased risk of death from silicosis, and increased risk of lung cancer have been observed with a cumulative dose of around 1-2 mg/m^3 x years (equivalent to a concentration of 0.025-0.05 mg/m^3 for 40 years). A non-effect level has not been identified. It has not yet been determined whether silicosis is a prerequisite for the development of lung cancer resulting from quartz exposure. However, genotoxicological studies suggest that cancer development is driven by the inflammatory response to quartz. Occupational exposure to quartz has been shown to give rise to chronic obstructive pulmonary disease (COPD), kidney disease and autoimmune diseases*

(scleroderma, rheumatoid arthritis, systemic lupus erythematosus). It has not been possible to establish effect levels but studies with rats and lung physiology data indicate that COPD can occur without signs of silicosis. An increased risk of tuberculosis has also been associated with occupational exposure to quartz dust. High exposure to quartz dust can cause acute silicosis (fulminant silicosis), often with rapid fatal outcome".

IARC (2012)

In 1997, The International Agency for Research on Cancer (IARC) classified crystalline silica as carcinogenic to humans (group 1) (IARC, 1997). This classification was reaffirmed in the IARC evaluation from 2012. IARC concluded:
"*There is sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.*
There is sufficient evidence in experimental animals for the carcinogenicity of quartz dust
There is limited evidence in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.
Crystalline silica in the form of quartz or cristobalite dust is carcinogenic to humans (Group 1)" (IARC, 2012).

SCOEL (2003)

The Scientific Committee on Occupational Exposure Limits (SCOEL) has previously made a risk assessment of respirable crystalline silica (SCOEL, 2003). SCOEL concluded:
"*The main effect in human of the inhalation of respirable silica dust is silicosis. There is sufficient information to conclude that the relative lung cancer risk is increased in persons with silicosis (and, apparently, not in employees without silicosis exposed to silica dust in quarries and in the ceramic industry). Therefore, preventing the onset of silicosis will also reduce the cancer risk. Since a clear threshold for silicosis development cannot be identified, any reduction of exposure will reduce the risk of silicosis. It was observed that the dose-response curve for silicosis appears to be sigmoidal and that maintenance of exposure below 0.05 mg/m³ would avoid being on the steeper part of the dose-response curve, in the region where relatively small increases in exposure entail significant increases in silicosis risk. The reduction of exposure to 0.05 mg/m³ of crystalline silica is expected to reduce the prevalence of silicosis, ILO category 1/1, to about or less than 5% whereas an average respirable silica concentration of 0.02 mg/m³ reduces prevalence of silicosis to about 0.25 % or less. It arises that an OEL should lie below 0.05 mg/m³ of respirable silica dust. No STEL or skin notation are needed*" (SCOEL, 2003).

NIOSH (2002)

In their report on crystalline silica, The National Institute for Occupational Safety and Health (NIOSH) concluded:
"*Although a large body of published literature describes the health effects of crystalline silica, some areas require further research. Many uncertainties exist, including (1) mechanisms and the influence of particle characteristics on development of disease; (2) toxicity and pathogenicity of non-quartz crystalline silica, silica substitutes, and dust mixtures; (3) translocation of particles from the lung; and (4) dose/ exposure-response relationships in animals and in humans. In addition, further information is needed about (1) methods for reducing dust exposures in a wide*

variety of industries and the feasibility of implementing such methods, (2) methods for effectively communicating to workers the dangers of inhaling silica dust and the importance of using appropriate control technologies and other protective measures, and (3) exposure sampling and analytical methods that will allow quantification of crystalline silica at low airborne concentrations (currently these techniques do not meet the accuracy criterion needed to quantify exposures at concentrations below the NIOSH recommended exposure limit (REL)).

Until improved sampling and analytical methods are developed for respirable crystalline silica, NIOSH will continue to recommend an exposure limit of 0.05 mg/m³ to reduce the risk of developing silicosis, lung cancer, and other adverse health effects. NIOSH also recommends minimizing the risk of illness that remains for workers exposed at the REL by substituting less hazardous materials for crystalline silica when feasible, by using appropriate respiratory protection when source controls cannot keep exposures below the NIOSH REL, and by making medical examinations available to exposed workers" (NIOSH, 2002).

Scientific basis for setting an occupational exposure limit

The scientific basis for setting an occupational exposure limit (OEL) is based on a critical evaluation of the risk calculations performed by OSHA and supplemented with own calculations on studies identified by our own literature search for studies published after the OSHA evaluation. The report by OSHA (OSHA, 2016) is based on a systematic review of health effects literature and preliminary quantitative risk assessment (OSHA, 2010) and a follow-up report (OSHA, 2013). In those reports, a systematic literature search aiming at identifying studies of occupational exposure to crystalline silica and risk of different diseases was performed. As previously mentioned, the present working group has decided to focus on lung cancer and silicosis as the critical effects of quartz exposure. The OSHA key studies used cumulative exposure (i.e. average exposure concentration * duration of exposure) as exposure metric in order to establish exposure-response relationships. Therefore, OSHA also used cumulative exposure for the risk assessment, and the present working group will adapt the same approach. The present chapter presents a critical evaluation of the risk calculations performed by OSHA supplemented with risk calculations performed by the present working group on studies identified by a literature search for studies published after the OSHA evaluation.

Lung cancer mortality

OSHA cancer key studies

In total, OSHA identified five studies that were considered suitable for a quantitative risk assessment of lung cancer. These were the studies by 1) Steenland et al., 2001 (Steenland et al., 2001), 2) Rice et al. (2002)(Rice et al., 2001), 3) Attfield and Costello (2004) (Attfield & Costello, 2004), 4) Hughes et al. (2001) (Hughes et al., 2001), and 5) Miller and MacCalman (2009)(Miller & MacCalman, 2010). These studies are briefly described below, followed by calculations of lung cancer risk. The risk assessments are carried out as described by OSHA, but based on the Danish lung cancer incidence. As a quality assessment of OSHA's risk estimates, these are compared with risk estimates from the original articles.

Steenland et al. (2001)/Steenland and Bartell (ToxaChemica, International, Inc, 2004)

Steenland et al. (2001) (Steenland et al., 2001) performed a pooled exposure-response analysis of 10 occupational silica-exposed cohorts with quantitative exposure data or studies for which exposure data were later developed by Mannetje et al. ('t Mannetje et al., 2002a). These cohorts were all included in the IARC monography (IARC, 2012). They consisted of 5 studies in mines (U.S. gold miners, South African gold miners, Australian gold miners, Chinese tungsten miners and Chinese tin miners) and 5 studies in industrial plants (U.S. diatomaceous earth workers, U.S. (Vermount) granite workers, Chinese pottery workers, Finnish granite workers, and U.S. industrial sand workers). A brief overview of the 10 individual studies are presented in Table 6. In total 65,980 workers and 1,072 lung cancer deaths were included in the 10 cohorts.

Exposure assessment

In most of the 10 studies in the pooled analysis the original exposure assessment was measured as particle counts and converted to mass of respirable quartz by use of conversion factors ('t Mannetje et al., 2002b): "*Existing quantitative exposure data for 10 silica-exposed cohorts were retrieved from the original investigators. Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligram per cubic meter (mg/m³) respirable crystalline silica. Quantitative exposure assignments were typically based on a large number (thousands) of raw measurements, or otherwise consisted of exposure estimates by experts (for two cohorts). Median exposure level of the cohorts ranged between 0.04 and 0.59mg/m³ respirable crystalline silica. Exposure estimates were partially validated via their successful prediction of silicosis in these cohorts*". OSHA evaluated that "*the cohort studies included in the pooled analysis relied in part on particle count data and the use of conversion factors to estimate exposures of workers to mass respirable quartz. A few studies were able to include at least some respirable mass sampling data. OSHA believes that uncertainty in the exposure assessments that underlie each of the 10 studies included in the pooled analysis is likely to represent one of the most important sources of uncertainty in the risk estimates*" (OSHA, 2010).

Table 6. Description of the 10 studies in the pooled analysis (from (Steenland et al., 2001)).

Studies (nonmine/mine)[a]	Reference	No. dead	No. of workers	End of follow-up[c]	Median cumulative exposure to respirable silica (mg/m³-years)	Median duration of exposure (years)	Median average exposure to respiratory silica (mg/m³)
US diatomaceous (nonmine)	Checkoway *et al.* 1997 [17]	749	2342	1994	1.05	4.3	0.18
Finnish granite (nonmine)	Koskela *et al.* 1993 [12]	418	1026	1993	4.63	9.2	0.59
US granite (nonmine)	Costello *et al.* 1988 [16]	1762	5408	1982	0.71	18.0	0.05
US industrial sand (nonmine)	Steenland *et al.* 2000 [14]	860	4027	1996	0.13	3.7	0.04
China pottery[b] (nonmine)	Chen *et al.* 1992 [13]	1592	9017	1994	6.07	26.4	0.22
China tin[b] (mine)	Chen *et al.* 1992 [13]	956	7858	1994	5.27	25.4	0.19
China tungsten[b] (mine)	Chen *et al.* 1992 [13]	4549	28,481	1994	8.56	25.9	0.32
South Africa gold (mine)	Hnizdo *et al.* 1997 [20]	1009	2260	1986	4.23	23.8	0.19
US gold (mine)	Steenland *et al.* 1993 [11]	1925	3348	1996	0.23	5.4	0.05
Australia gold (mine)	De Klerk *et al.* 1998 [15]	1351	2213	1993	11.37	26.8	0.43
Total		15171	65,980		4.27	23.9	0.19

[a] All studies are cohort studies.
[b] 50%, 40%, and 24% of Chinese pottery, tin, and tungsten cohorts were in largely unexposed jobs, and were assigned a minimum level of 0.01 mg/m³ silica; medians for exposure and duration are here reported for exposed only.
[c] Follow-up for three Chinese cohorts extended 5 years, for Finnish cohort 4 years, for US gold miner cohort 6 years, beyond original publication. Follow-up began at time of first exposure (after fulfilling any minimum required length of exposure), or in 19.40, whichever was later.

