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156. Respirable crystalline silica

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Executive summary

Crystalline silica is a mineral that is abundant in most rocks, sands and soils. The most common forms of crystalline silica are quartz, cristobalite and tridymite. When crystalline silica is cut or crushed, dust containing respirable crystalline silica (RCS) particles, is released into the air. These RCS particles can be inhaled deep into the lungs and cause diseases such as silicosis and lung cancer.

The Dutch Expert Committee on Occupational Safety (DECOS) and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) evaluated the health hazards and calculated cancer risk levels for occupational exposure to RCS. They carried out their evaluation at the request of the Dutch Minister of Social Affairs and Employment, and the work environment authorities of Denmark, Finland, Norway and Sweden.

DECOS and NEG both give scientifically based advice in order to protect workers against the potentially harmful effects of substances that they may encounter in the course of their work. The committees assess the toxic properties and health effects of these substances and make recommendations for health-based occupational exposure limits (OELs).

More information on the tasks of the committees can be found on the following websites www.gezondheidsraad.nl and www.nordicexpertgroup.org.

Occupational exposure to RCS in many industries

Because of the extensive natural occurrence and the wide use of crystalline silica, workers in a large variety of industries and occupations are potentially exposed to RCS. In general, any process that involves movement of earth or processing of crystalline silica-containing materials or products may potentially expose workers to RCS. Examples are mining, farming, construction, foundry processes and the production of glass, artificial stone, ceramics or cement.

While occupational exposure levels to RCS have generally decreased over the last sixty years, high exposures may still occur in some work situations. Over the last ten to twenty years the use of artificial stone products has increased, for example in kitchen and bathroom countertops. These artificial stone products can contain high percentages (> 93%) of finely crushed crystalline silica, which makes them an emerging source of exposure for workers who work in manufacturing or who work with artificial stone products.

RCS exposure can cause silicosis and lung cancer

Exposure to RCS has been associated with several diseases. Diseases considered by the committees in the current evaluation include chronic obstructive pulmonary disease (COPD), renal diseases, cardiovascular diseases, autoimmune diseases and other cancers than lung cancer. The underlying mechanisms by which exposure to RCS may cause these diseases are not fully understood yet and need further

research. However, based on epidemiological studies and current knowledge on underlying biological mechanisms, the committees conclude that there is very strong evidence for a causal relationship between exposure to RCS and silicosis and lung cancer.

Silicosis is an irreversible and incurable lung disease and one of the oldest known occupational diseases in the world. It is caused by the inhalation of RCS, which can result in inflammation and scarring (fibrosis) of the lungs. Progression of silicosis can result in death due to respiratory failure. Silicosis may be complicated by severe mycobacterial infections resulting in silicotuberculosis.

In recent years, numerous cases of silicosis have been reported among workers involved in artificial stone manufacturing or fabrication of products using artificial stone. Artificial stone-associated silicosis has a relatively high occurrence among workers with short exposure periods and with a more rapid progression compared to the more common chronic form of silicosis.

Exposure to RCS is also a known risk factor for lung cancer. Several epidemiological studies including meta- and pooled analyses reported an increased risk of lung cancer in workers exposed to RCS. RCS causes damage to the lung cells, resulting in inflammation and a tumour-promoting environment. The relationship between silicosis and lung cancer has been investigated as well. Recent studies have shown excess lung cancer risks among workers exposed to RCS even in the absence of silicosis. However, having silicosis does increase the risk of developing lung cancer.

Lung cancer is used as critical health effect

For the quantitative risk analysis, the committees first decided on a critical adverse health effect. This is the adverse health effect that occurs first at increasing exposure to RCS. As both lung cancer and silicosis can occur at low exposure levels to RCS, both diseases could be used as critical health effect. However, the committees preferred using lung cancer as the critical health effect. They considered the diagnostics and registration of lung cancer compared to silicosis to be better and found the available data for the exposure-response relationship between RCS and lung cancer to be of higher quality. They assumed that setting OELs based on lung cancer will also protect against other health effects associated with occupational exposure to RCS.

A non-threshold (risk-based) approach is used

The approach taken in the case of a carcinogenic substance such as RCS depends on the mode of action by which the substance causes cancer: the genotoxic mechanism. Based on the available research, the committees conclude that RCS can cause lung cancer mainly by means of an indirect genotoxic mechanism, but possibly also by a direct genotoxic mechanism. RCS can cause damage to lung cells because it causes an inflammatory response, resulting in oxidative stress. This condition can occur when there are too many unstable molecules, called free

radicals or oxidants (for example reactive oxygen species; ROS), in the body and not enough antioxidants to eliminate them. Oxidative stress can lead to cell and tissue damage, ultimately causing DNA damage in lung cells.

However, free radicals such as ROS can also be formed directly at the surface of RCS particles. These free radicals can enter the cell nucleus and directly cause DNA damage. This means that the possibility of a direct genotoxic mechanism of RCS cannot be excluded.

Because a direct genotoxic mechanism is possible, the committees decided to use a non-threshold (risk-based) approach for RCS. With this approach it is assumed that every level of exposure, however low, involves a certain risk of developing cancer. In that case, it is not possible to set an exposure level using a threshold-based approach. The non-threshold-based approach focuses on limiting the cancer risk involved by deriving health-based calculated occupational cancer risk values (HBC-OCRVs).

Calculation of cancer risk levels

The committees used a pooled analysis by Ge *et al.* (2020) as the key study for the calculation of cancer risk levels. They selected this study because it contained data of almost 40 000 predominantly European participants. In addition, this study obtained information and was able to control for potential confounding by smoking and co-exposures to other lung carcinogens in the workplace. Furthermore, this key study contained more recent exposure measurement data and was more representative of the Dutch and Nordic work populations compared to other available studies.

For the non-threshold (risk-based) approach the Dutch Minister of Social Affairs and Employment has established two cancer risk levels in advance: a target risk level (low level) and a prohibition risk level (high level). The target risk level is the level below which no extra protective measures have to be taken. The prohibition risk level should not be exceeded. In terms of cancer due to occupational exposure over a 40-year period, these risk levels correspond to four additional cancer deaths which are added to the number of deaths from all causes per 100 000 and per 1 000 workers, respectively.

Advice to the Dutch minister and regulatory Nordic authorities

The committees estimate that the HBC-OCRVs for RCS in the breathing zone are as follows:

- 4 additional deaths of lung cancer per 100 000 workers (4×10^{-5}), for 40 years of occupational exposure, equal to 0.00038 mg/m^3 (target risk level or low risk level).
- 4 additional deaths of lung cancer per 1 000 workers (4×10^{-3}), for 40 years of occupational exposure, equal to 0.0363 mg/m^3 (prohibition risk level or high risk level).

The recommended exposure levels are 8-hour time-weighted average (TWA) concentrations. This reflects an average working day of 8 hours.

Epidemiological studies showed that quartz, cristobalite and tridymite have generally similar toxicity and carcinogenic potential. Therefore, the committees recommend the same HBC-OCRVs for all three RCS polymorphs.

The committees note that the recommended cancer risk levels are considerably lower than the current legal OELs in the Netherlands, Denmark, Finland, Norway and Sweden. However, the recommended cancer risk levels are in line with recent recommendations from other international work environment organisations such as the Danish National Research Centre for the Working Environment (NFA) and the US Occupational Safety and Health Administration (OSHA).

Sammanfattning

Kristallin kiseldioxid är ett mineral som är vanligt förekommande i flertalet bergarter, sand och jord. De vanligaste formerna är kvarts, kristobalit och tridymit. När kristallin kiseldioxid skärs eller krossas bildas damm som innehåller partiklar av respirabel kristallin kiseldioxid (respirable crystalline silica, RCS). Vid inandning når RCS djupt ner i lungorna och kan orsaka sjukdomar som silikos och lungcancer.

Den holländska expertkommittén för arbetarskydd (Dutch Expert Committee on Occupational Safety, DECOS) och den nordiska expertgruppen för kriteriedokument om kemiska hälsorisker (NEG) har utvärderat hälsoriskerna och beräknat cancerrisknivåer för yrkesmässig exponering för RCS. Utvärderingen genomfördes på begäran av det nederländska social- och arbetsministeriet och arbetsmiljömyndigheterna i Danmark, Finland, Norge och Sverige.

DECOS och NEG ger vetenskapligt baserade råd för att skydda arbetstagare mot potentiellt skadliga effekter av kemiska ämnen som de kan exponeras för i sitt arbete. Kommittéerna bedömer ämnenas toxiska egenskaper och hälsoeffekter och ger rekommendationer om hälsobaserade yrkeshygieniska gränsvärden.

Mer information om kommittéernas uppgifter finns på www.gezondheidsraad.nl och www.nordicexpertgroup.org.

Yrkesmässig exponering för RCS förekommer i många branscher

På grund av den omfattande naturliga förekomsten och breda användningen av kristallin kiseldioxid kan arbetstagare i många industrier och yrken exponeras för RCS. Alla arbetsmoment där jord/mark, material eller produkter som innehåller kristallin kiseldioxid hanteras eller bearbetas kan medföra exponering för RCS. Exempel på verksamheter där exponering förekommer är gruvdrift, jordbruk, bygg- och anläggningsarbete, gjutning och tillverkning av glas, konststen, keramik eller cement.

Exponeringen för RCS har minskat under de senaste sextio åren, men höga nivåer kan fortfarande förekomma vid vissa arbetsmoment. Under de senaste två decennierna har användningen av konstgjorda stenprodukter (kvartskomposit), till exempel bänkskivor i kök och badrum, ökat. Dessa konstgjorda stenprodukter kan innehålla höga halter (> 93%) finkrossad kristallin kiseldioxid, och innebär ökad exponering för RCS inom tillverkning och bearbetning.

Exponering för RCS kan orsaka silikos och lungcancer

Exponering för RCS har associerats med flera sjukdomar. Baserat på epidemiologiska studier och aktuell kunskap om bakomliggande biologiska mekanismer anser kommittéerna att det finns mycket starka bevis för ett orsakssamband mellan exponering för RCS och silikos och lungcancer. DECOS och NEG har även utvärderat kroniskt obstruktiv lungsjukdom (KOL), njursjukdomar, hjärt- och

kärlsjukdomar, autoimmuna sjukdomar, och andra cancerformer än lungcancer. De underliggande mekanismerna genom vilka exponering för RCS kan orsaka dessa sjukdomar är inte helt klarlagda och ytterligare forskning behövs.

Silikos är en irreversibel och obotlig lungsjukdom och en av de äldsta kända yrkessjukdomarna i världen. Sjukdomen orsakas av inandning av RCS, som ger inflammation och ärrbildning (fibros) i lungorna. Långt gången silikos kan leda till dödsfall på grund av andningssvikt. Silikos kan förvärras av allvarliga mykobakteriella infektioner vilket leder till silikotuberkulos.

Under de senaste åren har många fall av silikos rapporterats i samband med tillverkning eller hantering av produkter innehållande konstgjord sten. Jämfört med den kroniska formen av silikos, är sjukdomsförloppet i dessa fall snabbare och uppkommer ofta efter kort tids exponering.

Exponering för RCS är även en känd riskfaktor för lungcancer. Flera epidemiologiska studier inklusive meta- och poolade analyser, visar en ökad risk för lungcancer hos arbetstagare som exponerats för RCS. Exponeringen orsakar skador på lungcellerna, vilket resulterar i inflammation och en tumörfrämjande miljö. Sambandet mellan silikos och lungcancer har också undersökts. En del studier visar ökad risk för lungcancer även i frånvaro av silikos, men silikos ökar risken att utveckla lungcancer.

Lungcancer är den kritiska hälsoeffekten

För den kvantitativa riskanalysen fastställde DECOS och NEG först den kritiska hälsoeffekten för RCS, dvs den negativa hälsoeffekt som uppstår först vid ökande exponering. Eftersom både lungcancer och silikos kan uppstå vid låga exponeringsnivåer för RCS kan båda sjukdomarna användas som kritiska hälsoeffekter. DECOS och NEG föredrog dock att använda lungcancer eftersom såväl diagnostik och registrering som data på exponering-responssamband var bättre för lungcancer än för silikos. Ett hygieniskt gränsvärde baserat på lungcancerdata bedöms också skydda mot andra hälsoeffekter orsakade av yrkesmässig exponering för RCS.

En riskbaserad (tröskellös) metod tillämpas

Arbetsgången för ett cancerframkallande ämne som RCS, beror på det verkningsmekanismen, i detta fall genotoxicitet. Utifrån tillgänglig forskning drar kommittéerna slutsatsen att RCS orsakar lungcancer huvudsakligen via en indirekt genotoxisk mekanism, men möjligen också via en direkt genotoxisk mekanism. RCS skadar lungcellerna genom att inducera ett inflammatoriskt svar, vilket resulterar i oxidativ stress. Detta tillstånd kan uppstå när det bildas ett överskott av reaktiva molekyler, så kallade fria radikaler eller oxidanter (till exempel reaktiva syreradikaler, ROS), i kroppen och inte tillräckligt med antioxidanter för att eliminera dem. Oxidativ stress kan leda till cell- och vävnadsskador, vilket i slutändan orsakar DNA-skador i lungcellerna.

Fria radikaler kan även bildas på ytan av RCS-partiklarna. Dessa fria radikaler kan ta sig in i cellkärnan och orsaka DNA-skador. En direkt genotoxisk mekanism kan därför inte uteslutas.

Eftersom en direkt genotoxisk mekanism inte kan uteslutas, beslutade kommittéerna att tillämpa en riskbaserad (tröskellös) metod. Detta innebär att all exponering (för RCS i detta fall), hur låg den än är, antas innebära en risk för att utveckla cancer. Det är därmed inte möjligt att sätta ett gränsvärde utifrån en tröskelnivå. Den riskbaserade metoden syftar i stället till att begränsa cancerrisken via hälsobaserade beräknade yrkesmässiga cancerrisknivåer (health-based calculated occupational cancer risk values, HBC-OCRVs).

Beräkning av cancerrisknivåer

Kommittéerna använde en poolad analys av Ge och medarbetare (2020) för beräkning av cancerrisknivåer. Denna studie valdes för att den inkluderar data från nästan 40 000, huvudsakligen europeiska, deltagare. Dessutom har studien kontrollerat för potentiella förväxlingsfaktorer (confounders) såsom rökning och samtidig exponering för andra lungcancerframkallande ämnen på arbetsplatsen. Vidare innehåller studien nyare exponeringsdata och ansågs vara mer representativ för Nederländerna och Norden än andra tillgängliga studier.

För det riskbaserade (tröskellösa) tillvägagångssättet har det nederländska social- och arbetsministeriet fastställt två cancerrisknivåer: en målrisknivå (låg nivå) och en förbudsrisknivå (hög nivå). Målrisknivån är den nivå under vilken inga extra skyddsåtgärder behöver vidtas. Förbudsrisknivån ska inte överskridas. När det gäller cancer på grund av yrkesexponering under en 40-årsperiod motsvarar dessa risknivåer fyra extra cancerdödsfall som läggs till antalet dödsfall av alla orsaker per 100 000 respektive per 1 000 arbetstagare.

Råd till det nederländska ministeriet och tillsynsmyndigheterna i Norden

Kommittéerna uppskattar att HBC-OCRVs för RCS i andningszonen är följande:

- 4 extra dödsfall i lungcancer per 100 000 arbetare (4×10^{-5}) efter 40 års yrkesmässig exponering för 0,00038 mg/m^3 (målrisknivå eller lågrisknivå).
- 4 extra dödsfall i lungcancer per 1 000 arbetare (4×10^{-3}) efter 40 års yrkesmässig exponering för 0,0363 mg/m^3 (förbudsrisknivå eller högrisknivå).

De rekommenderade exponeringsnivåerna är 8-timmars tidsvägda medelvärden (time-weighted average, TWA). Detta återspeglar en genomsnittlig arbetsdag på 8 timmar.

Epidemiologiska studier visar att kvarts, kristobalit och tridymit generellt sett har liknande toxicitet och cancerframkallande potential. Därför rekommenderar kommittéerna samma HBC-OCRVs för alla tre polymorfer av RCS.

Kommittéerna noterar att de rekommenderade cancerrisknivåerna är avsevärt lägre än de nuvarande hygieniska gränsvärdena i Nederländerna, Danmark, Finland, Norge och Sverige. De rekommenderade cancerrisknivåerna är dock i linje med de

senaste rekommendationerna från andra internationella arbetsmiljöorganisationer som det danska arbetsmiljöinstitutet (NFA) och den amerikanska arbetarskyddsmyndigheten (OSHA).

1. Scope

1.1 Background

The current evaluation of RCS is a collaboration between DECOS and NEG. At the request of the Dutch Minister of Social Affairs and Employment, DECOS, a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of chemical substances that are used in the workplace. Similarly, NEG performs evaluations at the request of the regulatory authorities in Denmark, Finland, Norway and Sweden. The purpose of these evaluations is to derive health-based recommended occupational exposure limits (HBR-OELs) or HBC-OCRVs for the concentration of a substance in the air, provided that the data allows the derivation of such values. These recommendations serve as a basis in setting final, legally binding OEL values by the Dutch and Nordic authorities.

DECOS evaluated RCS in 1992, which resulted in an HBR-OEL of 0.075 mg/m^3 for quartz, cristobalite and tridymite (68). NEG evaluated RCS in 1993, but did not propose an health-based OEL (110). However, as a result of the evaluation, the Swedish Work Environment Authority did set binding OELs of 0.1 mg/m^3 for respirable quartz and 0.05 mg/m^3 for respirable cristobalite and respirable tridymite in 1996 (250). Since then, more scientific research has been published and some international work environment organisations on the evaluation of chemical substances have recommended or set lower OELs (e.g., American Conference of Governmental Industrial Hygienists (ACGIH), US National Institute for Occupational Safety and Health (NIOSH), US OSHA). In 2021, the Danish NFA published an evaluation on respirable quartz and other crystalline silica polymorphs and calculated an expected excess lung cancer risk for 1:1 000 at 0.004 mg/m^3, 1:10 000 at 0.0004 mg/m^3, and 1:100 000 at 0.00004 mg/m^3 (TWA), based on a 45-year working period with exposure to RCS (226).

This advisory report contains an evaluation of scientific literature and a recommendation for RCS.

1.2 Committees and procedures

This evaluation of RCS is a collaboration of DECOS and NEG. DECOS and NEG have an agreement to collaborate in the evaluation and recommendation of OELs if a chemical substance is on the work programme of both committees. The committees both have permanent roles in giving scientific advice to help protect workers against the potentially harmful effects of chemical substances that they may encounter in the course of their working life. In this connection, the committees assess the toxic properties and health effects of these substances and make recommendations for health-based OELs. The joint advisory report can be used as basis by the regulatory authorities in the Netherlands and in the Nordic countries when setting legally binding OELs. Additional information on the tasks of the committees can be found at www.gezondheidsraad.nl and at

www.nordicexpertgroup.org. The members of DECOS and NEG, and the consulted experts, are listed in Annex VIII of this advisory report.

The draft evaluation on RCS was prepared and first reviewed by DECOS, and thereafter by NEG. The version for public review, as well as the final version, was reviewed by both committees. In December 2023, the president of the Dutch Health Council released a draft of this advisory report for public review. The comments received have been considered by the committees of both DECOS and NEG in deciding on the final recommendation and contents of this advisory report. The comments and the replies can be found on the website of the Dutch Health Council.

The first part of this advisory report provides an overview of the toxicity of RCS. The overview is followed by the committees' evaluation of the predominantly epidemiological data and derivation of exposure levels corresponding to predefined target (low) and prohibition (high) risk levels.

1.3 Data

For the evaluation of the toxicity of RCS, publicly available scientific data were used. Several comprehensive and up-to-date epidemiological studies and evaluations were available on the occurrence and adverse health effects of RCS. Evaluating all published scientific data was beyond the scope of this advisory report. Consequently, the committees focused on the most relevant studies. For the current evaluation, the committees predominantly consulted international evaluations, such as:

- National Toxicology Program (NTP). *Silica, crystalline (respirable size)*. Report on Carcinogens (RoC) 15th edition. US Department of Health and Human Services, 2021 (194).
- National Research Centre for the Working Environment (NFA). *Respirable quartz and other crystalline silica polymorphs: scientific basis for setting a health based occupational exposure limit*. Copenhagen, Denmark, 2021 (226).
- Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological profile for silica*. US Department of Health and Human Services, Centers for Disease Control and Prevention, 2019 (13).
- French Agency for Food, Environmental and Occupational Health & Safety (ANSES). *Updating knowledge on the hazards, exposure and risks associated with crystalline silica*. Maisons-Alfort, France, 2019 (10).
- Occupational Safety and Health Administration (OSHA). *Occupational exposure to respirable crystalline silica*. US Department of Labor, Washington, 2016 (196).
- International Agency for Research on Cancer (IARC). *Silica dust, crystalline, in the form of quartz or cristobalite*. IARC monograph volume 100C. Lyon, France, 2012 (124).
- Scientific Committee on Occupational Exposure Limits (SCOEL). *Recommendation from the SCOEL for silica, crystalline (respirable dust)*. SCOEL/SUM/94. European Union, Luxembourg, 2003 (232).

- National Institute for Occupational Safety and Health (NIOSH). *Health effects of occupational exposure to respirable crystalline silica*. US Department of Health and Human Services, Centers for Disease Control and Prevention, Cincinnati, Ohio, 2002 (188).
- World Health Organization (WHO)/International Programme on Chemical Safety (IPCS), *Crystalline silica, quartz.* Concise international chemical assessment document 24. Geneva, Switzerland, 2000 (273).
- The Health Council of the Netherlands. *Quarts: Evaluation of the carcinogenicity and genotoxicity*. The Hague, the Netherlands, 1998 (103).
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). *Crystalline silica*. Stockholm, Sweden, 1993 (110).
- Dutch Expert Committee on Occupational Safety (DECOS). *Health-based recommended occupational exposure limit for crystalline forms of silicon dioxide (free silica).* Ministry of Social Affairs and Employment, Labour Inspectorate, The Hague, The Netherlands, 1992 (68).

This is not a complete list of published international evaluations, but the listed evaluation reports served as a basis for the current evaluation.

In addition, a literature search of scientific papers was performed using the online databases PubMed and SCOPUS, with variations of the following key words: crystalline silica, quartz, cristobalite, tridymite, pulmonary toxicity, lung cancer, silicosis, cardiovascular effects, nephrotoxicity, occupational exposure, exposure-response relationship, adverse health effects and CAS registry number. For more details on keywords and literature search see Annex I.

The last update of the literature search was performed in June 2023.

1.4 Quality assessment

The data retrieved were evaluated for relevance, reliability and validity. For more information on the evaluation of animal and human data, the committees refer to the "Guidance for recommending classifications and health-based occupational exposure limits" (2021) published by the Health Council of the Netherlands (105). In this guidance the advisory process and the general principles used in the recommendation of health-based OELs are outlined. In Chapter 9 of the current advisory report the committees describe the key literature and underlying judgement of the advisory process for the calculated cancer risk estimates for RCS. For more information on the calculation of cancer risk estimates, the committees refer to the "Guideline for the calculation of occupational cancer risk values for carcinogenic compounds" (2012) also published by the Health Council of the Netherlands (104).

2. Identity, properties and monitoring

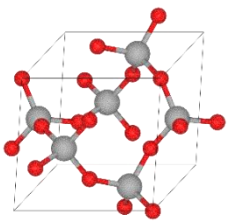
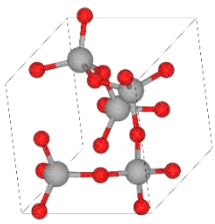
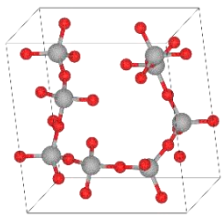
2.1 Identity

Silica, or silicon dioxide (SiO_2) occurs naturally in crystalline and amorphous (non-crystalline) forms. Silica is naturally released into the environment through the weathering of rocks and volcanic activity (13, 117, 123, 188, 273).

The silicon-oxygen tetrahedron is the basic unit of all crystalline and amorphous silica forms. In each silicon-oxygen tetrahedron, each silicon atom is surrounded by four oxygen atoms; each oxygen atom is shared by two tetrahedra (Table 1). The word "crystalline" implies that the silicon and oxygen atoms are oriented and related to each other in a fixed pattern. Differences in the orientation and position of the tetrahedra create the differences in symmetry and cell parameters that give rise to the various forms, or polymorphs (13, 117, 123). There are seven polymorphs of crystalline silica with different surface chemistry characteristics. For a single polymorph, surface characteristics may vary due to processing and particle ageing, even for polymorphs within the same industry. The most common polymorphs of crystalline silica are quartz, cristobalite, and tridymite (10, 13, 117, 123, 188, 194, 273). Table 1 shows the nomenclature and the chemical identities of these three forms.

Silica is abundantly found in the environment, with over 95% of the earth's crust made of minerals containing silica. At least a trace amount of crystalline silica, in

Table 1. The nomenclature and chemical identities of common forms of crystalline silica (13, 123).

	Quartz	Cristobalite	Tridymite
CAS No.	14808-60-7	14464-46-1	15468-32-3
EC List No.	238-878-4	238-45-4	239-487-1
Synonyms (including IUPAC name)	Crystalline silica; α-quartz; quartz; agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; Tripoli	Crystalline silica; cristobalite; α-cristobalite; β-cristobalite	Crystalline silica; Silica, crystalline-tridymite; α-tridymite; β1-tridymite; β2-tridymite
Basic chemical formula	SiO_2	SiO_2	SiO_2
Basic molecular weight (g/mol)	60.09	60.09	60.09
Basic molecular formula	O=Si=O	O=Si=O	O=Si=O
Crystal system	Trigonal	Tetragonal	Orthorhombic
			

the form of quartz, is present in all soils. Consequently, workers are potentially exposed to quartz dust in many occupations and industries (Chapter 4). Cristobalite and tridymite are predominantly found in volcanic rocks (10, 13, 188, 232, 273).

All three forms of crystalline silica, i.e., quartz, cristobalite and tridymite, are interrelated and may change their form under different temperature and pressure conditions (Table 2). As a result, cristobalite and tridymite can be produced during industrial processes when quartz or amorphous silica is heated, such as foundry processes, calcining of diatomaceous earth, brick and ceramics manufacturing, and silicon carbide production (13, 123, 124, 188, 194, 232, 273).

In this advisory report only RCS in the form of quartz, cristobalite and tridymite are evaluated. Other polymorphs of RCS are not included in the current evaluation, because of their rare existence and lack of data as a result.

2.2 Physical and chemical properties

Crystalline silica is insoluble in water at 20°C and chemically unreactive in the environment. Quartz is only slightly soluble in body fluids, where it forms silicic acid and is excreted by the urinary system. The amount of crystalline silica dissolved depends on various material-related factors, including particle size, shape, and structure; and environmental factors such as temperature, viscosity, pH, the proportion of dust to liquid, and the presence of trace minerals (13, 123, 124, 188, 194).

Table 2 shows the physical and chemical properties of the three selected crystalline silica forms. No data are available on other chemical and physical properties, such as partition coefficients, vapour pressure, and conversion factors.

Table 2. Physical and chemical properties of quartz, cristobalite and tridymite (13, 123).

	Quartz	Cristobalite	Tridymite
Colour and physical state	Colourless, white, black, purple or green solid	Colourless, white, or yellowish solid	Colourless or white solid
Melting point	573 °C (α-quartz transforms into β-quartz); 870 °C (β-quartz transforms into tridymite)	1 713 °C (α-cristobalite transforms into β-cristobalite)	1 470 °C (tridymite transforms into cristobalite)
Boiling point	2 230 °C	2 230 °C	2 230 °C
Density (g/m^3) at 20 °C	2.648 (α-quartz)	2.318 (α-cristobalite)	2.269 (α-tridymite)
Solubility in water at 20 °C	Insoluble	Insoluble	Insoluble
Solubility in other solvents	Dissolves in hydrofluoric acid; insoluble in most other acids and organic solvents	Dissolves in hydrofluoric acid	Dissolves in hydrofluoric acid

2.3 Measurement methods

Crystalline silica-related health effects are all the result of inhalation of respirable particles of crystalline silica. The proportion of total particulate matter which is inhaled into a human body depends on the properties of the particles, on the speed and direction of air movement near the body, on breathing rate, and whether breathing is through nose or mouth.

For the health effects caused by inhalation of crystalline silica, the respirable fraction is particularly relevant. The respirable fraction is the mass fraction of inhaled particles (inhalable fraction is the total of airborne particles which is inhaled through the nose and mouth) penetrating to the unciliated airways (the alveolar region of the lungs). The respirable fraction consists of particles with a D_{50} (aerodynamic diameter) of 4 μm or smaller, which can reach the alveolar region of the lungs. Larger particles are less likely to reach the alveolar region but will be deposited higher up in the airways (e.g., extrathoracic tracheobronchial region) (13, 42, 123, 273).

A combination of a sampling device and analytical method is used to determine the amount of RCS in the air of the workplace.

2.3.1 Workplace sampling and analytical methods

Historically, several methods have been used to measure occupational exposure to airborne crystalline silica (quartz, cristobalite or tridymite). Airborne samples are collected using a sampling device. Sampling devices can be classified according to their sampling rates: high flow rate or low flow rate. Furthermore, sampling devices can be cyclones with a filter or multi-fraction samplers with a foam matrix as medium for size-selective dust collection. The subsequent preparation of the collected sample for RCS determination differs depending on the type of analytical technique used. Three analytical techniques can be used for the quantitative determination of RCS: X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectrometry, or colorimetric spectrophotometry (VIS). XRD and FT-IR spectrometry are the most used techniques for crystalline silica analyses. XRD can directly identify different RCS materials (such as quartz, cristobalite or tridymite) present in the sample, unlike FT-IR spectrometry (10, 13, 188, 287).

See Tables 3, 4a, 4b and 4c for an overview of the commonly used sampling and analytical methods.

2.3.2 Biological monitoring of exposure

Currently, there are no standardised biological exposure monitoring methods for RCS, although there are some initial developments in practical monitoring methods to assess exposure to RCS in exhaled breath condensate (150, 175).

Table 3. Sampling and analysis of airborne (respirable) dust particles (188).

Source	Method	Specifications	Ref.
ISO	ISO 7708:1995	Air quality: Particle size fraction definitions for health-related sampling.	(128)
CEN	EN-481:1993	Workplace atmospheres - Size fraction definitions for measurement of airborne particles.	(42-45)
	EN-482:2021	Workplace exposure – Procedures for the determination of the concentration of chemical agents.	
	EN-13205-1:2014	Workplace exposure – Assessment of sampler performance for measurement of airborne particle concentrations – Part 1: General requirements.	
	EN-13205-2:2014	Workplace exposure – Assessment of sampler performance for measurement of airborne particle concentrations – Part 2: Laboratory performance test based on determination of sampling efficiency.	
NIOSH	Method 7500, 7601, 7602 and 7603	Cyclone + filter sampling of crystalline silica, and analysis by XRD, VIS and FT-IR spectrometry, respectively.	(189-193)

CEN: European Committee for Standardization, FT-IR: Fourier transform infrared, ISO: International Organization for Standardization, NIOSH: National Institute for Occupational Safety and Health, VIS: colorimetric spectrophotometry, XRD: X-ray diffraction.

Table 4a. Analytical methodologies for determination of RCS concentrations in dust samples: XRD method (188).

Method	Measurement range	Lower limit of detection	Polymorphs	Ref.
NIOSH Method 7500	0.02–2 mg	0.005 mg	Quartz, cristobalite, tridymite	(189)
OSHA Method ID-142	0.050 mg	0.012 mg 0.025 mg	Quartz Cristobalite	(197)
MSHA Method P-2	0.020–0.500 mg	0.005 mg	Quartz, cristobalite	(176)
HSE MDHS 101/2 [a]	0.020–1 mg	Varies depending on equipment specifications	Quartz, cristobalite	(118)
ISO 24095:2021 ISO 16258-1:2015 ISO 16258-2:2015	n.s.	n.s.	Quartz, cristobalite, tridymite	(129-131)

[a] Direct-on-filter method.

HSE: Health and Safety Executive, ISO: International Organization for Standardization, MDHS: Methods for the Determination of Hazardous Substances, MSHA: Mine Safety and Health Administration, NIOSH: National Institute for Occupational Safety and Health, n.s.: not specified, OSHA: Occupational Safety and Health Administration, XRD: X-ray diffraction.

Table 4b. Analytical methodologies for determination of RCS concentrations in dust samples: FT-IR spectrometry method (188).

Method	Measurement range	Lower limit of detection	Remarks	Ref.
NIOSH Method 7602	0.010–0.160 mg	0.005 mg	Quartz, cristobalite in respirable dust	(191)
NIOSH Method 7603	0.010–0.500 mg	0.001 mg	Quartz in respirable coal mine dust	(192)
MSHA Method P-7	0.020–0.700 mg	0.004 mg	Quartz in coal mine dust	(177)
HSE MDHS 101/2 [a]	0.020–1 mg	0.003–0.010 mg	Quartz, cristobalite	(118)
ISO 24095:2021	n.s.	n.s.		(131)

[a] Direct-on-filter method.
FT-IR: Fourier transform infrared, HSE: Health and Safety Executive, ISO: International Organization for Standardization, MDHS: Methods for the Determination of Hazardous Substances, MSHA: Mine Safety and Health Administration, NIOSH: National Institute for Occupational Safety and Health, n.s.: not specified.

Table 4c. Analytical methodologies for determination of RCS concentrations in dust samples: VIS [a] spectrophotometry method using molybdate as reagent (188).

Method	Measurement range	Lower limit of detection	Remarks	Ref.
NIOSH Method 7601 [a]	0.100–2.5 mg	-	Analyte silico-molybdate	(190)
	0.020–0.150 mg	0.010 mg	Analyte molyb-denum blue	

[a] The method cannot separate the different RCS polymorphs.
NIOSH: National Institute for Occupational Safety and Health, VIS: colorimetric spectrophotometry.

3. Sources and uses

Because of its unique physical and chemical properties, crystalline silica has many uses. Crystalline silica occurs naturally as agate, amethyst, chalcedony, cristobalite, flint, quartz, tridymite, and, in its most common form, crystalline silica-containing sand (123).

Silicates are structures composed of crystalline silica bound to cations such as magnesium, aluminium or iron. Examples of silicates include mica, soapstone, and talc tremolite.

Crystalline silica sand deposits, commonly quartz or derived from quartz, typically have a crystalline silica content of 95%; however, impurities may be present at up to 25%. Crystalline silica sand has been used for many different purposes over many years (123, 194). Sand and gravel are used in road building and

concrete construction. Sand with more than 98% crystalline silica is used in the manufacture of glass and ceramics. Crystalline silica sand is also used as a filler in plastics, rubber, and paint, as an abrasive in soaps and scouring cleansers, to form moulds for metal castings in foundries, and in abrasive blasting operations (13, 117, 123, 124, 196).

Crystalline silica is also used in artificial or engineered stone products which have been used frequently in kitchen and bathroom countertops in the last ten to twenty years. Depending on the specific type of artificial stone product, the crystalline silica content in these products can exceed 90 percent (199). The highest crystalline silica levels in stone products are associated with engineered or artificial countertops (also known as manufactured stone, agglomerated or conglomerated quartz) of quartz-resin stone (> 93% silica content) followed by naturally occurring quartzite (90–95%), sandstone (60%), and granite (10–45%). Engineered or artificial porcelain/ceramic stone products contain far less crystalline silica with 10 to 30 percent. Naturally occurring calcium-based stones (e.g., limestone) and certain types of marble contain little or no silica (199).