The authors considered different models for the relationship between silica exposure and lung cancer risk and different time lags (0, 5, 10, 15, and 20 years). They found that log of cumulative exposure, with a 15-year lag, was the best predictor of lung cancer (p=0.0001) and provided only little heterogenicity between the studies (test for heterogenicity: p=0.34):

Log linear model: $\log RR = (\beta \times \ln(E+1))$ (β=0.062)

Where RR = relative risk of lung cancer, β = coefficient, and E = logged cumulative exposure in the unit ln(mg/m^3-days +1).

In the original article by Steenland et al (Steenland et al., 2001), the unit of the log linear model was not unclearly stated, but appeared to be ln(mg/m^3-**years**+1). However, in a corrigendum (Steenland et al., 2002b), the unit was specified as ln(mg/m^3-**days** +1). Furthermore, in Steenland et al, β was 0.062 (Steenland et al., 2001). In the OSHA report, β was 0.060 in the text (p. 273), but 0.60 in table II-2 (OSHA, 2010). The unit was in both cases ln(mg/m^3-**days** +1). The current working group notes that this results in uncertainty regarding the unit of the log linear model.

The authors discussed a number of limitations in their study (Steenland et al., 2001): 1) There was no information on smoking in most of the studies. However, the authors believe that the effect of smoking is small because the high and low silica exposed workers are expected to have similar smoking habits, 2) The possibility of confounding by exposure to other occupational carcinogens such as radon could have influenced the results. The authors do not believe that radon is a confounder in these studies because exclusion of the cohort with radon exposure did not result in significantly changed results, 3) A possibility for the observed differences in risks between the studies are discussed to be due to the physical differences of silica between the cohorts. The present working group agrees with the interpretations by the authors regarding small significance of confounding by smoking and radon in the present studies. Furthermore, the present working group finds it likely that the physical properties of the silica dust such as the freshness of particle cleavage may affect the toxicity (Fubini et al., 1995; Harrison et al., 1997) and thereby may explain the differences between the cohorts. However, the current working group shares the concern raised by OSHA that '*uncertainty in the exposure assessments that underlie each of the 10 studies included in the pooled analysis is likely to represent one of the most important sources of uncertainty in the risk estimates'.*

On OSHA's request, Steenland and Bartell (Steenland & Bartell, 2004) undertook a reanalysis of the Steenland study (Steenland et al., 2001). Before doing this re-analysis, some of the cohorts were updated and the follow-up periods were extended (Steenland & Bartell, 2004). In general, this resulted in insignificant changes of exposure-response coefficients compared to the values obtained in the original analyses performed by Steenland et al. (Steenland et al., 2001).

OSHA modelled the association between crystalline silica and lung cancer incidence using three different models (*log-linear, linear, and linear spline*):

Log-linear: logRR= β *ln (E + 1) equals log(RR)/β = ln(E+1) equals E =exp(log (RR)/ β)) - 1
Where β=0.060 with a standard error of 0.015 (model with cumulative exposure (mg/m^3*days +1))

The current working group furthermore notes that this specific mathematical model leads to dose-response relationships that deviate substantially from linearity both at high risk levels (due to the use of relative risk) and at low exposure levels because of the use of logging cumulative exposure and the addition of 1).

Linear: RR = 1 + β x (E +1) equals E= $(RR - 1 - \beta)/\beta$
Where β=0.074950 with a standard error of 0.024121 (model with cumulative exposure (mg/m^3*days +1))

The linear model is only valid for RR≥1.07

Linear-spline: RR =1 +β_1 x; if x≤ 2.19 mg/m^3 years ~48.7 μg/m^3
X = (RR-1)/β_1
(2.19 mg/m^3 years/45 years *1000 μg/mg=48.7 μg/m^3)

β1=0.16498 with a standard error of 0.0653 (model with cumulative exposure (mg/m^3 years).

In Denmark, the lifetime risk of developing lung cancer (0-74 years) is 4.9% for men and 4.5% for women. The relative risk caused by occupational exposure to a carcinogen, which causes cancer at the different risk levels (1%, 0.1%, 0.01% and 0.001%) are given in **Table 7**.

Table 7. Relative risk of lung cancer for carcinogens that cause 1%, 0.1% or 0.01% excess lung cancer risk in a population with the current Danish lung cancer incidence.

	Men	Women
Life time risk (0-74 years) 2011-2015 in Denmark[1]	4.9%	4.5%
Excess lung cancer risk level	RR	RR
1:100	RR= (4.9+1)/ 4.9= 1.20	RR= (4.5+1)/4.5= 1.22
1:1,000	RR= (49+1)/49= 1.02	RR= (45+1)/45=1.02
1:10,000	RR= (490+1)/490= 1.002	RR= (450+1)/450= 1.002
1:100,000	RR= (4,900+1)/4900= 1.000 2	RR= (4,500+1)/4500= 1.000 2

1) http://www-dep.iarc.fr/NORDCAN/DK/StatsFact.asp?cancer=180&country=208

Log-linear modelling
Using the **log-linear model** and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

logRR = β x ln (E+1)
E=Exp(log(RR)/β) -1 (mg/m^3*days)

Using β = 0.060 from OSHA the crystalline silica concentration =
Exp(log(RR)/β) -1 = Exp(log(1.02)/0.060) -1= 0.154 mg/m^3 x days

For a 45-year worklife (45 years x 45 weeks/year x 5 days/week = 10,125 days) this would correspond to 0.154 mg/m^3*days/10,125 days = 1.52 *10^{-5} mg/m^3= 0.015 μg/m^3

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in Table 8.

The current working group notes that this specific mathematical model leads to dose-response relationships that deviate substantially from linearity due to the use of log transformation of the cumulative exposure.

Linear modelling

Because the **linear model** is only valid for RR≥1.075 we are only using the linear model assuming 1:100 excess lung cancer incidences among men (corresponding to RR=1.2),

The calculation would be:

RR=1+0.074950*(E +1)
RR= 1 +0.07495 + 0.07495 E
(RR-1.07495)/0.07495 = E
E= (RR − 1 − 0.074950)/0.074950== (1.2 − 1 − 0.074950)/0.074950=1.668 mg/m^3

For a 45-year worklife (45 years x 45 weeks/year x 5 days/week = 10,125 days) this would correspond to 1.668 mg/m^3*days/10,125 days = 0.00016mg/m^3= 0.16 μg/m^3

The current working group notes that this model is only valid for RR≥1.075, corresponding to relatively high risk levels since the back ground lung cancer incidence is 5%. Therefore, this current working group disregards this model.

Linear spline modelling

Using the **linear spline** and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

RR =1 + 0.16498 x if x≤ 2.19 mg/m^3 years ~48.7 μg/m^3
X= (RR-1)/0.16498 = (1.2-1)/(0.16498) mg/m^3 years = 1.21 mg/m^3 years

For a 45-year worklife this would correspond to
1.21 mg/m^3 years *1,000 μg/mg/45 years =26.94 μg/m^3

Rice et al (2001)

Rice et al. performed a dose-response analysis of a California cohort of 2,342 diatomaceus earth workers including 77 lung cancer deaths (Rice et al., 2001). The study was included in the pooled analysis by Steenland et al (Steenland et al., 2001). The excess lifetime risk of lung cancer was 19/1,000 at an exposure to 0.05 mg/m^3. The exposure was primarily to cristobalite.

OSHA found that the following linear relative risk model with exposures lagged10 years, was the best predictor of lung cancer:

RR = 1 + (0.1441xE),

$$E=(RR-1)/0.1441$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 x years

Using the linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years = (1.02-1)/0.1441 = 0.138795 mg/m^3-years

For a 45-year worklife this would correspond to 0.138795 mg/m^3-years/45 years = 0.00308 mg/m^3= 3.08 $\mu g/m^3$

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in Table 8.

Attfield and Costello (2004)(granite workers exposed to rock dust)
This cohort of 5,414 U.S. granite workers was originally published by Costello and Graham (Costello & Graham, 1988) and was included in the pooled analysis by Steenland et al. (2001). Attfield and Costello extended the original follow-up period with 12 years (from 1982 to 1994), which increased the number of lung cancer deaths from 124 in the pooled analysis to 201 (Attfield & Costello, 2004). The results show a clear dose-response relationship for exposure to crystalline silica and lung cancer. The excess lifetime risk of lung cancer was 27/1,000 at an exposure to 0.05 mg/m^3. The present working group notes that the authors do not specify the type of crystalline silica. Therefore, it is not possible to specify which type of crystalline silica the relationship applies to (e.g. quartz, cristobalite or a mix).

OSHA found that the following log-linear relative risk model with exposures lagged 15 years, was the best predictor of lung cancer:

$$RR = \exp(0.19xE),\ E= \ln(RR)/0.19$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 x years.

Using the log-linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years =ln(RR)/ β =ln(1.02)/0.19= 0.104224 mg/m^3-years

For a 45-year worklife this would correspond to 0.1042 mg/m^3-years/45 years = 0.002316 mg/m^3= 2.32 $\mu g/m^3$

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in Table 8.

Hughes et al. (2001)
Hughes et al performed a nested case-control of 93 lung cancer deaths in a cohort of 2,670 workers in nine US and Canadian industrial sand plants (Hughes et al., 2001). The exposure was stated to be "*essentially.. pure quartz largely uncomplicated by the presence of other known carcinogens or by heat processes that may result on conversion of quartz to cristobalite*". After adjusting for the effect of smoking, significant exposure response trends were found. However, the length of employment was not significant. As stated by Steenland and Bartell (Steenland & Bartell, 2004) there is a significant overlap between the study by Hughes et al. (Hughes et al., 2001) and the pooled study of 10 cohorts by Steenland et al. (Steenland et al., 2001).

OSHA found that the following log-linear relative risk model with exposures lagged 15 years, was the best predictor of lung cancer:

$$RR = \exp(0.13xE),\ E=\ln(RR)/0.13$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 x years

Using the log-linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years $=\ln(RR)/\beta = \ln(1.02)/0.13 = 0.152328$ mg/m^3-years

For a 45-year worklife this would correspond to 0.152328 mg/m^3-years/45 years = 0.003385 $mg/m^3 = 3.39\ \mu g/m^3$

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in Table 8.