Furthermore, quartz is used in jewellery as a gemstone, and in electronics and optical industries. Cristobalite is used in ceramics, as filler, as an abrasive, in the production of waterglass, and in mixtures with quartz in other uses. Tridymite has no occupational use, but can be formed unintentionally in certain processes when quartz is heated (71, 117).

4. Exposure

Crystalline silica is an abundant and commonly found natural material. Human exposure to RCS, primarily quartz dust, occurs mainly in industrial and occupational settings. Non-occupational exposure to RCS results from natural processes and anthropogenic sources; crystalline silica is a common air contaminant. Residents near quarries, sand and gravel operations are potentially exposed to RCS. In addition, areas around recent volcanic eruptions (source of cristobalite and tridymite in the air), deserts and mine dumps can give rise to crystalline silica-containing dust under the influence of local weather conditions (7, 123, 194, 273).

Because of the extensive natural occurrence of crystalline silica and the wide use of materials containing crystalline silica, workers in a large variety of industries and occupations are potentially exposed. Activities in which workers could be exposed include movement of earth (e.g., mining, oil/gas extraction, hydraulic fracturing (fracking), farming, construction, quarrying), disturbance of crystalline silica-containing products (e.g., demolition of concrete or bricks), handling or use of crystalline silica sand or other crystalline silica-containing products (e.g., foundry processes; abrasive blasting; production of glass, ceramics, cement; manufacturing, finishing and installing of natural and engineered or artificial stone products) (83, 123, 124, 127, 188, 194, 199, 273).

Exposure may also occur during the use of a variety of consumer or hobby products, such as cleansers, cosmetics, paints and art clays (123, 124, 273).

The CAREX (CARcinogen EXposure) database (comprising data from 1990 to 1993) was designed to provide exposure data and estimates of the number of workers exposed to carcinogens per country for the member states of the European Union (EU). Based on the initial data approximately 32 million workers (23% of the European work population) were potentially exposed to selected carcinogens in the EU. Of these 32 million workers, 3.2 million workers were potentially exposed to RCS (135). The Institute of Occupational Medicine (IOM) has presented an update, using data from CAREX and the Health and Safety Executive (HSE), estimating that 5.3 million workers were potentially exposed to RCS in the EU in 2006 (28, 127). Most of these workers were exposed in construction, mining and quarrying, and the manufacturing of mineral, metal or chemical products (127).

An overview of major industries with potential exposure to RCS is given in Table 5.

Table 5. Overview of major industries and operations with potential exposures to RCS (83, 188, 199, 227).

Industry or activity	Operations and tasks	Source materials
Agriculture	Ploughing, harvesting, using machinery, processing agricultural products	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and nonmetal, coal), rock drilling, dredging	Ores, associated rock
Oil and gas extraction, hydraulic fracturing (fracking)	Sand transport and pneumatic handling	Quartz sand
Quarrying and related milling operations	Crushing stone, sand and gravel processing, stone monument cutting and abrasive blasting, slate work (e.g., pencil manufacturing), diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures and buildings, highway and tunnel construction, excavation and earth moving and digging, masonry, concrete work, demolition, dry sweeping and brushing, pressurised air blowing, jack hammering, laying railroad tracks, removing rust or paint, sanding and scaling, replacement of asphalt roofing, and hauling, pouring, mixing, or dumping silica-containing materials	Sand, concrete, rock, soil, mortar, plaster, shingles
Glass; including fibre glass	Raw material processing, refractory installation, and repair	Sand, crushed quartz, refractory materials

Table 5. Overview of major industries and operations with potential exposures to RCS (83, 188, 199, 227).

Industry or activity	Operations and tasks	Source materials
Cement	Raw material processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production, abrasive products fabrication	Sand, tripoli, sandstone
Ceramics; including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, moulding, glaze or enamel spraying, finishing, sculpting, firing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material
Silicon and ferro-silicon foundries (ferrous and nonferrous)	Raw materials handling, casting, moulding, and shaking out, abrasive blasting, fettling, furnace installation and repair	Sand, refractory material
Metal products; including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Engineered or artificial stone (also known as manufactured stone, agglomerated or conglomerated quartz) products, this includes quartz-resin stones and ceramic/porcelain stones	Saw, grind, polish, and drill slabs of manufactured (man-made, engineered, or cultured) stone as part of manufacturing, finishing, and installing countertops. Manufactured stone production, production of engineered or cultured slabs, involves mixing crystalline silica, resins, and pigments.	Quartz-resin stones: composites of quartz, coloured glass, shells, metals, or mirrors, bound by a polymer resin. Ceramic/porcelain stones: kaolin clays, feldspar, siliceous sands, and small percentages of other minerals.
Paint	Raw materials handling, site preparation	Fillers (diatomaceous earth, silica flour, tripoli)
Soaps and cosmetics	Manufacturing or occupational use of abrasive soaps and scouring powders	Silica flour
Jewellery	Cutting, grinding, polishing, buffing, etching, engraving, casting, chipping, sharpening, sculpting	Semiprecious gems or stones, abrasives, glass
Arts, crafts, sculpture	Pottery firing, ceramics, clay mixing, kiln repairs, abrasive blasting, sand blasting, engraving, cutting, grinding, polishing, buffing, etching, engraving, casting, chipping, sharpening, sculpting	Clays, glazes, bricks, stones, rocks, minerals, sand, silica flour
Dental material	Sand blasting, polishing	Sand, abrasives

4.1 Occupational exposures, variability, and trends

Occupational exposure concentrations of RCS are highly variable. Within the European industrial mineral sector, respirable quartz exposure concentrations varied up to three to four orders of magnitude. These exposure levels may vary from day to day or from worker to worker. Day-to-day differences can be influenced by environmental and work process related characteristics. However, long-term trends in day-to-day or worker-to-worker differences have hardly been studied, mainly because repeated workplace measurements collected over long time periods in the same workplaces and with the same workers are hardly available (285, 286).

Long-term trends in average exposure concentrations have been investigated more intensively and generally reflect a decline in RCS exposure levels over the past 60 years (see also Tables 6 and 7) (285). For instance, in the US an annual decline of 11% was observed in the industrial sand industry during the period 1946–1996. Other studies in sand industries in the US and the UK reported similar results. In the UK, exposure levels of RCS declined from 0.08 mg/m^3 (TWA) in the early 1980s to 0.04 mg/m^3 (TWA) in the late 1990s (30, 219, 220, 228). The reductions in the US and UK are probably the result of the introduction of guidelines, implementation of dust control programmes and in the US also the establishment of OSHA (220). In the mining industry, overall downward trends in exposure levels to RCS were reported as well (73, 172, 209). In the Australian mining industry a downward trend of 8% was observed for RCS levels between 1986 and 2014, flattening over the last decade (209). However, the mean exposure levels in the American mining industry showed fluctuations (73, 172). These fluctuations could be caused by changes in sampling and/or analytical methods, changes in work processes, production rates and/or type of mines across time (172).

In the European mineral industry (extraction and processing of minerals) an annual downward trend of almost 4% for respirable quartz levels was observed (285). This downward trend came to a halt and even reversed for respirable quartz levels during the years between 2008 and 2012. This was probably caused by the economic recession (e.g., downsizing of the workforce resulting in more diverse and dusty tasks, and less time for good housekeeping) that most European countries were facing around that time. In the SYNERGY project (pooled analysis of case-control studies in Europe and Canada) an annual decline of 6% in respirable quartz levels across a wide-range of industries was reported for the period between 1976 and 2009 (211).

Despite the overall decline, in some industries RCS exposure levels may still exceed recommended OELs. These higher exposure levels can be found in foundries, hydraulic fracturing (fracking), stone and brick sector, construction, mining industry, and some modern industries like artificial stone manufacturing (Section 4.2) (8, 16, 20, 28, 62, 73, 74, 83, 99, 107, 133, 172, 227, 285). It is difficult, if not impossible, to eliminate or substitute crystalline silica in some (traditional) industries, like mining, because quartz is so widely present in rocks and soil (172).

Table 6 shows an overview of RCS exposure levels in various industrial cohorts with quantitative exposure-response data. It provides an impression of average RCS exposure levels in certain occupations or industries. Table Ia from the Annex I served as a basis for this table. Only studies with measurement data collected in the past 25 years are presented in Table 6. Most of the industrial cohort studies presented in Table Ia used older measurement data in their analyses. Table 6 also demonstrates the overall decline in exposure levels, across time in various industries.

In recent years an overall decline in RCS levels was observed. Some results of more recent RCS measurements are shown in Table 7. Despite the overall decline in RCS levels, Misra *et al.* (2023) reported an increase in mean exposure levels in American metal and non-metal mines for the years 2018 (geometric mean 0.0459 mg/m^3) and 2019 (geometric mean 0.0529 mg/m^3) compared to the overall mean exposure level (geometric mean 0.0289 mg/m^3) for the period 2000–2019. The authors explained this increase in 2018 and 2019 by a possible change in sampling strategy, with more focus on sampling maximum risk workers or occupations in annual sampling campaigns with fewer total measurements (172).

4.2 Emerging risk of artificial materials

In the early 2000s, engineered or artificial stone material (also known as manufactured stone, agglomerated or conglomerated quartz) containing crystalline silica was introduced. In general, artificial stone is formed from finely crushed rocks (predominantly quartz) that are mostly bound by a polymer resin. These artificial materials, which include quartz-resin stones and ceramic/porcelain stones, have found extensive use in furnishing and building coatings such as kitchen and bathroom countertops, floor and wall coatings, thresholds and windowsills or furniture decoration. Particularly quartz-resin stones may contain high percentages of crystalline silica (17, 227). Exposure levels reported by studies vary considerably, as well as the crystalline silica content of the various artificial stone products (101, 218, 227).

A study among four artificial stone manufacturing facilities in Northern Italy reported exposure levels ranging from < 0.003 to 0.098 mg/m^3 (227). In contrast, another study in kitchen countertop manufacturing reported exposure levels ranging from 0.260 to 0.744 mg/m^3 (99). Differences in exposure levels in the breathing zone may be due to differences in tasks, dust reducing methods, and crystalline silica composition. In addition, the occurrence of other chemical substances (e.g., resin) in engineered stone products may also contribute to the potential health effects resulting from exposures to RCS in engineered stone products (62, 99, 101, 133, 213, 218, 227, 254).

Table 6. Overview of mean RCS concentrations in air samples in various industries, information derived from studies presented in Table Ia in Annex I with publications in the last 20 years and measurement data from the last 25 years.

Location, type of industry or operation	Measurement period	Mean concentrations RCS reported (presented as range of lowest and highest reported mean concentrations)	Ref.
China, metal mines	1960–2003	0.08–0.52 mg/m^3 AM (> 4 200 000 stationary samples in total for pottery and metal mines)	(54)
China, pottery industry	1960–2003 *1960–1980* *From 1990*	 0.15–0.30 mg/m^3 AM 0.12–0.15 mg/m^3 AM (> 4 200 000 stationary samples in total for pottery and metal mines)	(54)
Germany, porcelain industry	1959–2006	< 0.01–0.69 mg/m^3 GM (3 075 samples; only 189 personal samples, remaining are stationary)	(21)
Norway, silicon carbide industry	1967–2005 (2002–2003 comparative study)	0.0001–0.015 mg/m^3 GM (904 samples in total, 224 historical samples and 680 comparative study samples)	(34, 88)
South Africa, gold mining	2000	0–0.71 mg/m^3 AM (497 personal samples)	(60)
Sweden, iron mining	1910–1999 *From 1965*	 0.02–1.00 mg/m^3 GM (3 122 personal samples)	(108)
Sweden, iron foundry	2005–2006	0.016–0.060 mg/m^3 GM (435 personal samples)	(8)
The Netherlands, construction industry	Not indicated	0.002–0.42 mg/m^3 GM (67 personal samples)	(255, 256)
UK, sand industry	1978–2000	0.09 mg/m^3 GM (> 3 000 samples; 2 429 personal samples, 583 stationary samples)	(30)
USA North America, sand industry	*1947–1955* *1974–1998*	0.083–96.6 mg/m^3 (500 historical samples across industry) 0.020–0.107 mg/m^3 GM (14 249 samples, mostly personal samples)	(219)
USA, sand industry	1970–2013 *Before 1970* *1970–1980* *1980–1990* *1990–2000* *From 2000*	 0.678 mg/m^3 GM 0.148 mg/m^3 GM 0.103 mg/m^3 GM 0.036 mg/m^3 GM 0.019 mg/m^3 GM (> 49 000 personal samples in total)	(220)
USA Vermont, granite industry	1924–2004 *Before 1940* *From 1950*	 0.01–1.07 mg/m^3 AM (1 016 samples) 0.01–0.10 mg/m^3 AM (4 188 samples, mostly personal samples)	(265)

AM: arithmetic mean, GM: geometric mean.

Table 7. Overview of RCS concentrations in occupations in various industries in recent years.

Location/type of industry or operation	Measurement period	Mean concentrations (presented as range over time, between different jobs, or between different facilities) of RCS reported	Ref.
Europe, European Industrial Minerals Association (IMA)	2002–2016 *2002* *2016*	 0.012 mg/m^3 GM 0.007 mg/m^3 GM (22 593 personal samples in total)	(285)
Denmark, metal, construction, concrete workers, and others	2018	0.003–0.093 mg/m^3 GM (189 personal samples)	(28)
North-east Italy, fabrication of quartz-resin countertops	2016–2019 Until 2016 (company surveys)	4.3 mg/m^3-years (45 samples) 0.260–0.744 mg/m^3	(99)
Northern Italy, engineered stone processing industry	2018–2019	0.007–0.046 mg/m^3 (51 personal samples)	(227)
USA, metal and non-metal mining	2000–2019 *2013* *2019*	 0.0253 mg/m^3 GM 0.0529 mg/m^3 GM (55 265 personal samples in total)	(172)
USA, coal mining	1982–2017	0.01–0.09 mg/m^3 GM (54 040 samples) 44.1% of the samples exceeded the exposure limit (PEL 0.05 mg/m^3) in 1982. 3.0% of the samples exceeded the exposure limit in 2017.	(73)

GM: geometric mean, PEL: permissible exposure limit.

5. Kinetics and biomonitoring

How much particulate matter (particles) is inhaled into the human body depends on properties of the particles, the source strengths of emissions, the speed and direction of air movement near the body, breathing rate, and whether breathing is through nose or mouth. The site of deposition, or probability of exhalation, also depends on properties of the particle, breathing pattern, and other factors. It is generally considered that respirable particles (the mass fraction of inhaled particles that can reach the unciliated airways), like crystalline silica, consist of particles with a D_{50} (aerodynamic diameter) of 4 μm or smaller, which can reach the alveolar region of the lungs. Larger particles are less likely to reach the alveolar region and are more prone to be deposited higher up in the airways and subsequently cleared via the mucociliary escalator (see below) (13, 42, 123, 273).

5.1 Kinetics

5.1.1 Absorption

5.1.1.1 Absorption through inhalation

Uptake of RCS is primarily by inhalation. However, no quantitative estimates of absorption of RCS particles from the respiratory tract are available (13).

Inhaled RCS particles that deposit in the respiratory tract are subject to three general distribution pathways: 1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; 2) absorption and/or transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or 3) absorption to blood and/or lymph and subsequent transfer to other tissues (e.g., peripheral lymph tissues, kidney). These three processes are commonly referred to as particle clearance from the lungs. The relative contributions of each of these pathways and distribution rates vary with the physical characteristics (e.g., particle size) and biological reactivity (e.g., macrophage recruitment, activation, cytotoxicity). Larger particles are more prone to deposit higher up in the airways (e.g., extrathoracic, tracheobronchial regions) and are cleared primarily by mucociliary transport. Smaller particles, with a D_{50} of 4 μm or smaller, are more likely to be cleared primarily by lymph drainage, macrophage phagocytosis and migration, and upward mucociliary transport (13). Clearance of RCS particles from the pulmonary region consists of a faster and a slower phase. The faster phase consists of relatively rapid mechanical clearance (e.g., mucociliary transport), while the slower phase consists of phagocytosis and macrophage migration. Rates for slow-phase clearance can vary with the type of silica particles and the number of particles inhaled. Due to the slower clearance, RCS particles may accumulate in the lungs and cause injury. Injury to the lungs is more likely to occur when workers are repeatedly exposed to airborne RCS particles. Particles can be detected in the lungs even after cessation of exposure (10, 13, 123, 124, 273). Inhaled crystalline silica particles can enter the blood circulation and accumulate in the kidneys (13).

Because of the very low solubility of crystalline silica in general, the role of dissolution in the clearance is negligible. Quartz is only slightly soluble in body fluids, where it forms silicic acid (13).

5.1.1.2 Absorption through other routes

Absorption and systemic distribution via the gastrointestinal tract and skin is considered to be negligible (13).

5.1.2 Biotransformation

Crystalline silica is not metabolised by the human body (13).

5.1.3 Excretion

Inhaled crystalline silica particles can be systemically distributed and excreted by the kidneys in urine. Ingested crystalline silica particles are excreted through faeces (no absorption and systemic distribution from the gastrointestinal tract) (13).

5.2 Biomonitoring

Several studies used non-specific biomarkers in blood and urine to investigate the association between exposure to RCS and oxidative stress and inflammation. These biomarkers include lactate dehydrogenase (LDH), alkaline phosphatase, tumour necrosis factor (TNF), interleukins, immunoglobulins, Clara cell proteins, and proinflammatory cytokines. However, many other chemicals, inflammatory diseases, and oxidative stress in general, may affect these markers as well; so these markers are not sufficiently specific for RCS-induced effects. As a result, no specific biomarkers have been identified for RCS-induced health effects or for early detection of RCS-induced toxicity (10, 13, 124, 188).

6. Health effects

Exposure to RCS is associated with a diversity of health effects, predominantly silicosis and lung cancer. A summary of health effects associated with RCS exposure is given below.

In general, due to differences in study designs, outcome metrics, follow-up periods, or statistical approaches to estimate risks, results from various epidemiological studies may not be directly comparable.

Another complication is that various industrial processes generate different types of RCS particles (e.g., particle size, surface reactivity, fibrogenic potential), resulting in differences in toxic potential in addition to different individual susceptibility of workers to the toxic effects.

6.1 Respiratory diseases

6.1.1 Silicosis

Silicosis is a progressive, irreversible, fibrotic lung disease resulting from inhalation and pulmonary deposition of RCS particles.

Silicosis is one of the oldest known occupational diseases. The causal relation between exposure to RCS and silicosis is well established. Silicosis specifically occurs among workers occupationally exposed to RCS. Also, the pathological changes as observed in silicosis are unique for workers exposed to RCS.

Silicosis is not a single disease entity; several types can be distinguished. Chronic or simple silicosis (also called nodular silicosis) is the most common form. Other types of silicosis include acute silicosis (also known as silicoproteinosis) and accelerated silicosis (a rapidly progressing form of simple silicosis) which are severe forms observed in cases with (very) high exposures. Silicosis can result in death due to respiratory failure (10, 13, 188, 252).

Generally, the type and severity of silicosis can be determined by the intensity (also referred to as concentration), frequency, and duration of exposure (10, 13, 188).

Time from first exposure to onset of disease varies with intensity of exposure; a few weeks for acute silicosis and up to 20 or more years for simple silicosis. Once silicosis has been diagnosed, the progression of the disease continues even in the absence of further exposure. However, subjects who continue to be exposed after diagnosis of the disease are more likely to see their disease progress, compared to those without any further exposure (10, 13, 188, 196).

Several studies provide exposure-response data for silicosis morbidity based on estimated cumulative RCS exposure for various industries, including hard-rock mining (144, 179); underground mining of tin (56) and underground mining of gold (60, 113, 244); granite quarrying and processing (187); diatomaceous earth industry (predominantly exposure to cristobalite) (120, 202), and porcelain manufacturing (181). Overall, data from these studies consistently demonstrate an exposure-response relationship between estimated cumulative exposure to RCS and silicosis morbidity over a wide range of exposures. However, most of these studies used chest radiography to detect and diagnose silicosis. A study by Hnizdo *et al.* (1993) (113), comparing radiological and pathological diagnosis of silicosis among gold miners, found that a large proportion of the silicosis deaths, confirmed by pathological autopsy, were not diagnosed radiologically with silicosis within the three years prior to their death and autopsy (113, 226). In conclusion, chest radiography may not be the most sensitive tool for detection and diagnosis of silicosis, which may have resulted in underreporting of silicosis (196, 226). Another concern may be the differences in silicosis definitions used by several of these studies, which may have affected the risk estimates for silicosis (226).

Progression of silicosis can result in death due to respiratory failure. Several studies investigated silicosis mortality; in general studies report higher silicosis mortality rates among workers with higher estimated cumulative exposures (13). Statistically significant exposure-response trends were reported between estimated exposure and mortality [rate ratios or odds ratios (OR)] for workers in diatomaceous earth (47, 202), metal (54) and ore mining (108), granite (263), pottery (54), and sand industries (121, 166).

't Mannetje *et al.* (2002) (252) conducted a pooled analysis among six cohort studies in diatomaceous earth (47), gold mining (67, 244), granite (63, 142), and sand industries (246). The pooled dataset included 170 deaths with silicosis (n = 150) or pneumoconiosis (n = 20) as underlying cause of death, and a total population of 18 364 workers. The adjusted estimated silicosis mortality rate increased almost monotonically from 4.7 per 100 000 person years for the lowest exposure category (0–0.99 mg/m^3-years) to 299.1 per 100 000 person years for the highest exposure category (> 28.1 mg/m^3-years) [adjusted for age (4 categories), calendar period (8 categories), and study (6 categories)]. The authors also reported adjusted mortality rate ratios of 3.39 (95% confidence interval (CI) 1.42–8.08) for exposure category 0.99–1.97 mg/m^3-years; the lowest exposure category (0–0.99 mg/m^3-years) was the reference, and mortality rate ratio of 63.63 (95% CI 19.87–203.8) for the highest exposure category of > 28.1 mg/m^3-years. The estimated lifetime risk of death due to silicosis, up to age 65 after 45 years of RCS exposure

at 0.1 mg/m^3 (TWA), was 13 per 1 000 workers; and for RCS exposure of 0.05 mg/m^3 (TWA) the estimated lifetime risk of death was 6 per 1 000 workers. Four other cohorts, for which quantitative exposure estimates of crystalline silica were available to the researchers, could not be included in this pooled analyses because of differences in definitions for silicosis (differential definition for silicosis in coding of causes of death, or the International Classification of Disease (ICD) system to code death certificates was not used) (252). A more extensive summary of the publication by 't Mannetje *et al.* (2002) (252) can be found in Annex IV of this report.

6.1.1.1 Artificial stone-associated silicosis

In the past decade, an increasing number of silicosis cases has been reported among workers involved in artificial or engineered stone manufacturing where exposures can be high (see also Section 4.2). Cases have been reported in Spain, Israel, Italy, Australia, the US, Belgium, and China (18, 99, 115, 201, 227, 276). Based on results from, predominantly, case reports and cross-sectional studies, artificial stone-associated silicosis can be characterised by a relatively high incidence among young workers, short latency period, rapid radiologic progression, accelerated decline in lung function, and high mortality, or requirement for lung transplantation (17, 116, 153, 276). These characteristics are mostly in accordance with an accelerated type of silicosis. Artificial stone-associated silicosis is a rapidly progressive form of simple (chronic) silicosis. It develops 5–10 years after the start of exposure. Symptoms are similar to those of simple silicosis. Further research is needed to confirm the relation and determine an exposure-response relation (13).

6.1.1.2 Silicotuberculosis

Silica exposure, silicosis and tuberculosis co-occur in many working populations in multiple countries. Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis;* it is the most common form of infection in crystalline silica-exposed workers causing a condition well known as silicotuberculosis. The risk of a tuberculosis infection increases with the severity of silicosis. However, some studies have reported an increased risk of tuberculosis in RCS exposed workers without radiologically confirmed silicosis (10, 13, 125, 188). These results were confirmed in a qualitative meta-analysis by Ehrlich *et al.* (2021) (79). The authors reported a pooled relative risk of 4.01 (95% CI 2.88–5.58) among eight studies on subjects with both silicosis and tuberculosis. These eight studies consisted of two case-control and six cohort studies. Three of these studies used years of employment as proxy for exposure measure and only one study used cumulative dust exposure as exposure estimate. At least four studies included in the meta-analysis were among gold miners in South Africa (79).

Diagnosis of tuberculosis in patients with silicosis is difficult, due to non-specific clinical manifestations that may be difficult to distinguish from silicotic lesions on a chest X-ray (10, 79).

The risk of developing silicotuberculosis is higher if RCS-exposed workers also have a co-infection with human immunodeficiency virus (HIV) (10, 13, 79, 125, 188).

6.1.2 Lung cancer

Lung cancer is the most diagnosed malignant disease worldwide (13). There are several known risk factors for lung cancer, such as smoking, air pollution, previous lung diseases and occupational exposures such as asbestos and RCS (13, 235). Several meta- and pooled analyses reported an increased risk of lung cancer in workers exposed to RCS (13, 39, 90, 147, 235, 245).

A recent pooled analysis of case-control studies conducted by Ge *et al.* (2020) among 16 901 cases and 20 965 controls reported an association with lung cancer at low respirable quartz exposure levels. ORs for lung cancer ranged from 1.15 (95% CI 1.04–1.27) for the lowest (cumulative exposure category > 0–0.39 mg/m^3-years) to 1.45 (95% CI 1.31–1.60) for the highest exposed workers (cumulative exposure category ≥ 2.4 mg/m^3-years) (90). See also Annex IV for a more extensive summary of the study by Ge *et al.* (2020).

The pooled analyses of Ge *et al.* (2020) consist of data from 14 population and hospital-based case-control studies, also known as the SYNERGY project, carried out in 13 European countries (Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, and the UK) and Canada. Working lifetime job histories were available, which showed that the highest respirable quartz exposures occurred among chimney bricklayers, stone cutters or carvers, and hand monument carvers (90). See Table E1 of the supplementary material from the publication by Ge *et al.* (2020) (90) for details about the included case-control studies and Annex V for more details about the exposure data in the SYNERGY project.

A previous pooled analysis of industrial cohort studies conducted by Steenland *et al.* (2001) (245) among 65 980 workers exposed to RCS in diatomaceous earth (47), granite (63, 142), sand (246), pottery (51), and mining industries (e.g., gold, tin, tungsten) (51, 67, 111, 243), also found an increased risk for lung cancer. Silicosis status of each worker was undefined in the analysis and therefore not included. For the pooled cohort, with a median cumulative RCS exposure of 4.27 mg/m^3-years, a standardised mortality ratio (SMR) for lung cancer of 1.2 (95% CI 1.1–1.3) was reported. Increasing exposure was significantly associated with increased risk of death from lung cancer (245). See Annex IV for a more extensive summary on the pooled analysis by Steenland *et al.* (2001).

Elevated risks for lung cancer have been reported even after adjustments for potential confounders such as smoking and asbestos co-exposure (10, 90, 148, 194, 269). Studies that have assessed the interaction between smoking and occupational exposure to RCS regarding the risk of lung cancer report an additive or a multiplicative interaction (10, 90, 148). Ge *et al.* (2020) reported interactions beyond the additive model between smoking and occupational respirable quartz exposure for lung cancer [relative excess risk due to interaction (RERI) 2.34, 95%

CI 1.85–2.83], and a multiplicative joint effect of smoking and respirable quartz exposure was observed on lung cancer risk ($p < 0.01$) (90).

Several studies have explored the relationship between RCS exposure and silicosis, and between RCS exposure and lung cancer. In general, lung cancer has been reported in RCS-exposed workers with silicosis as well as without silicosis, but the association seems slightly stronger for workers with silicosis (10, 13, 81, 204, 214). However, the recently conducted pooled analysis by Ge *et al.* (2020) reported a positive association between respirable quartz exposure (lowest cumulative exposure category > 0–0.39 mg/m^3-years) and lung cancer in the absence of silicosis (OR 1.22, 95% CI 1.07–1.40). Silicosis status was available for 50% of the SYNERGY study population (n = 18 931, with 108 silicosis cases) (90).

6.1.3 Non-malignant respiratory diseases (other than silicosis)

Several studies have demonstrated that occupational exposure to RCS is associated with non-malignant respiratory diseases other than silicosis, primarily chronic obstructive pulmonary disease (COPD) (10, 196).

COPD is a progressive lung disease involving the airways and/or pulmonary parenchyma, resulting in airflow obstruction that is not reversible. In patients with COPD, either chronic bronchitis or emphysema may be present or both conditions may be present together (10, 13, 114, 196). A diagnosis of COPD includes respiratory symptoms and airflow obstruction defined as postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of < 0.70 (13). Brüske *et al.* (2014) conducted a systematic review and meta-analysis evaluating the relation between occupational exposure to respirable quartz and COPD. In general, most studies found a statistically significant negative association of FEV_1 and FEV_1/FVC related to increasing exposure to respirable quartz at the workplace. The six studies (four cross-sectional and two longitudinal studies) that were selected for meta-analysis included workers from a granite quarry, potato sorter, cement factory, tunnel industry (n = 2), and foundry operations (32). Average respirable quartz exposure levels in four of the included studies ranged from 0.034 mg/m^3 (geometric mean) in tunnel workers (259) to 0.16 mg/m^3 (arithmetic mean) in granite quarry workers (162). The fifth study (15), conducted on Norwegian tunnel workers, reported cumulative exposures of 0.01–3.6 mg/m^3-years (geometric means), depending on job category. The sixth study (109) presented data from a foundry, with exposure levels subdivided in four groups based on personnel records and a job-exposure matrix. The groups' average daily exposure to respirable quartz ranged from 0.006 to 0.28 mg/m^3. The average duration of employment ranged between 11 and 18 years. The meta-analysis of cross-sectional studies showed that the mean ratio FEV_1 to FVC was reduced (standardised mean difference -0.41 (95% CI -0.54, -0.28) %) and the FEV_1 of exposed workers was 4.6 (95% CI 7.18, 2.06) % less than predicted compared to the average FEV_1 in the population for any person of similar age, height, sex and ethnicity. In conclusion, occupational exposure to respirable quartz is associated with a decrease in FEV_1 and FEV_1/FVC, revealing airway obstruction consistent

with COPD (13, 32). An exposure-response relationship, however, could not be determined due to a lack of quantitative data in the meta-analysis.

A recent study among Swedish iron foundry workers (2022) reported statistically significant increased morbidity for COPD in all exposure groups (exposure categories range between ≤ 0.14 and > 0.39 mg/m^3-years). The highest standardised incidence rate (SIR) of 2.35 (95% CI 1.56–3.40) was reported for the lowest exposure category (cumulative exposure ≤ 0.14 mg/m^3-years) (152). A study by Ulvestad *et al.* (2020) among outdoor rock drillers reported significantly impaired pulmonary function and signs of airflow obstruction (fibrosis and emphysema) among workers exposed to RCS. The mean RCS exposure was 0.08 mg/m^3 over 21.7 years (260).

A review conducted by Hnizdo and Vallyathan (2003) reported that chronic exposure to lower levels of RCS may lead to the development of emphysema and/or chronic bronchitis that can lead to airflow obstruction, even in the absence of radiological signs of silicosis (114).

Smoking, a well-known risk factor for obstructive lung diseases, may have an additive effect on respiratory impairment (10, 114, 196). The individual studies in the meta-analysis by Brüske *et al.* (2014) had adjusted or stratified for smoking status in their analysis (32).

6.2 Renal diseases

A wide spectrum of renal pathologies has been associated with occupational exposure to RCS, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, glomerulonephritis, and renal damage associated with autoimmune disorders [e.g., anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (see also Section 6.4.1)].

There appear to be two types of RCS-induced renal disease: 1) a direct toxic effect of RCS accumulation in the kidney, and 2) an indirect toxic effect secondary to an autoimmune disease (see Section 7.3.4. for more details on mechanism of toxicity). Renal toxicity typically occurs at higher cumulative exposure levels (13).

Several studies, most retrospective or cross-sectional studies, have examined the relationship between exposure to RCS and risk of renal disease. In general, these studies have found an increased risk of renal disease and/or subclinical signs of renal dysfunction in workers exposed to RCS, and a limited number of studies report increasing risk with increasing cumulative exposure to RCS (13).

Steenland *et al.* (2002) analysed mortality from renal disease (ICD 9th revision codes 580–587) in a pooled cohort analysis of three occupational cohorts among industrial sand workers (247), gold miners (243) and granite workers (63) (with a total of 13 382 workers). Based on SMRs for the entire cohort (quartiles of estimated cumulative RCS exposure from > 0–0.15 to ≥ 1.67 mg/m^3-years), excess mortality (SMR 1.41, 95% CI 1.05–1.85; 51 deaths) due to renal disease was observed, with a monotonic increase over exposure quartiles (linear trend test; p = 0.0007). Based on ORs, a statistically significant increased risk for renal disease

was observed in the highest exposure quartile of ≥ 1.67 mg/m^3-years with an OR of 3.93 (95% CI 1.31–11.76), but not in lower exposure quartiles. Results of this pooled analysis suggest that exposure to RCS is associated with increased risk of death from renal disease. Based on the pooled data, excess lifetime risk at age 75 for death from renal disease after 45 years of exposure at 0.10 mg/m^3 (8-hour TWA) was estimated to be 1.8% (95% CI 0.8–9.7%) above a background risk of 0.3% (13, 242).

Mohner *et al.* (2017) conducted a meta-analysis of 23 occupational cohort studies (10 cohorts based on silicosis registry, and 13 industrial-based cohorts) and four case-control studies of chronic renal disease (predominantly ICD 9th revision codes 580–587, but some studies included the whole group) among workers in various industries where RCS exposures occur (e.g., granite, sand, and diatomaceous earth industry; mining; porcelain; and pottery industries). The case-control studies were heterogenous in outcome, as well as source of cases and controls, and the consideration of potential confounders. Cohort studies of workers with silicosis (n = 10) had a group mean SMR of 1.28 (95% CI 1.01–1.62; heterogeneity I^2 = 27.9%). Industrial cohorts (n = 13) showed a group mean SMR of 1.52 (95% CI 1.16–1.98; heterogeneity I^2 = 70.5%). The authors also performed random effect model analysis for groups of industries (sand and granite cohorts, n = 5; pottery cohorts, n = 2; coal and iron mining, n = 2; gold mining, n = 2). The results were rather mixed, with SMRs (95% CI; I^2) of 1.59 (0.91–2.78; 75.0%) in the sand and granite cohorts, 2.15 (1.13–4.08; 72.6%) in the pottery cohorts, 0.99 (0.78–1.25) also in the coal and iron mining cohorts and 1.51 (1.07–2.12) in the gold mining cohorts. Furthermore, the authors analysed six industrial cohorts with quantitative exposure-response information. The results were heterogenous, with 2 studies showing a significant positive association and 4 studies showing no increased risk with increasing cumulative exposure to RCS. The authors therefore concluded that the meta-analysis did not provide clear evidence of a relationship between RCS exposure and renal disease (173).

Despite several studies reporting excess risks for renal diseases, the overall evidence for an association is limited. Most studies did not evaluate the potential contribution of other work-related risk factors to renal disease, including exposure to other nephrotoxicants (e.g., cadmium, mercury), complications from lung disease or silicosis, or differential prevalence of other risk factors (e.g., diabetes, cardiovascular disease, smoking, medicine use) (10, 13). Another difficulty of studying renal disease is its relatively late diagnosis, due to the non-specific clinical manifestations in the early stages, and the usual absence of a renal biopsy for making a precise diagnosis (10, 173). Therefore, it is not possible to confirm that the proposed relationship between renal disease and RCS is solely due to occupational exposure.