Miller and MacCalman (2009)
This cohort of 17,820 British coal miners included 958 lung cancer deaths (Miller & MacCalman, 2010). The follow-up time was from 1959-2006. Adjusting for smoking was included in the analysis. Exposure to crystalline silica was found to be statistically significant associated with excess lung cancer.

OSHA found that the following log-linear relative risk model with exposures lagged 15 years, was the best predictor of lung cancer:

$$RR = \exp(0.0524xE),$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 x years

Using the log-linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years =ln(RR)/ β =ln(1.02)/0.0524= 0.377913 mg/m^3-years

For a 45-year worklife this would correspond to 0.377913 mg/m^3-years/45 years = 0.008398 mg/m^3= 8.40 μg/m^3.

Table 8. OSHA key studies – risk estimates based on the information in OSHA table II-2 (p.290)* (OSHA, 2010).

OSHA key studies	**OSHA model**	**Exposure unit**	**Excess risk**			
			1:100	1:1,000	1:10,000	1:100,000
			Concentration of silica in μg/m^3			
Steenland et al., 2001	Log-linear, logged exposure: log RR = 0.06*ln(E +1)	mg/m^3 days +1[1]	0.27	0.015	0.0014	0.00014
	Linear: RR=1+0.074950*(E +1)	mg/m^3 days +1	0.16	[2]	[2]	[2]
	Linear spline: RR=1 + 0.16498*E for x≤48 μg/m^3	mg/m^3 years	26.94	2.69	0.27	0.03
Rice et al., 2001	Linear: RR=1 + 0.1441*E	mg/m^3 years	30.84	3.08	0.31	0.03
Attfield and Castello, 2004	Log-linear: RR=exp(0.19*E)	mg/m^3 years	21.32	2.32	0.23	0.02
Hughes et al., 2001	Log-linear: RR=exp(0.13*E)	mg/m^3 years	31.17	3.39	0.34	0.03
Miller and MacCalman, 2009	Log-linear: RR=exp(0.0524*E)	mg/m^3 years	77.32	8.40	0.85	0.08

[1]For the linear model based on the Steenland et al study, a β=0.6 is stated in the table II-2 in the OSHA report. However, at page 273 in the OSHA report, a β=0.06 is stated and this value is used in the calculations in Table 8.
[2]The model is not valid for the lower excess risk estimates.

The present working group notes that the OSHA dose-response estimates for the Steenland et al. study (Steenland et al., 2001) are made using other statistical models as compared to the other studies. Furthermore, the estimated concentration levels in Table 8 based on the model parameters in the OSHA table II-2 for the log-linear and the linear models on the pooled cohort study deviates more than 100-fold compared to the rest of the models. Furthermore, the current working group noted a number of discrepancies in the formula reported in the original publication, in a later correction and in the OSHA report, leading to uncertainty regarding which statistical model is correct.

The present working group notes that the studies presented above show a strong association between exposure to crystalline silica and lung cancer mortality. The risk of lung cancer mortality varies to some extent between the studies which may be due to the use of different mathematical methods, the study design, exposure (e.g. characteristics of the silica) etc. The present working group further notes that for some of the studies, the exposure is primarily cristobalite (Rice et al., 2001) and primarily quartz (Hughes et al., 2001; Miller & MacCalman, 2010), respectively, while for the forth individual study, the type of crystalline silica is not specified (Attfield & Costello, 2004;). Overall, we find that the risk estimates for the cristobalite study and the quartz studies are at the same level and that these are similar to the rest of the studies where the type of crystalline silica is not specified. Therefore, the view of the present working group is that based on the OSHA key studies there is no reason to differentiate risk according to the type of crystalline silica. This is in agreement with OSHA's conclusion.

NFA literature search

The OSHA report (OSHA, 2016) is based on a background document from 2010 (OSHA, 2010) and a supplementary report from (OSHA, 2013). To be able to identify dose-response studies or meta-analyses of epidemiological studies published during the last decade, we performed a literature search in MEDLINE restricted to the time-period between 01.01.2010 and 31.12.2019. A detailed description of the literature search is included in appendix A. In brief, we combined search terms for "quartz" and "exposure" and ("meta-analysis" or "dose-response").

Based on the literature search, one study was identified that estimated excess lung cancer risk levels for different silica concentrations (Liu et al., 2013). The study by Liu is considered relevant for risk assessment and risk estimates are calculated similarly to the procedure followed for the OSHA key studies.

Liu et al., 2013

Liu et al. analyzed a cohort (1960-2003) of 34,018 Chinese workers without exposure to carcinogenic confounders including 546 lung cancer deaths (mean follow-up was 34.5 years). At lower silica levels, the authors found a clear exposure-response trend between silica exposure and lung cancer, while this trend was decreasing at high exposure levels. A model with continuous logged cumulative silica exposure gave the best fit (β=0.055 with a 15-year lag and 0.065 with a 25-year lag) (Liu et al., 2013). The present working group finds that this study is relevant to include in our risk assessment due to the following strengths of the study: 1) large cohort, 2) long follow-up period, 3) exclusion of persons with possible confounding carcinogenic exposure (tin and cupper miners), and 4) adjustment for smoking (time-dependent variable). Furthermore, the present working group notes that when comparing the coefficient for logged cumulative exposure with 15-years lag in the present study (β=0.055), it is similar to the coefficient found in the study by Miller and MacCalman(β=0.0524) (Miller & MacCalman, 2010).

With 15-year lag of exposure, Liu et al. found the following log-linear relative risk model as the best predictor of lung cancer:

$$RR = \exp(0.055xE),\ E=\ln(RR)/0.055$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 * years

Using the log-linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years =ln(RR)/ β =ln(1.02)/0.055= 0.360 mg/m^3-years

For a 45-year worklife this would correspond to 0.360 mg/m^3-years/45 years = 0.00801 mg/m^3= 8.0 μg/m^3

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in table 9.

Comparison of cancer studies

Different modelling was used for the calculation of excess lung cancer risk across the different studies.

In table 9, an overview of the excess lung cancer mortality risk is presented for the five OSHA lung cancer key studies and for the study by Liu et al (Liu et al., 2013) identified by our own literature search.

The present working group has decided to disregard the results from the Steenland study for several reasons (Steenland et al., 2001): 1) The OSHA dose-response estimates for the Steenland et al. study are made using other statistical models as compared to the other studies. The models deviate substantially from linearity at the higher exposure levels due to the use of logged cumulative exposure, 2) The estimated concentration levels in Table 8 based on the model parameters in the OSHA table II-2 for the log-linear and the linear models on the pooled cohort study deviate more than 100-fold compared to the rest of the models. 3) The current working group noted a number of discrepancies in the formula reported in the original publication, in a later corrigendum and in the OSHA report, leading to uncertainty regarding which statistical model is correct, 4) OSHA expresses concern related to the exposure characterization.

In summary, three of the five OSHA key studies (Attfield & Costello, 2004; Hughes et al., 2001; Miller & MacCalman, 2010) and the one study identified by our own literature search (Liu et al., 2013) used the same log-linear model. Two of these studies representing approximately 23,000 workers and approximately 1,100 deaths were also included in the Steenland study (Attfield & Costello, 2004; Miller & MacCalman, 2010). These studies represent about 60,000 workers and includes approximately 1,600 deaths which is approximately the same size as the Steenland study with 65,980 workers and 1,072 lung cancer deaths (Steenland et al., 2001). The present working group suggests to calculate an un-weighed mean β based on these four studies for the risk calculations, using the same approach as for the evaluation of Cr(VI) (NFA, 2019):

$$\frac{0.19 + 0.13 + 0.0524 + 0.055}{4} = 0.107$$

Thus, the calculated risk estimates for excess lung cancer risk would be:

$$RR = \exp(0.107xE),\ E=\ln(RR)/0.107$$

where E is cumulative respirable crystalline silica exposure in mg/m^3 * years

Table 9. Overview of excess lung cancer mortality.

Studies	Number of workers	Number of deaths	Exposure assessment	Type of RCS	Model	Exposure unit	Excess risk			
							1:100	1:1,000	1:10,000	1:100,000
							Concentration of silica in µg/m³			
OSHA key studies										
Steenland et al., 2001	65,980	1072	Pooled analysis of 10 studies. Partly particle count data and the use of conversion factors to estimate exposures of workers to mass of respirable quartz. A few studies included some respirable mass sampling data.	Mixed RCS	Log-linear, logged exposure: log RR = 0.06*ln(E +1)[1]	mg/m³ days +1	0.27	0.015	0.0014	0.00014
					Linear: RR=1+0.074950*(E +1)	mg/m³ days +1	0.16	[2]	[2]	[2]
					Linear spline: RR=1 + 0.16498*E for x≤48 µg/m³	mg/m³ years	26.94	2.69	0.27	0.03
Rice et al., 2001	2,342	77	More than 6000 measurements of exposure to dust. Cumulative exposures to respirable crystalline silica dust were estimated for each worker by linking the historical occupational hygiene data with detailed employment records.	"Mainly cristabolite"	Linear: RR=1 + 0.1441*E	mg/m³ years	30.84	3.08	0.31	0.03
Attfield and Castello, 2004 (included in Steenland et al., 2001)	5,414	201	Job-time exposure matrix	Not specified	Log-linear: RR=exp(0.19*E)	mg/m³ years	21.32	2.32	0.23	0.02

Table 9. Overview of excess lung cancer mortality (*continued*)

Studies	Number of workers	Number of deaths	Exposure assessment	Type of RCS	Model	Exposure unit	Excess risk			
							1:100	1:1,000	1:10,000	1:100,000
							Concentration of silica in µg/m³			
OSHA key studies (continued)										
Hughes et al., 2001	2,670	93	Exposures were estimated by linking work histories to a job-exposure matrix	"Essentially pure quartz"	Log-linear: RR=exp(0.13*E)	mg/m³ years	31.17	3.39	0.34	0.03
Miller and MacCalman, 2009 (included in Steenland et al., 2001)	17,820	958	Information on time-exposure measurements of quartz, individual work histories and individual smoking histories.	Quartz	Log-linear: RR=exp(0.0524*E)	mg/m³ years	77.32	8.4	0.85	0.08
NFA literature search										
Liu et al., 2013	34,018	546	Cumulative silica exposure was estimated by linking a job-exposure matrix to work history	Not specified	Log-linear: RR= exp(0.055*E)	mg/m³ years	73.67	8	0.81	0.08
NFA calculation based on 4 studies[3]										
Mean β	54,508	1597	[4]	Mixed RCS	Log-linear: RR= exp(0.107*E)	mg/m³ years	37.87	4.11	0.41	0.04

[1]For the linear model based on the Steenland et al study, a β=0.6 is stated in the table II-2 in the OSHA report. However, at page 273 in the OSHA report, a β=0.06 is stated and this value is used in the calculations in Table 9.
[2]The model is not valid for the lower excess risk estimates.
[3]The NFA calculation is based on a β based on four studies (Attfield & Costello, 2004; Hughes et al., 2001; Liu et al., 2013; Miller & MacCalman, 2010).
[4]See the individual studies.