6.3 Cardiovascular diseases

There is increasing recognition that RCS exposure may cause cardiovascular diseases. A recent study by Wiebert *et al.* (2023) among manual workers in Sweden reported increased risks of first time acute myocardial infarction, especially among women. A cumulative exposure to RCS of 0.62–1.54 mg/m^3-years was associated with hazard ratios (HRs) of 1.03 (95% CI 0.99–1.07) in males and 1.42 (95% CI 1.15–1.74) in females, after adjustment for age, socioeconomic group, and urbanisation index. At the highest cumulative RCS exposure (> 1.54 mg/m^3-years) the HR for acute myocardial infarction among men was slightly elevated by 1.07 (95% CI 1.03–1.10) (274). A study by Gellissen *et al.* (2019) also reported an increased risk (OR 6.46, 95% CI 1.34–31.3, adjusted for smoking, erythrocyte sedimentation rate and metabolic syndrome) of acute myocardial infarction but only in a small subgroup of highly exposed workers (5.74–14.60 mg/m^3-years) with long-term employment in the German uranium mines (274). Fan *et al.* (2018), who investigated cardiovascular diseases in the Swedish foundry industry, reported increased mortality from cardiovascular diseases (SMR 1.3, 95% CI 1.2–1.4) and mortality and morbidity from stroke (SIR 1.34, 95% CI 1.2–1.5), but not for myocardial infarction (87). Liu *et al.* (2014) who investigated heart disease mortality among Chinese pottery workers and metal miners reported increased risk of mortality from total heart disease, pulmonary heart disease, and a positive trend for ischaemic heart disease (IHD) with increasing exposure levels to RCS. A cumulative RCS exposure level of 0.56–0.87 mg/m^3-years was associated with an increased HR for IHD mortality of 1.52 (95% CI 1.02–2.27) (157). Björ *et al.* (2010) reported increased mortality from myocardial infarction with exposure to respirable dust (not specifically RCS) and whole-body vibration, respectively. However, the relationship with vibrations appeared to be stronger (23). Lastly, a study by Weiner *et al.* (2007) described an increased risk of mortality from IHD among miners, well borers, dressing plant workers, and other mine and stone workers in Sweden (270).

Overall, there is evidence of a relationship between RCS exposure and cardiovascular diseases, but the results of separate epidemiological studies on different types of cardiovascular diseases are not consistent (23, 47, 58, 87, 91, 157, 170, 270, 274). Most of these studies investigated mortality of cardiovascular diseases in relation to RCS exposure. However, the lethality rate of acute myocardial infarction in Sweden is about 12% (274). Also, some individual studies were unable to control for some major potential confounding factors (e.g., smoking, co-exposures, shift work, vibrations, noise, body mass index (BMI), blood pressure). There is also the possibility of a healthy worker effect; a worker with a RCS-related lung disease will probably not be able to continue to work in the same job, which results in a seemingly healthy working population.

Liu *et al.* (2020) and Esfahani *et al.* (2020) investigated the relationship between RCS exposure and cardiovascular diseases on a larger scale in two meta-analyses (82, 155).

Liu *et al.* (2020) conducted a meta-analysis among twenty industrial cohorts in foundry, mining (e.g., coal, metal, tungsten, iron, gold), stone workers, ceramic

workers, steel mills, pottery, diatomaceous earth, granite, and sand industries. The authors concluded that there was an increased risk among these cohorts for overall heart disease (meta-RR 1.08, 95% CI 1.03–1.13; heterogeneity I^2 = 96.0%), and for pulmonary heart disease (meta-RR 1.24, 95% CI 1.08–1.43) and a positive exposure-response association for pulmonary heart disease (meta-RR 1.39, 95% CI 1.19–1.62). For IHD a slightly negative non-significant meta-risk was reported (meta-RR 0.98, 95% CI 0.91–1.05). However, at a cumulative exposure level around 1 mg/m^3-years, there was a significant increase in the HR, which decreased at higher RCS exposures (155). Similar results were found in a meta-analysis conducted by Esfahani *et al.* (2020). Authors reported an increased SMR of 1.26 (95% CI 0.88–1.63; heterogeneity I^2 = 98.9%) for overall cardiovascular disease mortality. Results were based on seven industrial cohort studies among miners, foundry, stone, and factory workers (82).

Both NEG and the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) have evaluated the association between cardiovascular diseases and occupational exposure to RCS (230, 237). The outcomes of these evaluations are discussed below.

The SBU (2017) found limited evidence for an association between IHD (except *cor pulmonale*) and occupational exposure to RCS (230), based on eight epidemiological studies (6, 23, 96, 143, 145, 157, 182, 221). Furthermore, moderately strong evidence was reported for pulmonary heart disease (*cor pulmonale*), based on four studies (157, 182, 221, 266). The evidence for stroke was considered as insufficient, based on three studies (145, 208, 221). It should be noted that SBU used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system to evaluate the strength of evidence. GRADE is a widely used tool for grading the quality of evidence and for making clinical recommendations. GRADE is not directly applicable to occupational exposures as a randomised clinical trial is required to reach the grading "strong scientific evidence".

NEG (2020) concluded that there is strong evidence for an association between exposure to RCS and cardiovascular disease based on more than ten studies (237). The classification was primarily based on IHD, the strongest evidence was observed in a study by Liu *et al.* (2014) who investigated mortality of heart disease among Chinese workers in metal mines and pottery (157). The authors reported an association with exposure to RCS at 0.56–0.87 mg/m^3-years and increased mortality from IHD (157, 237).

Overall, there is clear evidence of a relationship between occupational RCS exposure and some cardiovascular diseases.

6.4 Other diseases

6.4.1 Autoimmune diseases

Autoimmune diseases form a collection of many complex disorders of unknown aetiology, resulting in immune responses to the body's own cells and tissues. A link

between RCS exposure and a wide spectrum of autoimmune diseases, including systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis, has been proposed since the 1950s. In general, the results indicate that exposure to RCS may lead to an increased risk of developing an autoimmune disease in some workers who also have other risk factors for autoimmune diseases (e.g., genetic predisposition, exposure to other chemicals) (10, 13, 171).

6.4.1.1 Systemic sclerosis

Systemic sclerosis (SSc), also referred to as scleroderma, is an autoimmune disease characterised by tissue thickening and fibrosis, often with the involvement of internal organs (13, 163, 225). The association between SSc and RCS exposure appears to be more pronounced in male patients with higher exposures and possibly associated with more severe forms of the disease (10, 163, 171, 225). Increased risks were also reported in a recent large cohort study by Boudigaard *et al.* (2021). The authors investigated the association between RCS exposure and several autoimmune diseases in the Danish working population of almost 3 million men and women using the SYN-JEM (job-exposure matrix developed for SYNERGY project) for exposure estimates. An incidence rate ratio (IRR) of 1.62 (95% CI 1.08–2.44) for highly exposed men (cumulative exposure category 0.94–16.22 mg/m^3-years) compared to non-exposed male workers was reported (29).

6.4.1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterised by systemic inflammation, with the hallmark of the disease being joint inflammation (synovitis) leading to progressive arthritic symptoms. RA is a chronic disease that can ultimately lead to joint destruction. RA is associated with specific autoantibodies, including rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) (seropositive RA refers to the presence of RF and/or ACPA in a patient with RA) (10, 13, 275).

Several studies report an increased risk of RA in relation to RCS exposure (223, 267). A registry-based case-control study conducted by Wrangel *et al.* (2021) in Sweden reported statistically significant increased ORs for seropositive (1.22, 95% CI 1.05–1.40) and seronegative (1.23, 95% CI 1.04–1.46) RA among men. Exposure status (exposed versus non-exposed) was established through linkage to an adjusted FIN-JEM , a job-exposure matrix (based on national census data of Finland) with information on RCS exposures per job (not further specified) (275). A large Danish cohort study found similar results with an incidence rate ratio for RA of 1.57 (95% CI 1.41–1.75) for high exposed men (cumulative exposure (RCS) category 0.94–16.22 mg/m^3-years). The authors also report equally elevated incidence rate ratios in sub-analyses of seropositive and seronegative RA in both men and women (29).

6.4.1.3 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys and blood vessels. Since it is a multi-system disease, clinical presentation often varies between patients. Results of studies show a higher prevalence of SLE in patients with a history of occupational exposure to RCS compared to controls, but no clear exposure-dependent relation has been found between RCS exposure and SLE (10, 13, 29, 203).

6.4.1.4 ANCA-associated vasculitis

Vasculitis associated with serum positivity for anti-neutrophil cytoplasmic antibodies (ANCAs) that affect small to medium-sized blood vessels are commonly known as ANCA-associated vasculitis (AAV). AAV is an autoimmune disorder that affects blood vessels systemically. The most associated diseases include granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). These diseases are clinically associated with lung involvement, and often associated with renal damage (glomerulonephritis) as well (13, 93). A meta-analysis of six case-control studies found an overall increased risk estimate for RCS exposure ("ever exposed") with development of AAV (OR 2.56, 95% CI 1.51–4.36) (10, 93).

6.4.1.5 Sarcoidosis

Sarcoidosis is an inflammatory disease that involves the formation of granulomas, mainly in the lung and/or intrathoracic lymph nodes. However, other organs, such as the skin, eyes, heart, liver, spleen, salivary glands, muscles, bones, kidneys and central nervous system may also be affected. Sarcoidosis is often seen in individuals between 20 and 45 years of age. Only a few studies have examined the relation between RCS exposure and sarcoidosis, but the results suggest a relationship exists (13, 94, 267). One of these studies is a cohort of RCS-exposed workers in Swedish iron foundries. The authors reported increased incidence rates for sarcoidosis of 3.94 (95% CI 1.07–10.08) for high exposed workers (RCS exposure category > 0.048 mg/m^3; TWA) compared to no or low exposed workers (RCS exposure category 0.012–0.023 mg/m^3; TWA) (267). Silicosis may be misdiagnosed as sarcoidosis, because silicosis with symptomless hilar enlargement and diffuse nodular lung shadows looks quite similar to sarcoidosis (94, 233).

6.4.2 Cancer other than lung cancer

Cancers of the stomach, intestine, oesophageal and kidney have been reported in crystalline silica-exposed workers. However, because of limitations in the studies, no exposure-response relationship has been established between these cancers and exposure to RCS (10, 13, 124, 188). Lee *et al.* (2016) conducted a meta-analysis of 29 studies (9 case-control and 20 cohort studies) examining gastric cancer in relation to RCS exposure. A significant relationship was found, but the meta-analysis was hampered by limited quantitative exposure data and lacked consideration of co-exposures (10, 149). Similarly, in a recent case-control study

examining kidney cancer in relation to RCS exposure an increased risk was reported, but no exposure-response association was found (206).

In general, the findings of these studies have been inconsistent, and studies often did not consider potential confounders. In many cases, observations of these cancers (not lung cancer) were made in studies investigating the association between RCS exposure and lung cancer, and appropriate adjustments for specific confounding factors were not considered (10, 13, 124).

6.5 Genotoxicity

For a summary on genotoxicity (and the carcinogenic mechanism) of RCS see Annex VI, which presents the findings on genotoxicity of RCS by the DECOS Subcommittee on the Classification of Carcinogenic Substances, citations are provided in the annex as well. In short, the subcommittee concludes that it is undisputable that exposure to RCS can cause tumours and that a genotoxic mechanism of action is involved. The carcinogenic potential of RCS primarily results from genotoxicity by indirect mechanisms related to damage of lung cells, leading to inflammation and a tumour-promoting inflammatory microenvironment. However, the possibility of a direct genotoxic mechanism involving particle-generated ROS, cannot be excluded.

6.6 Effects on reproduction

There are no data available on RCS-induced toxicity to reproduction.

7. Mechanism of toxicity

Many studies have focussed on the mode of action of RCS and have identified two major mechanisms involved in RCS-induced lung damage. In general, these major mechanisms include 1) direct damage to lung cells due to the specific surface properties of RCS particles, and 2) indirect damage to lung cells due to an inflammatory response and oxidative stress, due to apoptosis and necrosis of macrophages causing oxidative stress by the formation of reactive oxygen and nitrogen species (ROS and RNS). The major mechanisms are further detailed in the sections below and depicted in Figure 1, Section 7.1.

7.1 Surface and structural factors of silica particles

Physical and chemical properties play an important role in the degree of exposure and subsequent toxicity of inhaled particles. Properties such as chemical composition, particle diameter, particle surface area, shape, density, solubility, and hygroscopic and electrostatic properties may be important factors that affect toxicity resulting from inhalation of silica particles (10, 13, 123).

Surface-related factors which have been postulated to influence particle-induced toxicity include the presence of iron or other transition metals, and the ability of particles to accumulate iron. Crystalline silica polymorphs can contain trace impurities of substances, such as iron or aluminium, that can modify the surface reactivity [e.g., trace amounts of iron may increase the reactivity (41, 216), trace amounts of aluminium may decrease the reactivity (117)].

Another surface-related factor is the ability of particles to generate free radicals. Grinding, cutting, or otherwise fracturing crystalline silica generates Si and Si-O radicals (e.g., siloxyl radicals, silanol (SiOH) groups, ionised silanol groups) by breaking silicon-oxygen (Si-O) bonds in the crystal structure (10, 98, 117, 123, 216, 273). A third surface-related factor is the hydrophobicity of the particulate surface.

Exposure to water can break silicon-oxygen bonds on the surface of crystalline silica to form silanols. Silanol groups present on the surface of crystalline silica particles can form hydrogen bonds with oxygen and nitrogen groups found in biologic cell membranes, which then may lead to a loss of membrane structure, lysosomal leakage, and tissue damage followed by increased inflammatory reactions and genotoxic reactions.

Furthermore, a fourth surface-related factor is the piezoelectricity of quartz, cristobalite, and some forms of tridymite. Piezoelectricity is a property that produces opposite electric charges on opposite sides of the physical structure when pressure is applied directly to the crystal. It is theorised that piezoelectricity generates oxygen free radicals. All these processes may contribute to the development of lung scarring (2, 10, 13, 80, 98, 116, 123, 137, 279).

Natural aging of fractured silica, heating and amorphisation by wet grinding decreases or eliminates the amount of surface radicals and thus the surface reactivity (13, 40, 116, 117, 123, 215, 284). As an example, aging in the air decreases the amount of surface radicals with a half-life time of around 24 hours (40).

Structure related factors may also modify the degree of toxicity of crystalline silica, such as particle size and the surface density of silanol groups. The latter varies between different forms of crystalline silica. In addition, crystalline silica particles can readily absorb other minerals, which may alter its toxicity. However, it is still unclear to what extent these features influence toxicity (10, 13, 117, 123).

In conclusion, crystalline silica particles may differ in their toxic activity, depending on their crystal form, size, age, dust composition and the treatment they underwent.

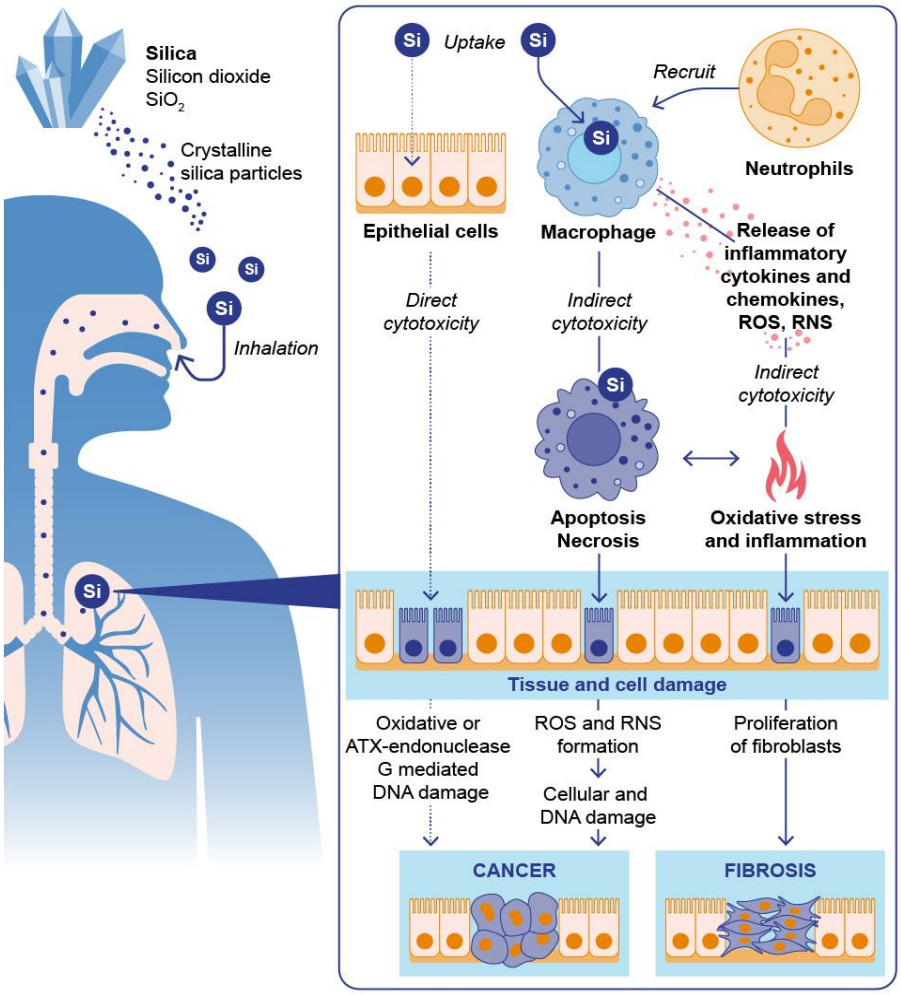


Figure 1. Overview of the proposed major processes underlying the pathogenesis of silicosis and lung cancer.