Using the log-linear model and assuming 1:1,000 excess lung cancer incidences among men, the calculation would be:

Crystalline silica concentration in mg/m^3-years =ln(RR)/ β =ln(1.02)/0.107= 0.1850 mg/m^3-years

For a 45-year worklife this would correspond to 0.1850 mg/m^3-years/45 years = 0.00411 mg/m^3= 4.11 μg/m^3

The estimated silica concentrations for different excess lung cancer risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in table 10 together with the individual studies that were used for the calculation of the mean β.

Table 10. Overview of excess lung cancer mortality studies used for the NFA calculation.

Studies	**Model**	**Exposure unit**	**Excess risk**			
			1:100	1:1,000	1:10,000	1:100,000
			Concentration of silica in μg/m^3			
Attfield and Castello, 2004	Log-linear: RR=exp(0.19*E)	mg/m^3 years	21.32	2.32	0.23	0.02
Hughes et al., 2001	Log-linear: RR=exp(0.13*E)	mg/m^3 years	31.17	3.39	0.34	0.03
Miller and MacCalman, 2009	Log-linear: RR=exp(0.0524*E)	mg/m^3 years	77.32	8.40	0.85	0.08
Liu et al., 2013	Log-linear: RR= exp(0.055*E)	mg/m^3 years	73.67	8.00	0.81	0.08
NRCWE calculation with a mean β	Log-linear: RR= exp(0.107*E)	mg/m^3 years	37.87	4.11	0.41	0.04

Two of the four studies stated that the exposure was "essentially/mainly" pure quartz (Hughes et al, 2001; Miller and MacCalman, 2001). If only these two studies are used for the calculation, the expected excess lung cancer risk is quite similar to the "unspecified" respirable crystalline silica exposure 1: 1,000 at 6 μg/m^3, 1: 10,000 at 0.6 μg/m^3 and 1: 100,000 at 0.06 μg/m^3 respirable quartz.

The present working group notes there is consistency between the risk estimates of the selected studies and the Rice et al study despite the fact that Rice et al, 2001 is based on linear modeling and the un-weighed NRCWE calculation is based on log-linear modeling.

Silicosis mortality

OHA silicosis mortality key studies

OSHA identified two studies that were considered suitable for a quantitative risk assessment of silicosis and non-malignant lung disease mortality, respectively. These were the studies by 1) Mannetje et al., 2002 ('t Mannetje et al., 2002a), 2) Park et al., 2002 (Park et al., 2002). The studies are described below. The silicosis risk assessments have been carried out as described by OSHA by the calculation of absolute risks. The reason for calculating absolute risk instead of excess risk is that there is no background

incidence of silicosis. Similar to the lung cancer calculations, OSHA's risk calculations have been compared with the calculations given in the original articles.

Mannetje et al./Steenland and Bartell (ToxaChemica, International, Inc, 2004)

Mannetje et al. ('t Mannetje et al., 2002a) conducted a pooled analysis of silicosis mortality on 6 of the 10 cohorts included in the pooled analysis by Steenland et al. (Steenland et al., 2001). Silicosis mortality was defined as death from either silicosis or pheumoconiosis. In total, these 6 cohorts consisted of 18,634 workers and included 170 silicosis deaths of which 20 were unspecified pheumoconiosis deaths. Small errors in the exposure assessment were corrected in the analysis by ToxaChemica resulting in insignificant changes in the dose-response analysis (Steenland & Bartell, 2004).

OSHA used the following model for the calculation of absolute risk (OSHA, 2010):

$$\text{Absolute risk} = 1 - \exp(-\sum \text{time}_i * \text{rate}_i)$$

where rate_i is the silicosis mortality rate associated with the level of cumulative exposure at age i.

The reason for calculating absolute risk instead of excess risk is that there is no background rate of silicosis.

In Table 10, the present working group has performed the calculations as described by OSHA: "*The rate ratio for each interval of cumulative exposure was multiplied by the annual silicosis rate assumed to be associated with the lowest exposure interval, 4.7 per 100,000 for exposures of 0-0.99 mg/m³ -years, to estimate the silicosis rate for each interval of exposure. The lifetime silicosis mortality risk is the sum of the silicosis rate for each year of life through age 85 and assuming exposure from age 20 to 65*" (OSHA, 2010)

The present working group checked the calculations by OSHA for the concentrations 0.05 and 0.1 mg/m³ and obtained the same result as OSHA, namely 7 and 11 deaths per 1,000 workers, respectively (Table 11). The lowest exposure range between 0.000 mg/m³ and 0.022 mg/m³ equals 2 silicosis deaths per 1000 workers. It is not possible to do further calculations to obtain exposure levels corresponding to lower risk levels and therefore the study by ('t Mannetje et al., 2002a) is not considered further in the present report.

Table 11. Silicosis mortality calculations based on the Mannetje et al study.

NFA calculations based on OSHA											Reported by OSHA	
Exposure				Rate ratio[1]	Annual silicosis rate[2]	$rate_i$ =rate ratio * annual silicosis rate	$time_i$	$(\Sigma time_i * rate_i)$	Risk of silicosis mortality		Exposure	Risk of silicosis mortality
mg/m^3 years		mg/m^3					years		Risk= 1 - exp(- $\Sigma time_i * rate_i$)	Deaths per 1,000 workers	mg/m^3	Deaths per 1,000 workers
0.00	0.99	0.000	0.022	1.00	4.70E-05	4.70E-05	45	2.12E-03	2.11E-03	2		
0.99	1.97	0.022	0.044	2.18	4.70E-05	1.02E-04	45	4.61E-03	4.60E-03	5		
1.97	2.87	0.044	0.064	3.35	4.70E-05	1.57E-04	45	7.09E-03	7.06E-03	7	0.05	7
2.87	4.33	0.064	0.096	4.27	4.70E-05	2.01E-04	45	9.03E-03	8.99E-03	9		
4.33	7.12	0.096	0.158	5.35	4.70E-05	2.51E-04	45	1.13E-02	1.13E-02	11	0.10	11
7.12	9.58	0.158	0.213	6.26	4.70E-05	2.94E-04	45	1.32E-02	1.32E-02	13		
9.58	13.21	0.213	0.294	7.42	4.70E-05	3.49E-04	45	1.57E-02	1.56E-02	16		
13.21	15.89	0.294	0.353	7.65	4.70E-05	3.60E-04	45	1.62E-02	1.60E-02	16		
15.89	28.10	0.353	0.624	9.20	4.70E-05	4.32E-04	45	1.95E-02	1.93E-02	19		
>28.10		>0.624		12.83	4.70E-05	6.03E-04	45	2.71E-02	2.68E-02	27		

[1]From Table 7 in (Steenland & Bartell, 2004)
[2]From p. 295 in (OSHA, 2010).

Park et al., 2002

Park et al. analyzed 2,570 diatomaceus earth workers with more than 12 months of work from 1942-1994 and quantified the relationship between cristobalite exposure and mortality from chronic lung diseases other than cancer (Park et al., 2002). The included diseases were pneumoconiosis (which includes silicosis), chronic bronchitis and emphysema, while pneumonia and other infectious diseases were excluded.

OSHA estimated the following linear relative rate model for relative risk of mortality from chronic lung disease other than cancer:

$$RR=1 + (0.5469*E),$$

where E is cumulative respirable crystalline silica exposure in mg/m^3*years.

Chronic obstructive pulmonary disease (COPD) is the primary chronic lung disease in the general population apart from lung cancer. On that background, the present working group decided to use the risk of COPD as an estimate for all lung diseases except for cancer, pneumonia and other infectious diseases.

It has not been possible to provide data for the background incidence of COPD in Denmark. Instead , we have identified Canadian data (Gershon et al., 2011) and used those for our calculations.

Table 12. Relative risk of COPD that causes 1%, 0.1%, 0.01% or 0.001% excess COPD risk in a population with the Canadian COPD incidence

	Men	Women
Life time risk (0-70 years) in Canada[1]	17.6%	16.0%
Excess lung cancer risk level	RR	RR
1:100	RR= (17.6+1)/ 17.6= 1.0568	RR= (16+1)/16= 1.0625
1:1,000	RR= (176+1)/176= 1.00568	RR= (160+1)/160=1.00625
1:10,000	RR= (1760+1)/1760= 1.000568	RR= (1600+1)/1600= 1.000625
1:100,000	RR= (17600+1)/17600= 1.000057	RR= (16000+1)/16000= 1.00063

[1](Gershon et al., 2011).

Using the **linear model** and assuming 1:1,000 excess COPD incidences among men, the calculation would be:

E=(RR-1)/0.5469 (mg/m^3*years)

Crystalline silica concentration =
(1.00568-1)/0.5469= 0.0103 mg/m^3 x years

For a 45-year worklife this would correspond to 0.0103 mg/m^3*years/45 years = 0.00023 mg/m^3= 0.23 μg/m^3

Similarly, concentrations of crystalline silica at other excess risk levels are tabulated in Table 13.

Table 13. Excess risk of chronic lung diseases other than cancer[1].

Study	**Model**	**Exposure unit**	**Excess risk**			
			1:100	1:1,000	1:10,000	1:100,000
			Concentration of silica in μg/m^3			
Park et al., 2002	Linear: RR=1 + (0.5469*E)	mg/m^3 years	2.31	0.23	0.023	0.0023

[1]The risk of COPD in a Canadian study is used as an estimate for all lung cancer diseases except for cancer

In comparison, OSHA calculated that the risk associated with 45 years of occupational exposure for silicosis and non-malignant lung disease mortality is 22 per 1,000 workers (equals 2 per 100) at 25 μg/m^3. We calculate that excess risk of chronic lung diseases other than cancer is 1 per 100 workers at 2.3 μg/m^3. Thereby, our risk estimate is approximately 5-fold higher that the OSHA calculation. The Canadian study does not take smoking history into account (Gershon et al., 2011). This is a limitation since smoking is important in the development of COPD. In addition, using Canadian data instead of Danish data probably underestimate the excess risk of COPD due to a lower smoking prevalence in Canada compared to Denmark.

The present working group notes that the risk calculated based on the Park study (Park et al., 2002) is more than 10 times higher than the risk estimates calculated for lung cancer. However, the present working group decided not to take the Park et al study into account in final risk assessment for the following reasons: 1) The lack of Danish life time risk of developing COPD, 2) The relatively small size of the study.

Summary of silicosis mortality studies

For silicosis mortality, OSHA evaluated a pooled exposure-response analysis performed by Mannetje et al. ('t Mannetje et al., 2002a) that was later reanalyzed by Steenland and Bartell (Steenland & Bartell, 2004), and a study by Park et al. (Park et al., 2002) which forms the basis for the silicosis mortality risk assessments performed by OSHA.

Only one of the two OSHA key studies on silicosis mortality was focused on quartz exposure. In that study, exposure to 0.000 mg/m^3 to 0.022 mg/m^3 was calculated to cause 2 silicosis deaths per 1000 workers ('t Mannetje et al., 2002a). Based on the equation used by OSHA, it is not possible to calculate exposure levels corresponding to specified risk levels e.g. 1:1,000, 1:10,000 and 1: 100,000.

The study by Park et al (2002) (Park et al., 2002) was focused on cristobalite exposure. The present working group did not take that study into account in the final risk assessment because of the relatively small size of the study and the lack of Danish numbers for lifetime risk of lung cancer diseases other than cancer.

The current working group notes that there is evidence that occupational exposure to crystalline silica causes silicosis to the same extent or more than lung cancer.

However, the present working group is of the opinion that the risk estimates for lung cancer mortality is better determined than the risk estimates for silicosis mortality.

Silicosis morbidity

OSHA identified five studies that were considered suitable for a quantitative risk assessment of silicosis morbidity. These were the studies by 1) Buchanan et al., 2003 (Buchanan et al., 2003), 2) Steenland and Brown, 1995 (Steenland & Brown, 1995), 3) Hnizdo and Sluis-Cremer, 1993 (Hnizdo et al., 1993); 4) Chen et al., 2001(Chen et al., 2001), and 5) Chen et al. 2005 (Chen et al., 2005). These studies are described below, and the concentrations of respirable crystalline silica are calculated based on the following absolute risks of silicosis morbidity: 1:100; 1:1,000; 1:10,000 and 1:100,000.

OSHA silicosis morbidity key studies

Buchanan et al., 2003

A statistically significant relationship between silicosis morbidity and cumulative quartz exposure was found in this cohort of 547 Scottish coal workers (Buchanan et al., 2003). Silicosis cases were considered to be the cases where the profusion of opacities on the radiographs were classified by three different physicians as category 2/1+ (2/1 or above). Exposure characterization was based on extensive respirable dust sampling followed by determination of quartz content by infrared spectrophotometry.

The present working group agrees with the overall evaluation by OSHA: "*OSHA has a high degree of confidence in the estimates of silicosis morbidity risk from this Scotland coal mine study, mainly because of the highly detailed and extensive exposure measurements, the radiographic records, and the detailed analyses of high exposure-rate effects*" (OSHA, 2010).

OSHA uses the following equation to estimate risk of silicosis morbidity associated with 45 years of occupational exposure (per 1,000 workers)

$$Prob\left(\frac{2}{1}+\right) = \frac{1}{1 + exp-(-4.83 + 0.443 \cdot cum.quartz_{<2.0} + 1.323 \cdot \text{cum. quartz}_{>2.0})}$$

Where Prop(2/1+) is the probability of profusion category 2/1 or higher and $cum.quartz_{<2.0}$ *and* $\text{cum. quartz}_{>2.0}$ are 100% respirable crystalline quartz below and above 2 mg/m^3, respectively, in g/m^3*h.

It appears from the equation that there is a cut point at 2 mg/m^3. At cumulative exposure above 2 mg/m^3, the coefficient for exposure concentrations (1.323) is about three times the exposure coefficient below 2 mg/m^3 (0.443).

Below the cut point 2 mg/m^3, the equation to estimate risk of silicosis morbidity associated with 45 years of occupational exposure (per 1,000 workers) is reduced to the following:

$$Prob\left(\frac{2}{1}+\right) = \frac{1}{1 + exp-(-4.83 + 0.443 \cdot cum.quartz_{<2.0})}$$

Since we are only looking at quartz exposures below 2 mg/m^3, this equation is the one that will be used for calculations in the present report.

We recalculated the calculations of risk associated with 45 years of occupational exposure per 1000 workers performed by OSHA:

First, we calculated the cumulative exposure at 25 μg/m^3 respirable crystalline silica during a worklife of 45 years with 2,000 working hours per year:

Cum.exposure = 25 μg/m^3 * 10^{-6} g/ μg *45 years * 2,000 h/year = 2.25 g/m^3 *h

Using the above equation, the calculation would be:

$$Prob\left(\frac{2}{1}+\right) = \frac{1}{1 + exp-(-4.83 + 0.443 \cdot 2.25)} = 0.021181$$

This fits well with the result presented by OSHA: Risk associated with 45 years of occupational exposure (per 1,000 workers) is 21 (Table VI-1, p. 16386) in (OSHA, 2016).

Similarly, calculations of risk were performed for the exposure levels 50 μg/m^3, 100 μg/m^3, 250 μg/m^3 and 500 μg/m^3. The results are presented in table 14. The NFA-calculations correspond to the OSHA calculations.

Table 14. Buchanan study: Cumulative risk estimates for silicosis morbidity – comparison of OSHA and NFA calculations.

	Respirable crystalline dust				
E (mg/m^3)	0.025	0.050	0.100	0.250	0.500
E(g/m^3)	0.000025	0.00005	0.0001	0.00025	0.0005
E (g/m^3 h)	2.25	4.50	9.00	22.50	45.00
E(mg/m^3 year)	1.125	2.25	4.5	11.25	22.5
Risk (NFA calculation)[1,2]	21:1000	55:1000	301:1000	994:1000	1000:1000
Risk (OSHA calculation)[1,3]	21:1000	55:1000	301:1000	994:1000	1000:1000

[1]Risk associated with 45 years of occupational exposure (per 1,000 workers)
[2]Risk calculated by NFA using $Prob\left(\frac{2}{1}+\right) = \frac{1}{1+exp—4.83+0.443 \cdot cum.quartz_{<2.0}}$
[3]Risk calculated by OSHA.

Next, we wanted to estimate silica concentrations for silicosis morbidity risk levels ranging from 1:100 to 1:100,000.

Calculation of the cumulative exposure corresponding to a 1:100 risk of silicosis associated with 45 years of occupational exposure to respirable silica was performed by solving the following equation:

$$0.01 = \frac{1}{1+exp\,-(-4.83+0.443 \cdot Cum.Exposure)} \rightarrow \text{Cum. Exposure} = 0.5302\ \text{g/m}^3\ \text{*h}$$

This corresponds to:

$$\frac{0.5302 \frac{\text{g}}{\text{m3}} * \text{h} * 1{,}000{,}000\ \mu\text{g/g}}{45\ \text{years} * 2000 \frac{\text{h}}{\text{year}}} = 5.89\ \mu\text{g/m}^3$$

The result is listed in Table 19. Due to the shape of the curve (the curve does not go through (0,0)), it was not possible to calculate the exposure values corresponding to the lower risk levels.

Steenland and Brown, 1995

This cohort study consists of 3,330 gold miners with high levels of silica exposure in a gold mine located in South Dakota (Steenland & Brown, 1995). 170 cases were identified either by death certificate (n=128), x-ray of category 1/1+ (n=19) or by both death certificate and x-ray category 1/1+ (n=13). Exposure characterization (mg/m^3) was based on a conversion of particle counts of respirable dust and an estimation of average silica content on 13%. The estimation of average silica content was based on 82 samples of respirable dust from two measurement campaigns in the 1970s (range 1%-48%).

Silicosis rates were for seven cumulative exposure categories determined based on Poisson regression. Since the equation is not presented in the OSHA report, the present working group has not performed any risk calculations based on this study.