Note with Figure 1. The uptake of inhaled crystalline silica particles by macrophages causes indirect cytotoxicity and apoptosis, leading to the release of intracellular crystalline silica as well as several inflammatory cytokines and chemokines, reactive oxygen species (ROS) and reactive nitrogen species (RNS). These inflammatory substances damage nearby cells causing an inflammation, resulting in the recruitment of more macrophages. In addition, anti-inflammatory and fibrogenic factors are released stimulating tissue repair and remodelling (not in Figure 1). The continued cycling between inflammation and repair mechanisms may eventually lead to fibrosis. Apoptosis of macrophages and inflammation also lead to oxidative stress by the formation of ROS and RNS, which can cause cellular and DNA damage. DNA damage can also be directly mediated by the formation of ROS on the surface of RCS-particles (oxidative DNA damage) or by the autotaxin (ATX)-mediated translocation of endonuclease G to the nucleus (ATX-endonuclease G mediated DNA damage).

7.2 Inflammatory response

RCS deposited in the lungs causes epithelial injury and macrophage activation, leading to inflammatory responses and proliferation of the epithelial and interstitial cells. RCS stimulates 1) the release of cytokines and chemokines from macrophages and epithelial cells, 2) release of ROS and RNS, 3) steps 1 and 2 cause oxidative stress in the lungs, 4) which leads to cell death with release of the RCS particle, and 5) the recruitment and activation of additional neutrophils and macrophages in the response to the RCS particle. All these reactions contribute to RCS-induced lung diseases, see also Figure 1, Section 7.1 (10, 194).

7.3 Mechanism of toxicity of respirable crystalline silica-related diseases

7.3.1 Silicosis

The general mechanisms of silicosis have been extensively investigated. Although the major biological processes leading to (chronic) silicosis have been well defined, and the role of surface and structural properties have been acknowledged, the molecular events leading to fibrosis have not been fully elucidated. The general underlying mechanism of silicosis is an inflammatory process (Figure 1, Section 7.1). In the lung, inhaled RCS particles are phagocytised by alveolar macrophages. Phagocytosis involves uptake of silica particles by scavenger recognition receptors, which results in apoptosis of macrophages and release of mediators [e.g., inflammatory cytokines, chemokines; notably tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1)] contributing to lung inflammation and fibrosis. This recurring cycle of macrophage phagocytosis, cell death of the alveolar macrophages, and release of intracellular contents results in a chronic inflammatory process (alveolitis). Injury to other pulmonary cells (e.g., epithelial cells and fibroblasts) resulting from interactions with RCS particles may also contribute to alveolitis. In addition to the inflammatory response, the body tries to repair the tissue damage in the lungs by releasing anti-inflammatory and fibrogenic factors [e.g., insulin-like growth factor 1 (IGF-1), IL-10, transforming growth factor beta (TGF-β)]. Furthermore, chronic damage to the so-called type I alveolar epithelial cells may lead to hyperplasia and hypertrophia of type II alveolar epithelial cells, which also triggers repair mechanisms. The persistent cycling between inflammatory and reparative processes leads to excess extracellular matrix deposition, which ultimately leads to fibrosis (13, 116, 229).

The forming of free radicals by either epithelial cells or macrophages that have taken up or phagocytised RCS particles, play an important role in the pathogenesis of acute and accelerated silicosis in particularly. As mentioned in Section 7.1 RCS are piezoelectric, which can contribute to the formation of free radicals on the surface of silica particles. Freshly fractured RCS has an increased redox potential on its surface and is highly reactive with hydrogen, oxygen, carbon and nitric oxide, and more likely to produce more free radicals. In its turn oxidative stress stimulates specific transcription factors through interaction with the receptor on alveolar

macrophages, which further increases cytokine expression, perpetuating inflammation, and fibrosis (17, 124, 229).

7.3.2 Lung cancer

The DECOS Subcommittee on the Classification of Carcinogenic Substances has evaluated the underlying carcinogenic mechanism of RCS. The report of the evaluation by the subcommittee can be found in Annex VI of this advisory report. In short, RCS may cause lung tumours and the carcinogenic potential results primarily from genotoxicity by indirect mechanisms, related to damage of lung cells with inflammation and a tumour-promoting inflammatory microenvironment as a result. However, the possibility of a direct mechanism involving particle-generated ROS, cannot be excluded.

The subcommittee has come to this conclusion because, according to the subcommittee's guideline, direct-acting genotoxic carcinogens include substances that (either in their unchanged form or as reactive metabolites) interact directly with DNA to induce genotoxic effects (106). According to the currently available scientific literature there is no evidence that RCS particles can enter the nucleus themselves (27, 154). However, the subcommittee notes that the available scientific data on intracellular translocation of RCS particles are limited. The subcommittee also notes that ROS can be generated directly at the surface of RCS particles, and that ROS, unlike RCS-particles, can enter the nucleus themselves and interact with DNA. The subcommittee considers genotoxic carcinogens that generate ROS directly also as direct genotoxic carcinogens, given the genotoxicity of the produced ROS (106). As a result, the possibility of a direct genotoxic mechanism, involving particle-generated ROS, cannot be excluded.

Besides inflammation-induced indirect genotoxic mechanism, another potential indirect genotoxic mechanism involves the activation of ATX at the plasma membrane by RCS particles. The activation of ATX may cause, through an intracellular signaling pathway, the translocation of endonuclease G to the nucleus, which can cause DNA damage (281). See also Figure 1, Section 7.1).

The conclusions of the subcommittee are in accordance with the conclusions of the IARC and NFA (124, 226). IARC reports that an inflammation is the most likely mechanism for the induction of lung cancer associated with exposure to RCS, but because of the direct formation of ROS a direct effect on lung epithelial cells cannot be excluded. In addition, the IARC reports that exposure to RCS causes an impaired alveolar macrophage-mediated clearance, which induces a persistent pulmonary inflammation, followed by the release of oxidants (or free radicals). The free radicals, formed after exposure to RCS, can induce exhaustion of antioxidant defences, epithelial cell lesions, resulting in proliferation of cells (123, 124).

7.3.3 Chronic obstructive pulmonary disease (COPD)

COPD is caused by chronic inflammation, remodelling of the small airways (bronchitis) and destruction of lung parenchyma (emphysema) as a result of oxidative stress induced by, for example, RCS. There are two potential mechanisms

by which RCS can initiate cell injury leading to COPD. These mechanisms include cytotoxicity leading to formation of ROS and RNS, followed by the release of cytokines, chemokines and fibrogenic factors inducing airway inflammation and emphysema. Another potential mechanism involves epithelial cell injury facilitating the penetration of cell walls by crystalline silica particles causing localised fibrosis (114). See also Figure 1, Section 7.1.

7.3.4 Renal diseases

RCS exposure is associated with two pathological mechanisms that could result in renal damage: 1) direct toxic effects associated with the accumulation of RCS induced immune-complexes (IgA) in the kidney, followed by inflammation, and 2) indirect toxic effects secondary to an autoimmune disease (AID) (13, 241). The first mechanism indicates that exposure to RCS leads to renal deposition and accumulation of silica particles in the kidneys, resulting in chronic inflammation progressing to fibrosis. This type of renal damage is most often described in individuals diagnosed with silicosis and a RCS overload would directly lead to renal failure. The second mechanism involves renal complications due to an autoimmune disease. Which renal complications will occur depend on the specific autoimmune disease present. Renal damage associated with ANCA-associated vasculitis and systemic sclerosis is associated with vascular pathology in the glomerulus, resulting in glomerulonephritis. Whereas renal pathology associated with systemic lupus erythematosus appears to be due to deposition of autoantibodies in the kidney (13).

7.3.5 Cardiovascular diseases

The biological mechanisms by which RCS exposure could cause cardiovascular diseases are not fully understood yet, but there are some theories. One theory involves oxidative stress and inflammation via arterial stiffness in the development of hypertension. Hypertension by itself is a major risk factor for the development of cardiovascular diseases. Exposure to RCS can produce ROS and increase oxidative stress which can not only play a role in the development of silicosis and lung cancer but also in the development of cardiovascular diseases, including atherosclerosis, IHD and acute myocardial infarction (82, 155, 274).

Another theory concerns pulmonary fibrosis caused by pulmonary inflammation which can occur after exposure to RCS. Inflammatory mediators pass through the blood circulation, including pulmonary and systemic circulations, and cause vascular injury. Very fine crystalline silica particles can also reach the vascular bed and disturb the vascular endothelium. Recurrent injury to pulmonary vascular tissues can result in the development of pulmonary hypertension (82, 91).

7.3.6 Autoimmune diseases

The cellular mechanisms that lead to autoimmune diseases are not fully understood yet. One proposed pathway is that when RCS particles are phagocytised by macrophages, the immune system is activated by the secretion of cytokines, chemokines and lysosomal enzymes, which activates antigen-presenting and in turn antibody-producing cells (13, 29, 188, 215). Immune activation by RCS may be

linked to scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and several other autoimmune diseases (13, 188). Autoimmune disorders following exposure to RCS may occur secondary to silicosis, as a chronic immune stimulation in the lungs can cause systemic effects (13). However, development of fibrosis and nodular lesions may not be required for the development of an autoimmune disease (215).

8. Existing guidelines, standards and evaluation

8.1 General population

No relevant guidelines, standards or evaluations related to crystalline silica exposure in the general population have been found.

8.2 Working population

8.2.1 Occupational exposure limits

Tables 8a and 8b show OELs for RCS (as respirable dust fraction), as established, or recommended in European countries and the US. A more detailed description and motivation of the legal and recommended OELs is presented in Annex III Table IIIa of this advisory report.

8.2.2 Classification of carcinogenic properties

This paragraph provides a short overview of national and international classifications on the carcinogenic properties of RCS, in chronological order starting with the oldest. A more extensive summary including motivation and key references on which other international organisations based their classification of RCS can be found in Annex III Table IIIb.

The NIOSH has also classified RCS as a *potential occupational carcinogen*. In 1989, NIOSH recommended crystalline silica to be considered a potential occupational carcinogen (188).

The IARC has retained their previous classification of RCS as carcinogenic from 1997. The IARC conclude in their report from 2012 that RCS in the form of quartz or cristobalite are *carcinogenic to humans (Group 1)*. Furthermore, IARC concludes that there is sufficient evidence of carcinogenicity in humans for quartz and cristobalite, and in animals for quartz, and limited evidence in animals for tridymite and cristobalite (124).

In the Netherlands, the Subcommittee on the Classification of Carcinogenic Substances classified quartz as a carcinogen in 1998 (103). In 2019 the Ministry of Social Affairs and Employment published a report in which quartz, cristobalite and tridymite are classified as a carcinogen in Category 1 *(known or presumed human carcinogen)*. In addition, working activities in which workers are exposed to generated RCS are classified as Category 1 *(carcinogenic work processes)* (251).

Table 8a. Legal OELs for RCS (8-hour TWA).

Country	Respirable fraction (mg/m^3)				Remarks	Ref.
	Crystalline silica dust	Quartz CAS No. 14808-60-7	Cristobalite CAS No. 14464-46-1	Tridymite CAS No. 15468-32-3		
Belgium	n.s.	0.1	0.05	0.05		(186)
Denmark	0.1	0.1	0.05	0.05		(12, 186)
Finland	0.05	0.05	0.05	0.05		(186, 236)
France	n.s.	0.1	0.05	0.05		(10, 186)
Germany (BMAS)	n.s.	0.05	0.05	0.05	AGW	(186)
Norway	n.s.	0.05	0.05	0.05		(11, 186)
Sweden	n.s.	0.1	0.05	0.05		(186, 250)
EU	0.1	n.s.	n.s.	n.s.	BOEL	(85)
Netherlands	n.s.	0.075	0.075	0.075		(68, 186)
UK (HSE)	0.1	0.1	0.1	0.1	WEL	(119, 186)
USA (OSHA)	0.05	0.05	0.05	0.05	PEL [a]	(196)

[a] PEL for general industry, construction, or shipyard employment. PEL for any other operations or sectors, see OSHA (2019) (198).

AGW: Arbeitsplatzgrenzwert, BMAS: Bundesministerium für Arbeit und Soziales, BOEL: binding occupational exposure limit, HSE: Health and Safety Executive, n.s.: not specified, OEL: occupational exposure limit, OSHA: Occupational Safety and health Administration, PEL: permissible exposure limit, TWA: time-weighted average, WEL: workplace exposure limit.

Table 8b. Recommended OELs for RCS (8-hour TWA).

Country	Respirable fraction (mg/m^3)				Remarks	Ref.
	Crystalline silica dust	Quartz CAS No. 14808-60-7	Cristobalite CAS No. 14464-46-1	Tridymite CAS No. 15468-32-3		
EU (SCOEL)	< 0.05	n.s.	n.s.	n.s.		(232)
Germany (DFG)	n.s.	n.s.	n.s.	n.s.	MAK	(72)
USA (NIOSH)	0.05 [a]	n.s.	n.s.	n.s.	REL [a]	(188)
USA (ACGIH)	0.025	0.025	0.025	withdrawn	TLV	(4, 5)

[a] REL is expressed as 10-hour TWA.

ACGIH: American Conference of Governmental Industrial Hygienists, DFG: Deutsche Forschungsgemeinschaft, MAK: Maximale Arbeitsplatz-Konzentration, NIOSH: National Institute for Occupational Safety and Health, n.s.: not specified, OEL: occupational exposure limit, REL: recommended exposure limit, SCOEL: Scientific Committee on Occupational Exposure Limits, TLV: threshold limit value, TWA: time-weighted average.

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) classified the respirable dust fractions of crystalline silica (quartz, cristobalite and tridymite) in Category 1 *(substances that cause cancer in man and can be assumed to make a significant contribution to cancer risk)* (71).

In their final rule from 2016, OSHA concludes that the available data provide ample evidence that exposure to RCS increases the risk of lung cancer among workers (196).

Although there is no harmonised classification in the EU, quartz, cristobalite and tridymite are notified as *carcinogen 1A may cause cancer* (H350) as well as *carcinogen 2 suspected of causing cancer* (H351) in the Classification & Labelling Inventory database of the European Chemicals Agency (ECHA) (78). In addition, work involving exposure to RCS dust generated by a work process was added to Annex I in the Directive 2004/37/EC list of carcinogenic substances, mixtures and processes of the Carcinogens, Mutagens and Reproductive substances Directive (CMRD) in 2017 (84).

The ANSES reports that crystalline silica is currently not recognised as a carcinogen under French Labour Code. However, ANSES recommends recognition of work involving exposure to crystalline silica dust as carcinogenic processes, and transposed into French law (10).

The NTP has classified RCS, primarily quartz dusts occurring in industrial and occupational settings, as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans (194).

8.2.3 Classification of the reproduction toxic properties

RCS has not been classified for effects on fertility or development.

8.2.4 Biological limit values

No biological limit value has been set for RCS.

8.2.5 Skin and sensitisation notation

RCS is not known to cause (skin) sensitisation and it has no skin notation in any list of OELs.

9. Hazard assessment

With this advisory report the committees of the DECOS and NEG aim to calculate risk levels as a basis for setting a risk-based OEL for RCS.

In general, health-based OELs are average concentrations of a substance in the air of a workplace that should offer sufficient protection against possible adverse health effects. The health-based OELs are obtained by a quantitative risk analysis in which the committees must make decisions on:

- the critical adverse health effect(s);
- choosing a threshold- or non-threshold (risk-based) approach. The threshold approach will lead to a health-based recommended occupational exposure level (HBR-OEL), whereas the non-threshold approach will lead to health-based calculated occupational cancer risk values (HBC-OCRVs);
- the choice of the key study (or studies) as point of departure;
- the derivation method.

In the next sections the committees describe the risk assessment for RCS. For more details on the general procedures, the committees refer to the DECOS guidelines "Guidance for recommending classifications and health-based occupational exposure limits" (2021) (105) and "Guideline for the calculation of occupational cancer risk values for carcinogenic compounds" (2012) (104).

9.1 Critical health effect(s)

A health-based OEL is an exposure level below which no or almost no significant adverse health effects are expected during and after working life. Which adverse health effects are considered in deriving an HBR-OEL or HBC-OCRVs depends on whether the evidence for a causal relationship or association is sufficiently demonstrated. In addition, an HBR-OEL or HBC-OCRVs are derived from data on the adverse health effect that occurs first at increasing exposure, also called the critical health effect (105).

9.1.1 Evaluation of adverse health effects

In Chapter 6, the committees give an overview of the adverse health effects associated with occupational exposure to RCS.

In summary, there is extensive evidence of a causal association of occupational exposure to RCS with silicosis and lung cancer. Silicosis is one of the oldest occupational diseases known. A pooled analysis among six industrial cohort studies reported an adjusted mortality rate ratio of 3.39 (95% CI 1.42–8.08) for cumulative RCS exposure levels between 0.99 and 1.97 mg/m^3-years (252).

Almost all the studies investigating the relationship between occupational exposure to RCS and silicosis used chest radiography (chest X-ray) to detect or diagnose silicosis. However, Hnizdo *et al.* (1993) compared radiological and pathological diagnoses of silicosis and showed that the chest radiograph may not be

the most sensitive tool to detect or diagnose silicosis (113). This may have resulted in false negative diagnoses of silicosis and underestimation of the silicosis risk.

Whereas the causal association between RCS exposures and silicosis is undisputed, it was not until IARC classified respirable quartz and cristobalite as "carcinogenic to humans (Group 1)" in 1997 that the focus of further research shifted towards lung cancer. The IARC conclusion was somewhat controversial, particularly at that time, because there were inconsistencies in the epidemiological data available and a lack of extensive exposure-response data (123). In response to the IARC report (1997), Steenland *et al.* (2001) conducted a large pooled-analysis among 10 industrial cohorts investigating the relation between exposure to RCS and lung cancer. This pooled analysis is also known as the IARC multicentre study (245). The authors reported a SMR for lung cancer of 1.2 (95% CI 1.10–1.30) for a median cumulative RCS exposure level of 4.27 mg/m^3-years (245). More recently, around 2009, a large pooled-analysis of 14 case-control studies on the joint effects of exposure to occupational carcinogens and smoking on the development of lung cancer was established. RCS is one of the five lung carcinogens that was investigated in this project, also known as the SYNERGY project (207, 210-212). In 2020, Ge *et al.* published the results of a pooled analysis using the SYNERGY data to investigate the relation between lung cancer and respirable quartz (measurement data on other crystalline polymorphs than quartz was limited, with the result that Ge *et al.* (2020) only used data on quartz). The authors reported an increased OR of 1.15 (95% CI 1.04-1.27) for lung cancer at relatively low exposure levels (exposure category > 0–< 0.39 mg/m^3-years) of respirable quartz (90).