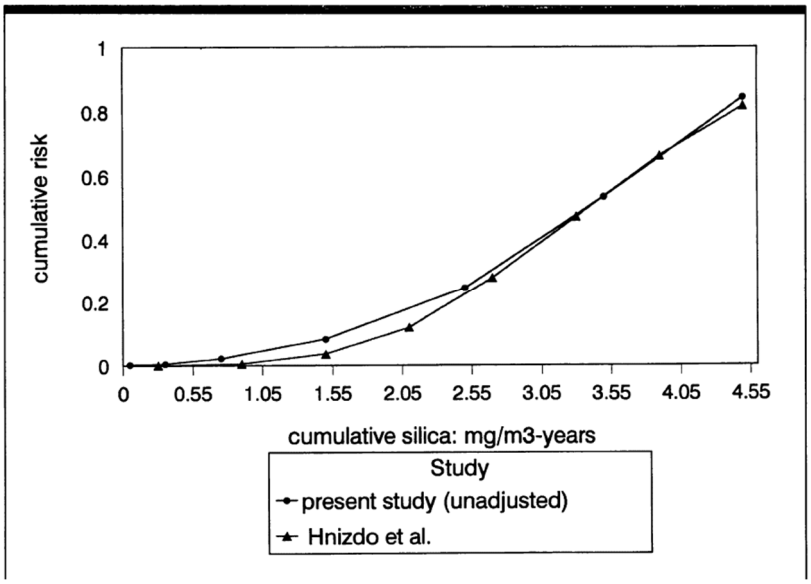

Figure 2. Cumulative risk of silicosis by cumulative respirable silica exposure (Figure 1 from Steenland and Brown, 1995).

However, from Figure 2 the cumulative risk of silicosis by cumulative respirable silica exposure appears to be consistent with the findings by Hnizdo and Sluis-Cremer (Hnizdo & Sluis-Cremer, 1993)(described in the next paragraph).

The authors (Steenland & Brown, 1995) and OSHA (OSHA, 2010) mention a number of limitations of the study including: 1) Estimation of exposure is based on a conversion of dust count to mass concentration. The conversion factor that was used (10 mpccf = 0.1 mg/m^3) was based on 82 samples collected in the 1970s. There is no measurements on the content of respirable silica before this point in time and the silica content may have varied over time, 2) No dust measurements were performed before 1937 and therefore estimates of exposure was used, 3) Silicosis was for the majority of cases diagnosed based on death certificates. This makes comparison to other studies using x-ray for diagnosis difficult. The present working group notes that exposure estimation is an important source of uncertainty in the study.

Hnizdo and Sluis-Cremer, 1993

This is a retrospective cohort study of 2,235 gold miners including 313 cases with silicosis classification 1/1 or greater (Hnizdo & Sluis-Cremer, 1993). Silicosis diagnosis was based on X-ray evaluation by one physician. To estimate the cumulative exposure, particle counts were converted to respirable dust measurements. It was assumed that the quartz content was 30%.

OSHA uses the following equation to estimate risk of silicosis morbidity associated with 45 years of occupational exposure (per 1,000 workers):

$$CR = 1 - \frac{1}{1 + exp\left(-\frac{2.439}{0.2199}\right) \cdot CDE^{\frac{1}{0.2199}}}$$

where CR is cumulative risk of silicosis and CDE is cumulative respirable dust in mg/m^3 years. The content of respirable quartz is assumed to be 30%.

Our comparison of OSHA report (OSHA, 2016) and the original paper (Hnizdo & Sluis-Cremer, 1993)(Hnizdo and Sluis-Cremer) showed identical coefficients. However, in the OSHA-report the minus in the parenthesis is lacking.

We recalculated the calculations of risk associated with 45 years of occupational exposure per 1000 workers performed by OSHA:

First, we calculated the cumulative exposure at 25 μg/m^3 respirable crystalline silica during a worklife of 45 years:

$Cum.exposure_{respirable\ silica}$ = 0.025 mg/m^3 * 45 years = 1.125 mg/m^3 *year

The content of respirable quartz is assumed to be 30%. Therefore, the calculation of cumulative exposure of respirable total dust is:

$Cum.exposure_{respirable\ total\ dust}$ = $Cum.exposure_{respirable\ silica}$/0.30
=1.125 mg/m^3 *year /0.30
=3.75 mg/m^3*year

Using the equation (2), the calculation would be:
$CR = 1 - \frac{1}{1+exp\left(-\frac{2.439}{0.2199}\right)\cdot 3.75^{\frac{1}{0.2199}}}$=0.00618 ~ 6:1000

This fits well with the result presented by OSHA: Risk associated with 45 years of occupational exposure (per 1000 workers) is 6 (Table VI-1 in (OSHA, 2016)).

Similarly, calculations of risk were performed for the exposure levels 50 μg/m^3, 100 μg/m^3, 250 μg/m^3 and 500 μg/m^3. The results are presented in table 15. It can be seen that the NFA-calculations correspond to the OSHA-calculations. It can also be seen that OSHA used the correct equation in their calculations and just "forgot" the minus when they referred to the equation.

Table 15. Cumulative risk estimates for silicosis morbidity – comparison of OSHA and NFA calculations.

	Respirable crystalline dust				
E (mg/m^3)	0.025	0.050	0.100	0.250	0.500
E (mg/m^3 year)	1.125	2.250	4.500	11.250	22.500
	Total dust				
E (mg/m^3)	0.0833	0.167	0.333	0.833	1.67
E(mg/m^3 year)	3.75	7.5	15	37.5	75
Risk (NRCWE calculation)[1,2]	6:1,000	127:1,000	773:1,000	995:1,000	1,000:1,000
Risk (OSHA calculation)[1,3]	6:1,000	127:1,000	773:1,000	995:1,000	1,000:1,000

[1]Risk associated with 45 years of occupational exposure (per 1,000 workers)
[2]Risk calculated by NFA using $CR = 1 - \frac{1}{1+exp\left(-\frac{2.439}{0.2199}\right)\cdot CDE^{\frac{1}{0.2199}}}$
[3]Risk calculated by OSHA

Next, we wanted to estimate silica concentrations for different risk levels for silicosis morbidity ranging from 1:100 to 1:100,000.

Calculation of the cumulative exposure corresponding to a 1:100 risk of silicosis associated with 45 years of occupational exposure to total respirable dust was performed by solving the following equation:

$$0.01 = 1 - \frac{1}{1+exp\left(-\frac{2.439}{0.2199}\right)\cdot CDE^{\frac{1}{0.2199}}} \rightarrow \text{CDE= 4.1726 mg/m}^3\text{ *years}$$

This corresponds to:

$$\frac{4.1726\frac{mg}{m3}*years}{45\text{ years}} = 0.0927\text{ mg total respirable dust/m}^3$$

The content of respirable quartz is assumed to be 30%. Therefore, the amount of respirable quartz corresponds to

0.0927 mg/m^3 *0.3= 0.0278 mg/m^3 = 27.8 μg/m^3

The estimated silica concentrations for different silicosis risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in 16.

Table 16. Hnizdo and Sluis-Cremer study: Respirable crystalline silica concentrations for different silicosis risk levels

Cumulative risk		**Total dust containing 30% respirable crystalline silica**		**Dust containing 100% respirable crystalline silica**		
CR	**CR**	**E (mg/m³*years)**	**E(mg/m³)**	**E(mg/m³ year)**	**E(mg/m³)**	**E(μg/m³)**
1:100	**0.01**	4.173	0.0927	1.252	0.0278	27.8
1:1000	**0.001**	2.510	0.0558	0.753	0.0167	16.7
1:10,000	**0.0001**	1.512	0.0336	0.454	0.0101	10.1
1:100,000	**0.00001**	0.911	0.0203	0.273	0.00608	6.1

Chen et al., 2001

This is a retrospective Chinese cohort study of 3 010 underground tin miners (Chen et al., 2001). The authors found a clear exposure-response relation for silicosis. Silicosis diagnosis was based on X-ray evaluation (classification 1/1 or greater). Since 1950, the exposure data were short-term gravimetric total dust measurements. Before 1950, the exposure concentrations were estimated from the 1950 data. For the conversion from total dust to respirable dust, it was assumed that the respirable quartz content was 3.6% of total dust. This was based on the ratio between respirable silica dust and the corresponding total dust collected at a sampling survey in 1988-1989 where two sampling devices were run in parallel.

OSHA uses the following equation to estimate risk of silicosis morbidity associated with 45 years of occupational exposure (per 1,000 workers):

$$CR = 1 - exp(-0.0076 \cdot E)^{2.23}$$

where E is cumulative exposure in mg/m^3 * years.

Our comparison of the above equation in the OSHA report (OSHA, 2016) and the original paper (Chen et al., 2001) showed identical coefficients.

We recalculated the calculations of risk associated with 45 years of occupational exposure per 1,000 workers performed by OSHA:

First, we calculated the total dust concentration equivalent to 25 μg/m^3 respirable crystalline silica:

Exposure$_{\text{Total dust}}$ = 25 μg/m^3 * 10^{-3} mg/μg /0.036 = 0.694 mg/m^3

Then, we calculated the cumulative exposure at 25 μg/m^3 respirable crystalline silica (equivalent to 0.694 mg total dust/m^3) during a worklife of 45 years:

Cum.exposure$_{\text{Total dust}}$ = 0.694 mg/m^3 * 45 years = 31.25 mg/m^3 * years

Using the above equation, the calculation would be:

$CR = 1 - exp(-0.0076 \cdot 31.25)^{2.23}$ =0.040

This fits well with the result presented by OSHA: Risk associated with 45 years of occupational exposure (per 1,000 workers) is 40 (Table VI-1 in (OSHA, 2016)).

Similarly, calculations of risk were performed for the exposure levels 50 μg/m^3, 100 μg/m^3, 250 μg/m^3 and 500 μg/m^3. The results are presented in table 17. The NFA calculations correspond to the OSHA calculations.

Table 17. Chen et al., 2001: Cumulative risk estimates for silicosis morbidity – comparison of OSHA and NFA calculations.

	Respirable crystalline dust				
E (mg/m^3)	0.025	0.050	0.100	0.250	0.500
E (mg/m^3 year)	1.125	2.25	4.50	11.25	22.50
	Total dust				
E (mg/m^3)	0.694	1.389	2.778	6.944	13.889
E(mg/m^3 year)	31.25	62.5	125.0	312.5	625.0
NRCWE calculation[1,2]	40:1,000	173:1,000	590:1,000	999:1,000	1,000:1,000
OSHA calculation[1,3]	40:1,000	170:1,000	590:1,000	1,000:1,000	1,000:1,000

[1]Risk associated with 45 years of occupational exposure (per 1,000 workers)
[2]Risk calculated by NFA using $CR = 1 - exp(-0.0076 \cdot E)^{2.23}$
[3]Risk calculated by OSHA.