Exposure to RCS is also associated with other adverse health effects. Several epidemiological studies reported increased risks for COPD, renal diseases, cardiovascular diseases, and autoimmune diseases in relation to RCS exposure.

For COPD there is strong evidence of an association with exposure to RCS. The meta-analyses by Brüske *et al.* (2014) reported an association between occupational exposure to quartz and a decrease in FEV_1 and FEV_1/FVC, indicating airway obstruction consistent with COPD (32). However, the available data do not allow for the quantification of an exposure-response relationship due to the lack of extensive quantitative exposure data.

For renal diseases there is limited evidence for an association with RCS exposure. While a pooled analysis among three industrial cohorts reported an increased risk for renal disease mortality with increasing exposure quartiles (242). A meta-analysis conducted by Mohner *et al.* (2017) among 23 epidemiological studies reported rather mixed results (173). Most of the studies investigating renal diseases did not evaluate the contribution of potential confounders. Furthermore, results are often based on small numbers of deaths or cases, probably due to the non-specific clinical manifestations and the usual absence of a biopsy for a good diagnosis. This may lead to underreporting but also to potentially less certain risk estimates.

For cardiovascular diseases, in general, there is moderately strong evidence for an association with occupational exposure to RCS. However, the results of individual studies as well as the two meta-analyses were inconclusive for the

specific types of cardiovascular diseases. Both meta-analyses reported an association between RCS exposure and total heart diseases (82, 155). Liu *et al.* (2020) also found a positive association with pulmonary heart disease (155). The evaluations by the SBU (2017) (230) and the NEG (2020) (237) reported limited and strong evidence, respectively, for IHD. The SBU also reported moderately strong evidence for an association with pulmonary heart disease (230). Most of the studies investigating the relationship between cardiovascular diseases and exposure to RCS used mortality data, while morbidity data may be more appropriate for some types of cardiovascular diseases with lower lethality rates. Another concern is that many of the studies were unable to control for some potential confounders, which may have affected the risk estimates.

Regarding autoimmune diseases there is limited evidence for an association with occupational exposure to RCS. Several epidemiological studies suggest an association between RCS exposure and autoimmune disease, including systemic sclerosis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and ANCA-associated vasculitis. However, the available data do not allow for a quantitative risk analysis due to the lack of extensive exposure-response data.

Alongside the evaluation of the exposure-response relationships between adverse health effects and exposure to RCS, the committees also considered data on physical and chemical properties (Chapter 2), toxicokinetics (Chapter 5), pathogenesis, and mechanisms of toxicity (Chapter 7) to understand how RCS induces these adverse health effects. This knowledge, in particularly the data on the pathogenesis and mechanism of toxicity, supports the evidence for a causal relationship between RCS and the adverse health effects described above. For non-malignant respiratory health effects, such as silicosis or COPD, the underlying biological mechanism is that of an inflammatory response to RCS particles in the lungs.

For lung cancer, the DECOS Subcommittee on the Classification of Carcinogenic Substances has concluded that the carcinogenic mechanism of RCS results primarily from genotoxicity by an indirect mechanism, related to damage of lung cells resulting in inflammation and a tumour-promoting inflammatory micro-environment. However, the possibility of a direct genotoxic mechanism, involving particle-generated ROS, cannot be excluded (see also Section 7.3.2 and Annex VI).

For renal diseases and cardiovascular diseases, one of the proposed possible mechanisms is that of an inflammatory response which may lead to fibrosis in the kidney or pulmonary region. Inflammation and fibrosis may cause hypertension in the pulmonary region, which is a major risk factor for cardiovascular diseases. For autoimmune diseases one of the possible mechanisms is the activation of the immune system in response to secretion of cytokines and chemokines after the uptake of silica particles by alveolar macrophages. However, autoimmune diseases may also occur secondary to silicosis and renal diseases may occur because of an underlying autoimmune disease. In conclusion, several potential mechanisms are suggested but the underlying mechanisms causing renal, cardiovascular, and autoimmune diseases are not fully understood yet and need further research.

Overall, the committees conclude that evidence for a causal relationship between exposure to RCS and silicosis and lung cancer is very strong, based on epidemiological studies and current knowledge on the underlying biological mechanisms. For COPD epidemiological studies suggest a relationship with exposure to RCS, but more research is needed because of the lack of quantitative exposure-response data. For renal diseases and autoimmune diseases, the evidence from epidemiological studies as well as the underlying biological mechanisms need further research to confirm initial findings and determine quantitative exposure-response relationships. For cardiovascular diseases, the results from epidemiological studies suggest a relationship but are somewhat inconsistent for the specific types of cardiovascular diseases. Further research is needed to confirm the findings and establish quantitative exposure-response relationships.

9.1.2 Is silicosis a prerequisite for RCS-associated lung cancer?

Regarding the association between occupational exposure to RCS and lung cancer, there has been some debate about whether silicosis is a prerequisite for lung cancer, because results of some earlier studies did not show a consistent association with lung cancer after excluding subjects with silicosis (90, 124). According to the Working Group of the IARC (2012), the studies which restricted their analysis to subjects without silicosis potentially limited the exposure range, because individuals with the highest exposures were excluded from the analyses. Limiting the range of exposure results in reduced power to detect associations (124). In their evaluation, OSHA (2016) concluded that there are no convincing data to demonstrate that silicosis is a prerequisite for lung cancer (196). Some recent studies have specifically addressed this issue and reported a positive relationship between RCS exposure and lung cancer in the absence of clinical silicosis (90, 214). Recent evaluations by ANSES (2019), ATSDR (2019), and NFA (2021) have concluded that exposure to RCS is associated with lung cancer in the absence of silicosis, although having silicosis does increase the risk of developing lung cancer (10, 13, 226).

9.1.3 Conclusion on the critical health effect

As mentioned, the premise of the committees is that an HBR-OEL or HBC-OCRVs are derived from data on the adverse health effect that occurs first at increasing exposure, also called the critical effect. The committees assume that other adverse effects are then also prevented.

Section 9.1.1 shows that for both lung cancer and silicosis there is very strong evidence of a causal relationship with occupational exposure to RCS.

Epidemiological studies generally show that silicosis is associated with higher exposure levels to RCS. This is demonstrated in the pooled analysis by ‘t Mannetje *et al.* (2002), in which the increased risk of silicosis was particularly high for cumulative exposure to RCS of more than 28.10 mg/m^3-years (rate ratio 63.63, 95% CI 19.87–203.8) (see also Annex IV for a more detailed study summary). However, also at lower RCS exposure levels (cumulative exposure to RCS 0.99–1.97 mg/m^3-

years) increased risk of silicosis was observed, rate ratio 3.39 (95% CI 1.42–8.08) (252). Previous evaluations by the SCOEL (2003) and ATSDR (2019) concluded that it was not possible to identify a threshold or a no observed adverse effect level (NOAEL) for silicosis, because silicosis and death due to silicosis was observed for the lowest cumulative exposure ranges reported. In addition, the SCOEL concluded that any reduction of exposure will reduce the risk of silicosis (13, 226, 232).

Also, for lung cancer epidemiological studies reported increased risk at relatively low exposure levels to RCS. Ge *et al.* (2020) reported an increased risk (OR 1.15, 95% CI 1.04–1.27) of lung cancer for the lowest exposure levels to respirable quartz (> 0–0.39 mg/m^3-years) (90). OSHA (2016) concluded that the risk of lung cancer can be increased even at or below the permissible exposure limit (PEL) of 0.05 mg/m^3. In addition, their risk assessment even indicated a significant risk at the action level of 0.025 mg/m^3 (196). The NFA (2021) noted that, based on the evaluation by OSHA, there is evidence that occupational exposure to RCS causes silicosis morbidity and mortality as well as lung cancer to approximately the same extent. However, the NFA is of the opinion that the available quantitative epidemiological data for the association with lung cancer is more extensive, more transparent and comparable than the available data for silicosis (226).

After considering the scientific evidence outlined in this advisory report, the committees agree with NFA that RCS can cause silicosis as well as lung cancer approximately to the same extent. The committees therefore decided, in line with the NFA, for lung cancer as the critical health effect. The committees are of the opinion that, compared with the available quantitative epidemiological evidence for silicosis, the available quantitative data for relationship with lung cancer generally has a higher quality, due to a thorough registration and better diagnostics of lung cancer mortality. In addition, the pooled analysis by Ge *et al.* (2020) which contains data of almost 40 000 participants including 16 901 lung cancer cases, shows that increased risk of lung cancer is associated with the lowest exposure levels to respirable quartz (90). This is in line with the definition of the critical health effect, as described in the guidelines (104, 105).

9.2 Suitable studies for the derivation of cancer risk estimates

In deriving an OEL, in the form of cancer risk estimates, the committees prefer using human data from epidemiological studies rather than animal experiments, because epidemiological data do not involve the uncertainties associated with the biological differences between animals and humans. Furthermore, the exposure conditions in epidemiological studies reflect real life exposure circumstances. Data from animal experiments are considered only if epidemiological data are of insufficient quality or too limited.

If multiple suitable epidemiological studies, with quantitative exposure-response data, are available, then a meta-analysis or a pooled analysis is considered to serve as a point of departure. A meta-analysis is a statistical analysis that combines the results of several conceptually similar epidemiological studies to derive pooled risk

estimates. An advantage of meta-analyses compared to individual studies is that meta-analyses increase the statistical power, and it provides more precise and robust risk estimates. However, a meta-analysis also has some shortcomings, such as the application of incorrect inclusion and exclusion criteria for individual studies, the possibly high degree of heterogeneity among individual studies causing difficulties in statistical analyses, and the general lack of control for potential confounders. Most of these shortcomings can be overcome by using a pooled analysis instead. Pooled analyses have several advantages over meta-analyses of published studies including use of individual raw data, common exposure measures and a uniform approach to statistical analysis with the possibility to adjust for potential confounders (104, 105).

There are numerous cohort and case-control studies available on lung cancer among workers exposed to RCS. There even are several meta-analyses, and two pooled analyses available. Because of the benefits of a pooled analysis the committees examined whether either of the two published pooled analyses could be used as a key study to derive OELs for RCS. One pooled analysis, by Steenland *et al.* (2001), investigated lung cancer in relation with occupational exposure to RCS in ten industrial cohorts from five different countries (245). The second pooled analysis, by Ge *et al.* (2020), comprised of fourteen case-control studies conducted in thirteen European countries and Canada (90).

A summary of these pooled analysis is described below. An extensive summary can be found in Annex IV of this advisory report.

9.2.1 Steenland et al. (2001) – the IARC multicentre study

When IARC classified RCS as a human carcinogen (Group 1) in 1997, there were limitations in the epidemiological data, including inconsistencies across studies and the lack of extensive exposure-response data (123). For the authors this was a reason to conduct a large pooled-analyses study with quantitative exposure-response data on RCS to investigate the relationship with lung cancer. A meta-analysis would be impossible because the studies that did include quantitative exposure-response data used different exposure metrics (252).

Steenland *et al.* (2001) started with a literature search to identify cohort studies with quantitative exposure response data. This resulted in 13 potential cohort studies, of which 10 were included in the final analysis. Three cohorts were excluded due to confidentiality issues, unavailable data, or incompatible data. Furthermore, there were restrictions for coal mines and foundries. Coal mines were excluded due to low and possibly different RCS exposures, due to coating of silica particles with clay which affects the biological activity of RCS particles. Cohort studies of foundries were excluded as well because of the likely presence of co-exposures to other lung carcinogens in the work environment (245). Mines with low exposures to radon decay products were included but were also considered separately. Exposure estimates in any other metric than milligram per cubic meter (mg/m^3) RCS were converted in order to permit a direct comparison between the studies (253). The 10 cohort studies that were included in the pooled analysis also

have individual publications. Five of these cohort studies were updated (since their latest publications) for mortality, specifically for the pooled analysis [USA gold mining (243), Finland granite industry (142), China pottery (51), China tungsten and tin mining (51)]. One cohort was newly developed alongside this pooled analysis [USA sand industry (246)]. Furthermore, new quantitative exposure measures by job and calendar time have been developed or modified for several of the 10 included cohort studies [Australia gold mining (67), USA granite industry (63), USA sand industry (246), Finland granite industry (142), China pottery (51), China tungsten and tin mining (51)]. The USA cohort on diatomaceous earth industry (47) did not require additional effort to be included in the analysis. The South African cohort on gold mining (111) only needed some minor edits to be included in the pooled analysis. The final pooled cohort consisted of 65 980 workers (44 160 miners, 21 820 non-miners) and 1 072 lung cancer deaths (663 miners, 409 non-miners) (245). For most cohort studies at least the job history at the worksite was available (253). The authors reported a positive relationship with lung cancer mortality (SMR 1.2, 95% CI 1.1–1.3), based on 992 lung cancer deaths, with median cumulative exposure of 4.27 mg/m^3-years. An extensive summary of the results including the exposure-response coefficients reported by the authors can be found in Annex IV.

9.2.1.1 Exposure assessment

Reliable exposure assessment is essential to investigate exposure-response relationships in epidemiological studies. In a separate publication, the authors of the pooled analysis by Steenland *et al.* (2001) (245) describe the exposure assessment and how they created a more common exposure metric across the studies. Exposure estimates had to be specific for all the different jobs within each cohort and cover all time periods when exposures occurred. If existing exposure estimates were available in gravimetric total dust, respirable dust or particle count, these estimates had to be converted to milligram per cubic meter (mg/m^3) RCS, which is a common exposure metric, which allowed for direct comparison of the 10 cohorts. All the exposure data of the ten cohorts had to be converted to create one common exposure metric across all ten cohort studies. In most of the 10 cohort studies the original exposure assessment was based on particle counts, which were converted to mass of RCS by use of conversion factors. In addition, due to differences in sampling and analytical methods, different conversion factors and in some studies even multiple conversion factors were used to construct a common exposure metric (see Table 1 in ‘t Mannetje *et al.* (2002) (253) for more details). The time periods in which the exposure measurements were carried out differed between the ten selected cohorts and are relatively far in the past. For the USA granite industry most exposure measurements were taken in 1972 and 1973 and for the cohorts on South African and American gold mining, the exposure measurement periods were between 1956 and 1960, and 1937 and 1977, respectively. The USA sand industry provided the most recently dated exposure measurements over a measurement period from 1974 to 1996 (253).

9.2.1.2 Smoking history

Smoking is strongly associated with lung cancer and thus may have influenced the lung cancer risk estimates. The majority of the ten industrial cohorts included in the pooled analysis by Steenland *et al.* (2001) did not have data on smoking. However, in most studies in the exposure-response analysis, workers with high exposures were compared to workers with low exposures, and these two groups of workers were presumed to share similar smoking habits. This makes confounding by smoking less likely. This is supported by the studies with partial or complete information on smoking (South African gold mining, Australian gold mining, USA diatomaceous earth industry, and Finnish granite industry); only little confounding of exposure-response trends was observed (245).

9.2.1.3 Co-exposures

Another source for bias is the possible presence of carcinogenic substances that may cause lung cancer, other than RCS. In the mining industry co-exposures to dust, asbestos, radon and diesel engine emissions (the lorries and other mechanical equipment in underground mines usually run on diesel), could have influenced the risk estimates of RCS-induced lung cancer.

From the ten industrial cohorts included in the pooled analysis by Steenland *et al.* (2001), at least five cohort studies were conducted in underground mines, where co-exposures can occur. However, the authors performed sub-analyses for miners and non-miners, which showed that the exposure-response trends were rather similar for both the mining and non-mining cohorts (245).

9.2.1.4 Other considerations

There has been some debate about whether the risk of the different RCS polymorphs is the same, since there have been theories that the risk of lung cancer is higher for workers exposed to respirable cristobalite or tridymite. However, Steenland *et al.* (2001) could not find any evidence for a possible difference. In the USA diatomaceous earth industry, the workers are predominantly exposed to cristobalite, but the exposure-response trend in this cohort did not differ from the exposure-response trend in the other cohorts (245). Other currently available epidemiological and experimental data also do not show differences in toxicity or carcinogenic potential between the different polymorphs of RCS (10).

Another concern may be the former employment in other high-risk occupations for lung cancer, which could have biased the lung cancer risk estimates. For most of the industrial cohorts included in the pooled analysis by Steenland *et al.* (2001), only the complete job history at the worksite was available. For the Chinese cohorts on pottery, tin and tungsten mining only one job title was available for every cohort member. Only for the Finnish granite industry a lifelong job history (including the job history before or after work in the granite industry) was available (245, 253).

9.2.2 Ge et al. (2020) – the SYNERGY project

The SYNERGY project consists of a pooled analysis of case-control studies on the joint effects of known occupational lung carcinogens [RCS, asbestos, chromium,

nickel and polycyclic aromatic hydrocarbons (PAH)] and smoking in the development of lung cancer. The project included almost 40 000 subjects, 16 901 lung cancer cases and 20 965 population and hospital-based controls from 13 European countries (Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, and the UK) and Canada (an overview of the included case-control studies can be found in Annex IV). Lifelong job and smoking histories were available for all subjects. Self-reports of physician-diagnosed silicosis were collected by in-person or next-of-kin interviews at the clinic. Occupational exposure to quartz was estimated using a quantitative general-population job-exposure matrix (JEM) especially developed for the SYNERGY project, called the SYN-JEM (90, 211). Quantitative respirable quartz exposure estimates were derived for each job title, region, and year combination (90). The SYN-JEM uses 23 640 historical personal quartz measurements derived from the ExpoSYN exposure database. The authors reported ORs for lung cancer mortality ranging from 1.15 (95% CI 1.04–1.27) for the lowest exposure category (> 0–0.39 mg/m^3-years) to 1.45 (95% CI 1.31–1.60) for the highest exposure category (≥ 2.4 mg/m^3-years). Furthermore, cumulative respirable quartz exposure was associated with increasing lung cancer risk (p-trend < 0.01) even in the absence of silicosis (p-trend < 0.01, using continuous exposure data) and in current, former, and never smokers (p-trend < 0.01, using continuous exposure data).