Next, we wanted to estimate silica concentrations for different excess silicosis morbidity risk levels ranging from 1:100 to 1:100,000.

Calculation of the cumulative exposure corresponding to a 1:100 risk of silicosis associated with 45 years of occupational exposure to total respirable dust was performed by solving the following equation:

$0.01 = 1 - exp(-0.0076 \cdot E)^{2.23} \rightarrow$ E= 16.722 mg/m^3 *years

This corresponds to:

$$\frac{16.722\ \frac{mg}{m3} * years}{45\ \text{years}} = 0.3716\ \text{mg total respirable dust/m}^3$$

The content of respirable silica is assumed to be 3.6%. Therefore, the amount of respirable silica corresponds to

0.3761 mg/m^3 *0.036= 0.0134 mg/m^3 = 13.4 μg/m^3

The estimated silica concentrations for different silicosis risk levels ranging from 1:100 to 1:100,000 are calculated similarly as described above and are listed in table 18.

Table 18. Chen (2001) study: Respirable crystalline silica concentrations for different silicosis risk levels.

Cumulative risk		**Total dust containing 3.6% resp cryst silica**		**Dust containing 100% respirable crystalline silica**		
CR	**CR**	**E (mg/m³*years)**	**E(mg/m³)**	**E(mg/m³ year)**	**E(mg/m³)**	**E(μg/m³)**
1:100	**0.01**	16.72	0.372	0.602	0.0134	13.4
1:1000	**0.001**	5.943	0.132	0.214	0.00475	4.8
1:10,000	**0.0001**	2.116	0.0470	0.0762	0.00169	1.7
1:100,000	**0.00001**	0.753	0.0167	0.0271	0.000603	0.6

CR: Cumulative risk; E: Exposure

Chen et al., 2005

In 2005, Chen et al. (Chen et al., 2005) investigated risk of silicosis morbidity in three cohorts: 1) pottery workers (n=4,547), tin miners (n=4,028) and tungsten miners (n=14,427). The evaluation of silicosis morbidity was classified by scoring x-rays as described in the earlier study by Chen et al (Chen et al., 2001). Exposure characterization was also based on the previous study (Chen et al., 2001). In addition, the surface alumino-silicate occlusion of silica particles was also measured in 47 dust samples. This results in information on the percent of the particle surface that is estimated to be occluded.

OSHA has estimated cumulative silicosis risk based on figure 2B in Chen et al (Chen et al., 2005)(Figure 3). The present working group notes the reduced toxicity in the pottery workers compared to tungsten and tin workers may be due to coating of silica particles.

The present working group is of the opinion that it does not make sense to try to extract the corresponding cumulative respirable dust below a cumulative risk of 0.1 (10%) from the figure, and therefore, this study is not further considered in the present report.

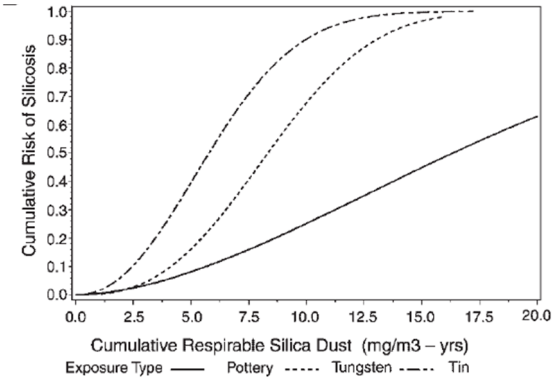

Figure 3. Cumulative risk of silicosis versus cumulative respirable silica dust in the study by Chen et al (Figure 2B from (Chen et al., 2005)).

NFA literature search

Leso et al., 2019

Leso et al. has provided a recent systematic review of studies of silicosis and exposure to artificial stone (Leso et al., 2019). Artificial stone is produced by mixing of finely crushed rocks with polymeric resin. The silica content is approximately 90%. Artificial stone is a material that is used for manufacturing of kitchen and bathroom countertops. The authors concluded that "*the characteristics of artificial stone associated silicosis were comparable to those that were reported for the disease in traditional silica exposure settings, some critical issues emerged concerning the general lack of suitable strategies for assessing/managing silica risks in these innovative occupational fields*".

The present working group notes that the review by Leso et al. (Leso et al., 2019) illustrates that exposure to crystalline silica may occur in new occupational settings. No calculations of risks are performed by Leso et al. and therefore the manuscript is not discussed further in the present report.

Comparison of silicosis morbidity studies

Four of the five OSHA key studies on silicosis morbidity have defined silicosis when chest x-ray was classified as category of 1/0 or greater (Chen et al., 2005; Chen et al., 2001), or 1/1 or greater (Hnizdo et al., 1993; Steenland & Brown, 1995). In the fifth OSHA key study of silicosis morbidity, silicosis was defined when x-ray was classified as 2/1 or greater (Buchanan et al., 2003).

The present working group notes that the use of different definitions of silicosis across studies may affect the silicosis risk estimates. Thus, when silicosis is defined as 2/1 or greater, a lower risk of silicosis is expected compared to a definition of silicosis starting at 1/1 or greater. However, according to Table 5, the risks of silicosis associated with occupational exposure to respirable crystalline silica based on the Buchanan study does not seem to differ significantly from the other studies.

Among the five studies that OSHA has used as key studies of silicosis morbidity, the current working group was able to perform calculations for three of the studies

(Buchanan et al., 2003; Chen et al., 2001; Hnizdo & Sluis-Cremer, 1993). These are presented in Table 19. For comparison, in addition, figure 4 shows dose-response relationships based on the equations for the relationship between cumulative exposure to respirable crystalline silica and the cumulative risk of silicosis morbidity from the studies by Hnizdo and Sluis-Cremer (1993), Chen et al. (2001) and Buchanan et al. (2003). For two of the studies, calculations have not been performed by the present working group because of lack of information on equation to be used for risk calculations (Chen et al., 2005; Steenland & Brown, 1995).

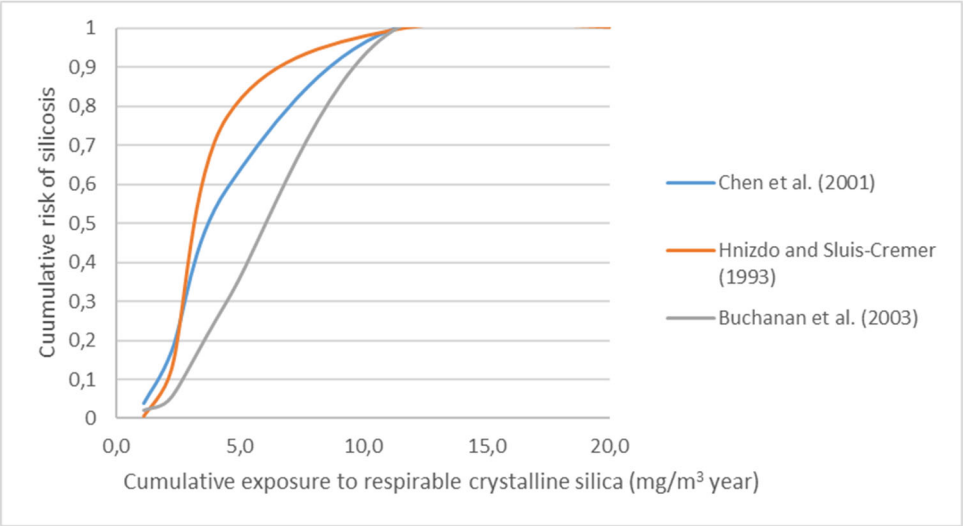

Figure 4. Relation between cumulative risk of silicosis and cumulative exposure to respirable crystalline silica.

Among the remaining three studies on silicosis morbidity, the present working group finds it difficult to compare these because they are all based on different mathematical equations. Furthermore, the current working group notes that the dose-response relationships are unusually steep (see table 19).

Table 19. Summary of risk estimates for silicosis morbidity.

Absolute silicosis morbidity	Respirable crystalline silica exposure			
	µg/m³			
	Buchanan et al., 2003	Hnizdo and Sluis-Cremer, 1993	Chen et al., 2001	Mean
	Coal miners	Gold miners	Tin miners	
1:100	5.9	27.8	13.4	15.7
1:1,000	[1)]	16.7	4.8	10.8
1:10,000	[1)]	10.1	1.7	6.0
1:100,000	[1)]	6.1	0.6	3.0

[1]Not possible to calculate the risk at lower levels (the graph does not go through (0,0).

The current working group notes that there is evidence that occupational exposure to crystalline silica causes silicosis morbidity to the same extent as the exposure causes lung cancer.

However, the present working group is of the opinion that the risk estimates for lung cancer mortality are better determined than the risk estimates for silicosis morbidity.

Conclusion

In this report, a working group at NFA reviewed data relevant to risk assessment of respirable quartz. Quartz is the most abundant form of crystalline silica. The working group assessed human studies, toxicokinetics, animal studies, mechanisms of toxicity, previous evaluations of quartz/crystalline silica, scientific basis for setting an OEL and finally the present working group summarizes and suggests the same risk levels for the respirable crystalline silica polymorphs quartz, cristobalite, and tridymite. The focus of this report is on occupational exposure by inhalation.

Quartz is found in sands, soils and most rock types. Cristobalite and tridymite are examples of other types of crystalline silica. All three forms occur both in α- and β-forms. Occupational exposure to quartz occurs in many different sites, including 1) activities that involve the movement of earth, 2) disturbance of silica-containing products, and 3) handling or use of sand- and other silica-containing products in transportation, construction, railroad and mining industries (IARC, 2012).

The current Danish occupational exposure limit for respirable quartz is 0.1 mg/m^3. A recent study of Danish demolition workers showed that the geometric mean value for respirable crystalline silica was 0.12 mg/m^3. The air concentrations ranged from below the limit of detection to 0.92 mg/m^3 (Kirkegaard et al., 2016). A recent Swedish study of respirable quarts exposure in industries in Southern Sweden showed that the median value and the geometric mean value for quartz were 0.01 and 0.02 mg/m^3, respectively. The highest measured concentration was 17 mg/m^3. A detection level of 0.002 mg/m^3 was reported in the Swedish study (Hedmer, 2017). IARC states that "*it has been estimated that respirable crystalline silica levels in the low μg/m^3 range are common in ambient air*" (IARC, 1997).

In 1997, IARC classified crystalline silica dust as a human carcinogen (Group 1) (IARC, 1997). This evaluation was further confirmed when IARC reassessed crystalline silica in 2012 (IARC, 2012). IARC concluded that there is sufficient evidence in humans that crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

In the present report, endpoints were evaluated based on reported adverse effects of quartz exposure in reports and in the scientific literature. Especially the recent report by OSHA on crystalline silica (OSHA, 2016) including the background documents for this report (OSHA, 2010, 2013) were used as basis for the present report. OSHA evaluated several adverse health effects for crystalline silica. OSHA did not provide specific evaluations for each of the different crystalline silica polymorphs because they concluded that both epidemiological and experimental evidence show that quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency. The current working group agrees with this view and therefore decided to include all epidemiological studies of crystalline silica in the current evaluation. OSHA estimates that at their final permissible exposure limit of 50 μg/m^3 respirable crystalline silica as an 8-hour time-weighted average, the excess lung cancer mortality is 5 to 23 deaths per 1,000 workers, the silicosis morbidity is 20 to 170 per 1,000 workers, the silicosis and non-malignant lung disease mortality is 7 to 44 per 1,000 workers, and the renal disease mortality is 32 per 1,000 workers. Overall, the present working group regards the OSHA report (OSHA, 2016) as a thorough evaluation of the available scientific evidence for the

toxicity of respirable crystalline silica and the scientific evidence for dose-dependent induction of cancer, silicosis and renal disease.

The OSHA report does not assess cardiovascular effects as an endpoint. However, a recent criteria document on occupational chemical exposures and cardiovascular disease from NEG concludes that there is strong evidence for an association between exposure to crystalline silica and cardiovascular disease, and we have therefore chosen to consider this endpoint as well (NEG, 2020). However, the present working group does not consider cardiovascular disease as one of the most critical effects of crystalline silica exposure because cancer and silicosis may occur at lower exposure levels.

The OSHA concluded that for autoimmune diseases no quantitative exposure-response data are available for a quantitative risk assessment (OSHA, 2016). The present working group identified a very recent Danish cohort study on occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases with more than 3 million workers including approximately 17,000 cases (Boudigaard et al., 2021). The present working group considers that this is an important study showing an exposure-dependent association between exposure to respirable crystalline silica and autoimmune rheumatic diseases. However, since no mathematical relationship between exposure to respirable crystalline silica and autoimmune rheumatic diseases is presented, the present working group does not consider it possible to perform a quantitative risk analysis for this endpoint.

Based on the evaluation, the present working group regards lung cancer and silicosis as the critical effects.

The mechanism of action of crystalline silica-induced lung cancer is not clear, but primary genotoxicity caused by particle surface reactivity cannot be excluded, and therefore, the current working group decided to use a non-threshold approach. This is in line with the mathematical equations used for the risk calculations by OSHA. For silicosis, no threshold could be established in epidemiological studies.

The scientific literature on the health effects of quartz is enormous and therefore the present working group chose to focus the evaluation on the studies that OSHA considered appropriate for their final risk assessment. However, to ensure that the most recent literature also was assessed, a literature search was performed to identify studies published since the publication of the OSHA report. For the critical effects selected by the present working group, OSHA based their final risk assessment on 5 lung cancer mortality studies, 2 silicosis and non-malignant lung disease mortality studies, and 5 silicosis morbidity studies. In our own literature search, one additional study on lung cancer was identified that was considered relevant for inclusion in the final risk assessment. The current working group notes that the OSHA risk estimates for lung cancer, silicosis and renal disease were of similar magnitude.

The current working group notes that there is evidence that occupational exposure to crystalline silica causes silicosis morbidity and mortality to the same extent or more potently as the exposure causes lung cancer. However, the present working group is of

the opinion that the risk estimates for lung cancer mortality are better determined than the risk estimates for silicosis morbidity.

The current working group is of the opinion that the available quantitative epidemiological data for the dose-response relationship with lung cancer are more extensive, more transparent and comparable than the available data for silicosis and renal disease. The current working group therefore decided to use the quantitative epidemiological data for lung cancer as the most adequate and reliable basis for the risk assessment of crystalline silica.

All the quantitative studies on lung cancer risk provided models for the dose-response relationship between cumulative exposure to crystalline silica and lung cancer. The models varied between the studies (linear, log-linear, and linear spline models were used). Log-linear models were frequently used, and the present working group chose to base the risk estimation of cancer risk on the individual studies with log-linear equations. This approach made it possible to base the calculations of lung cancer risk on four studies which all used log-linear models. In summary, three of the five OSHA key studies (Attfield & Costello, 2004; Hughes et al., 2001; Miller & MacCalman, 2010) and one additional study identified in our own literature search (Liu et al., 2013) used log-linear model. These studies represent almost 60,000 workers and includes approximately 1,600 deaths. The present working group suggests to calculate an un-weighed mean β based on these four studies for the risk calculations, using the same approach as for the previous evaluation of Cr(VI) by the present working group (NFA, 2019). Thus, the equation for the log-linear relationship between relative risk (RR) and cumulative exposure (E, mg/m^3*years) is: RR= exp(0.107*E).

Based on this equation, the expected excess lung cancer risk based on an un-weighed mean β based on four epidemiological studies is 1: 1,000 at 4 μg/m^3, 1: 10,000 at 0.4 μg/m^3 and 1: 100,000 at 0.04 μg/m^3 respirable crystalline silica. The corresponding risk estimates for the current Danish OEL of 0.1 mg/m^3 would be 30 per 1,000 exposed, and 2 per 1,000 exposed at 0.01 mg/m^3.

In comparison, OSHA estimates that at their final permissible exposure limit of 50 μg/m^3 respirable crystalline silica as an 8-hour time-weighted average, the excess lung cancer mortality risk with 45 years of occupational exposure is 5 to 23 deaths per 1,000 workers, the silicosis morbidity is 20 to 170 per 1,000 workers, the silicosis and non-malignant lung disease mortality is 7 to 44 per 1,000 workers and the renal disease mortality is 32 per 1,000 workers. Based on four epidemiological studies with almost 60,000 participants, the current working group estimates that occupational exposure to 38 μg/m^3 crystalline silica for 45 years will cause 10 excess lung cancer cases per 1,000 exposed. At 50 μg/m^3, this would correspond to 13 excess lung cancer cases per 1,000 exposed, and is therefore very similar to the risk estimates of 5 to 23 cases by OSHA.

The present working group concludes that it is evidenced that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency, whereas the carcinogenic potency of silica dust may be modified depending on age and level and type of impurities. However, the information is insufficient to

conclude to what extent these factors affect the toxicity. The present working group therefore recommends to adapt the same OEL for crystalline silica polymorphs quartz, cristobalite, and tridymite.

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Appendix A

Literature search

A number of key articles were identified before the actual search was carried out to be used as guidance for constructing the search strategy.

A literature search addressing peer reviewed original journal articles were performed in the bibliographic database, PubMed.

The elements in the search strategy comprised of *what* (quartz, etc.) *AND why* (outcome of interest: meta-analysis OR dose-response of health effects, occupational exposure, etc.)

The search profile was limited to 2010-2019 AND human studies in English. The result (#7 in the PubMed search shown below) was compared to key articles. The search proved satisfactory and no alterations were made.

The search strategy combined sets of keywords using AND/OR terms in Boolean logic.

In PubMed appropriate index terms and their synonyms were identified in the thesaurus.

From the unique 367 items, a maximum of 10 articles had direct relevance to the specific topic in question, the rest were remotely relevant (for perspectives, etc.).

History

Search "QUARTZ" AND "EXPOSURE" AND "(META-ANALYSIS OR DOSE-RESPONSE…)" – limits: Humans; English

Search	Query	Items found
#7	**(#1 AND #2 AND #5)** Filters: **Humans; English; Publication date from 2010/01/01 to 2019/12/31**	367
#6	**(#1 AND #2 AND #5) QUARTZ AND EXPOSURE AND (META-ANALYSIS OR DOSE-RESPONSE)** Filters: **Humans; English**	905
#5	**(#3 OR #4) META-ANALYSIS OR DOSE-RESPONSE**	411761
#4	**((((("exposure-response"[Title/Abstract]) OR "dose-response"[Title/Abstract]) OR "dose response"[Title/Abstract]) OR "risk assessment"[Title/Abstract]) OR risk assessment[MeSH Terms])) AND ("humans"[MeSH Terms] AND English[lang]) DOSE-RESPONSE**	277320
#3	**((((("meta-analysis"[Title/Abstract]) OR "meta analysis"[Title/Abstract]) OR "meta-analyses"[Title/Abstract]) OR "meta analyses"[Title/Abstract])) OR ("Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh])) AND ("humans"[MeSH Terms] AND English[lang]) META-ANALYSIS**	143486
#2	**(((((((exposure*[Title/Abstract]) OR exposed[Title/Abstract]) OR (occupational exposure[MeSH Terms])))))) AND ("humans"[MeSH Terms] AND English[lang])))) EXPOSURE (adjusted)**	549226

Search	Query	Items found
#1	**(((((quartz[MeSH Terms]) OR (quartz[Title/Abstract]) OR (crystalline[Title/Abstract]) OR (silicon dioxide[MeSH Terms]) OR ((silicon[Title/Abstract]) AND dioxide[Title/Abstract]) OR (silica[Title/Abstract]) OR ("SiO2"[Title/Abstract]) OR (14808-60-7[EC/RN Number]))) AND ("humans"[MeSH Terms] AND English[lang]))) QUARTZ**	37313

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