9.2.2.1 Exposure assessment

Ideally, exposure measurements would be used from the population under study. However, such measurements are usually not available in retrospective population-based epidemiological studies. Therefore, an exposure database was developed for the SYNERGY project, called the ExpoSYN. This database contains measurement data derived from national databases, industry-specific or exposure-specific multinational databases, and measurement data from research institutes or research groups from across Europe and Canada. Only individual exposure measurement data were used. The results of the historical personal crystalline silica measures were combined with the exposure ratings derived from the Dom-JEM, so that the exposure assessment would not exclusively be based on measurements. The Dom-JEM is a semi-quantitative general population JEM using 5-digit ISCO 1968 [International Standard Classification of Occupations 1968 (126)] job-codes and intensity scores based on assumed prevalence and intensity of exposures as judged by three experts (211).

For RCS (93% of all measurements contained solely quartz) 34 017 personal exposure measurements corresponding to 23 640 datapoints for RCS were available for the statistical analyses. For the analysis in the publication by Ge *et al.* (2020) only data from quartz measurements were used (90). Exposure measurements covered the time period between 1951 and 2009 (but data before 1960 was scarce). The ExpoSYN database contains measurement data on RCS from 13 European countries (Denmark, Finland, France, Germany, Italy, the Netherlands, Norway,

Poland, Romania, Slovakia, Sweden and the UK) and Canada (210, 211). In Annex IV an overview of the available data in the ExpoSYN database can be found.

It can be questioned whether measurements in the ExpoSYN database are representative of the general working situation and if they reflect true occupational exposure levels. However, countries with few measurements could use the data on similar jobs and industries in neighbouring countries (210). The exposure estimates used by Ge *et al.* (2020) may be affected by some exposure misclassification, which makes them less accurate than estimates from an industrial-based cohort study with complete and detailed work history and extensive historical exposure measurements. However, the misclassification in the study by Ge *et al.* (2020) would likely be nondifferential with respect to case status and would result in a bias of risk estimates toward the null (90). In addition, the robustness of the exposure estimates has been tested, and appeared to be plausible for exposure levels described in literature. Further tests on the possible effects of some crucial decisions taken in the development of the SYN-JEM showed no critical changes in cumulative exposure levels used in the SYNERGY project (207). In addition, a recent publication by Ohlander *et al.* (2024) tested the different dimensions of the SYN-JEM regarding to job-specific estimates, region-specific estimates and prior expert ratings, to see how variations in these dimensions may influence risk estimates. The exposure-response relationships between lung cancer and RCS exposure were only marginally influenced by varying the dimensions of SYN-JEM. The SYN-JEM as applied by Ge *et al.* (2020) provided the best results and model fit (195).

In the publication by Ge *et al.* (2020) of all respirable quartz measurements, 41% was below the limit of detection (LOD). For these samples a single imputation as described by Lubin *et al.* (2004) was used. This method uses a random fill-in value for each measurement below LOD using the maximum likelihood estimation from the log-normal distribution of the data, assuming that the missing data follow the same distribution as the observed data (161). Analyses of the SYNERGY data using a multiple imputation method did not alter the results (212). For 4% of the measurements no LOD was available and for these measurements a LOD of 0.01 mg/m^3 was assumed, which was the mean level of all known measurement LOD values (211).

Availability of full-shift measurements in the ExpoSYN exposure database was limited, but by correcting for sampling duration (8-hour work shift equals 480 minutes) the exposure estimates could be standardised to 8-hour work-shift exposure levels (207, 211). Cumulative exposure estimates were calculated as the sum of the products of modelled exposure intensities and years of employment for all jobs over a subject's entire working life (90).

9.2.2.2 Smoking history

One of the strengths of the SYNERGY project is the availability of lifelong smoking history for every subject in the pooled analysis. Smoking information was predominantly collected through interviews with the subjects themselves (92% of

cases, 94% of controls). Smokers were defined as subjects who smoked more than one cigarette per day for more than one year. A current smoker was defined as someone who had smoked for more than 1 year and still smoked in the year of the interview or in the year before. Former smokers were defined as persons who had smoked for at least 1 year but quit smoking at least 2 years before the date of the interview. Subjects who had smoked for less than 1 year were considered occasional smokers and were treated as never smokers in the analyses.

Information on smoking history included the number of cigarettes smoked per day in calendar-year periods and the age at smoking cessation for former smokers. Pack-years were calculated as the sum of the products of smoking duration in years and average smoking of 20-cigarette packs per day (90, 268). Ge *et al.* (2020) have performed stratified analyses for smoking status (never, former, or current smoker) and investigated interactions between RCS exposure and smoking on risks of overall lung cancer and lung cancer subtypes. The stratified analyses showed that regardless of smoking status [for the lowest cumulative exposure category (> 0–0.39 mg/m^3-years), never-smokers OR 1.17 (95% CI 0.85–1.57) vs current smokers OR 1.19 (95% CI 1.03–1.39); for the highest cumulative exposure category (≥ 2.4 mg/m^3-years), never-smokers OR 1.40 (95% CI 1.03–1.86) vs current smokers OR 1.39 (95% CI 1.20–1.62)], increasing cumulative silica exposure was associated with increased risk of lung cancer. Interactions beyond the additive model between smoking and occupational respirable quartz exposure were observed for overall lung cancer (RERI 2.34, 95% CI 1.85–2.83) (90).

9.2.2.3 Co-exposures

The SYNERGY project was designed to investigate the joint effects of well-known lung carcinogens in the development of lung cancer, which allowed Ge *et al.* (2020) to control for the effects of potential confounders like smoking and exposures to other occupational lung carcinogens. As an alternative to adjusting for co-exposures to other lung carcinogens with ever employment in a "List A jobs", the authors also performed sensitivity analyses controlling for ever exposure to diesel engine exhaust, hexavalent chromium, asbestos and PAH in a categorical exposure model. The results were similar, with an OR of 1.12 (95% CI 1.01–1.24) for the lowest cumulative exposure category (> 0–0.39 mg/m^3-years) compared to an OR of 1.15 (95% CI 1.04–1.27) for the same exposure category in the main analysis. The so-called "list A jobs" are occupations with well-known occupational lung cancer risks (e.g., welders, long-distant truck drivers, boiler operators). The sensitivity analyses excluding subjects with ever-employment in mining and adjustment for list A jobs also gave similar results compared to the main results (90).

9.2.2.4 Other considerations

In the pooled analysis by Ge *et al.* (2020), the silicosis status was known for 50% of the study population which allowed the authors to perform sub-analyses for lung cancer cases with and without silicosis. The results were similar for subjects without silicosis (OR 1.22, 95% CI 1.07–1.40 for the lowest cumulative exposure category

> 0–0.39 mg/m^3-years) compared to the results of the main analyses (OR 1.15, 95% CI 1.04–1.27) (90). Some other recent studies also reported increased risk of lung cancer among cases exposed to RCS but without presence of silicosis (158, 214). In addition, recent evaluations by ANSES (2019), ATSDR (2019), and NFA (2021) also conclude that there is an association between RCS and lung cancer in the absence of silicosis (10, 13, 226).

9.2.3 Conclusions on suitable studies for the derivation of cancer risk estimates

In conclusion, for lung cancer data of two pooled analyses are available: One pooled analysis based on industrial-based cohort studies and a pooled analysis based on population-based case-control studies. These two pooled analysis studies are very different in their setting, type of included studies, exposure assessment, health assessment, and statistical approaches.

9.2.3.1 Study setting

The pooled analysis on industrial based cohorts by Steenland *et al.* (2001) (245) is predominantly set in non-European countries and includes types of industries that are not very relevant for the Dutch and/or Nordic work situation, such as gold mining and diatomaceous earth industry. More relevant is the pooled analysis based on case-control studies conducted by Ge *et al.* (2020) (90), which predominantly consists of case-control studies conducted in Europe. The ExpoSYN exposure database also predominantly contains exposure measurement data from European countries (210).

9.2.3.2 Study design

Also, the pooled analysis studies differ in the type of studies they included in the analyses, with respect to their study design. The pooled analysis by Steenland *et al.* (2001) (245) uses industrial-based cohort studies whereas Ge *et al.* (2020) (90) performed a pooled analyses on population-based case-control studies. Cohort studies and case-control studies are both suitable designs for investigating relationships between exposure to a substance and a disease of interest. However, the setup of the studies is different. A cohort study entails the recruiting of healthy subjects with and without exposure to the substance under study. Individuals exposed to the substance under study are followed over time and their health status is observed and recorded during the follow-up of the study. To compare the occurrence of disease in exposed subjects with its occurrence in non-exposed subjects, the health status of a group of non-exposed individuals is followed in the same way as that of the exposed individuals. In an industrial-based cohort, non-exposed individuals are often office workers or others employed by the same company or at the same worksite but not exposed to the substance under study (49, 50).

A case-control study entails all (or a sample of) incident cases diagnosed with the disease under study in the source population over the risk period. The cases' job history, exposure(s), and other characteristics (smoking or other potential confounders), prior to onset of the disease, are recorded retrospectively through

interviews, questionnaires and sometimes by means of records and other sources. A comparison group consisting of individuals without the disease under study (controls) is assembled as well, often from the general population, and their information is gathered the same way (49, 50). The pooled analysis by Ge *et al.* (2020) predominantly used general population controls, but hospital controls as well (90). The main difference for the pooled analysis by Ge *et al.* (2020) from other case-control studies is that the authors used modelled exposure estimates based on personal exposure measurements, limiting the possibility of bias in the exposure assessment.

Because of the differences in the study designs of the individual studies which were included in the pooled analyses, there are differences in the approach to exposure assessment, health assessment, and statistical analyses. This can be demonstrated by the measure of association used. In a cohort study, the relative risk (also named risk ratio, RR) is used as a measure of association. This is the ratio of the risk of the disease under study among the exposed subjects versus the risk of the disease under study in the non-exposed subjects. The measure of association between exposure and occurrence of disease in case-control studies is the OR. This is the ratio of odds of exposure in diseased subjects to the odds of exposure in the non-diseased (49, 50).

9.2.3.3 Other notifications

In their 2012 evaluation, the IARC concludes that the strongest evidence supporting the carcinogenicity of RCS results from the pooled analysis by Steenland *et al.* (2001), which demonstrated a clear exposure-response relation that was confirmed by several meta-analyses (124). Like the committees of DECOS and NEG, OSHA (2016) and NFA (2021) have considered the study by Steenland *et al.* (2001) as a key study in their evaluations as well. OSHA reports that most of the 10 cohort studies included in the pooled analysis by Steenland *et al.* (2001) relied in part on particle count data and the use of conversion factors to estimate exposures of workers to mass RCS. This may have lead to uncertainty in the risk estimates (196). The NFA (2021) also noted some discrepancies in the statistical models OSHA (2016) applied for Steenland *et al.* (2001), compared to the other key studies considered by the OSHA: the estimated concentration levels deviated about a 100-fold. Furthermore, the models for the Steenland *et al.* (2001) study deviated substantially from linearity at the higher exposure levels due to the use of log cumulative exposure. In addition, the NFA noted that in the original publication by Steenland *et al.* (2001) and a corrigendum published later by the authors, different units of the log-linear model were reported, ln(mg/m^3-years+1) and ln(mg/m^3-days+1), respectively. This has led to uncertainty about which model is correct (226).

Furthermore, the committees are of the opinion that the method applied by Steenland *et al.* (2001) to log-transform the exposure data is questionable, as adding 1 mg/m^3-years to all the exposures minimises the influence of the studies with the lowest exposure levels.

9.2.3.4 Conclusions on suitable studies

Despite the differences, both pooled analyses report an increased risk of lung cancer among individuals occupationally exposed to RCS, and thus support the growing evidence of a causal relationship between exposure to RCS and lung cancer.

Considering the two pooled analyses by Steenland *et al.* (2001) (245) and Ge *et al.* (2020) (90), the committees prefer the pooled analysis conducted by Ge *et al.* (2020) as the key study. The committees are of the opinion that the study was well conducted, because it is a large study with almost 40 000 participants and had the possibility to control for potential confounding by smoking and co-exposures to other lung carcinogens in the workplace. In addition, the pooled analysis by Ge *et al.* (2020) (90) contains extensive and particularly more recent exposure measurement data (contains exposure measurement data from 1960 until 2009), compared to the pooled analysis by Steenland *et al.* (2001), where most exposure measurement data stem from the 1970s and 1980s, with only one study covering data until 1996 (245). Therefore, the estimates based on the study by Ge *et al.* (2020) provide a better reflection of current exposures in workplaces. Moreover, the study population in Ge *et al.* (2020) is more representative of the Dutch and Nordic work populations as both the underlying case-control studies and the exposure measurements were mainly carried out in Europe. Finally, the committees have some concerns about the exposure characterisation, the exposure-response estimates and statistical methods used by Steenland *et al.* (2001) in their pooled analysis.

9.3 Point of departure in the derivation of cancer risk estimates

For the recommendation of a health-based OEL, the mode of action by which RCS can induce lung cancer must be ascertained because this determines which approach must be used. Generally, two approaches are possible: a threshold-based approach for indirect-acting genotoxic or non-genotoxic substances, or a non-threshold (risk-based) approach for direct-acting genotoxic substances. The DECOS subcommittee concluded that the carcinogenic potential of RCS primarily results from genotoxicity by indirect mechanisms, related to damage of lung cells with consequently inflammation and a tumour-promoting inflammatory microenvironment. However, the possibility of a direct genotoxic mechanism involving particle-generated ROS, cannot be excluded (see also Annex VI). Because a direct genotoxic mechanism cannot be excluded, the committees take a precautionary approach based on the DECOS guidelines (104, 105), as well as the recommendations by ECHA (2019) (77), NFA (2021) (226), and NEG (2022) (122), all stating that if the decision on a threshold or a non-threshold mode of action is not easy to make, then the assumption of a non-threshold approach would be a prudent choice. Thus, the committees have decided on a non-threshold (risk-based) approach for RCS, in which OELs in the form of HBC-OCRVs will be calculated.

9.4 Calculation of cancer risk estimates

According to the DECOS guideline, an HBC-OCRV is an exposure level (a concentration in the breathing zone) corresponding with a predefined (set by the Dutch authority) extra risk of developing cancer. Occupational cancer risk values are expressed as a lifetime risks of additional cases of cancer due to occupational exposure, based on a working period of 40 years (8 hours per day, 40 hours per week), in relation to the disease risk of the general population which is not occupationally exposed (104, 105). The predefined extra risk levels of cancer due to occupational exposure (HBC-OCRVs) are as follows:

- The target risk level or low risk level: 4 additional cases of cancer due to occupational exposure over a 40-year working life period per 100 000 exposed workers.
- The prohibition risk level or high risk level: 4 additional cases of cancer due to occupational exposure over a 40-year working life period per 1 000 exposed workers.

This means that the HBC-OCRVs are based on 4 extra deaths of lung cancer due to 40 years of occupational exposure to RCS, which are added to the number of lung cancer deaths per 1 000 (4×10^{-3}) and 100 000 (4×10^{-5}) exposed workers.

In addition, the committees prefer using life-table analyses to estimate the excess risk of cancer. A life-table describes, for each age, the mortality and survival patterns of subjects in a fictitious cohort followed up from birth or entry into the workforce. Age-specific all-cause and cancer-specific mortality rates are then used to estimate the probability of dying and the probability of dying from (or contracting) cancer in specific age intervals conditional on being alive at the start of the interval. Starting with two hypothetical cohorts of (all) exposed and non-exposed subjects, these calculations can be used to estimate the cumulative risk of death from cancer in each of the cohorts. This requires specification of an exposure scenario, e.g., exposure to 0.001 mg/m^3 RCS for 8 hours a day, for 5 days a week from age 20 to 60, and a risk function that links an appropriate exposure metric derived from that scenario (typically cumulative exposure) to an increase in the hazard rate for the selected cancer outcome. This also makes it possible to account for time- and age-dependent factors in the development of cancer, such as latency.

The excess risk of death from cancer due to the exposure can then be estimated by subtracting the cumulative risk of cancer in the non-exposed cohort from that in the exposed cohort. Estimation of the cumulative exposure associated with a specific excess risk level is then performed iteratively, starting from an arbitrary exposure level, by comparing the estimated excess risk to the target risk and adjusting the exposure (either upwards or downwards) until convergence. In practice, a general optimisation (hill-climbing) algorithm is used, and convergence is achieved in 5 or 6 iterations.

More detailed information on the use of this analysis is provided in the DECOS "Guideline for the calculation of occupational cancer risk values for carcinogenic compounds" (104).

Information on the average population size and number of deaths from all causes and from lung cancer for the EU were obtained from Eurostat 2008 (86), and used to estimate all-cause and cancer-specific mortality rates.

Excess risk calculations were truncated at the age of 100 years, assuming that deaths occurring beyond this age are unlikely to be related to occupational exposure to RCS (104).

To calculate the excess risk level of lung cancer because of occupational exposure to RCS, the committees used the slope (ß) derived from the linear model equation that fitted the exposure-response relationship best, as described in the publication by Ge *et al.* (2020) (90). This best fitting model was based on unlagged cumulative exposure to respirable quartz. The continuous model with untransformed exposure showed that every 1 mg/m^3-years increase in cumulative respirable quartz exposure increased the lung cancer risk by a factor of 1.06 (OR) (95% CI 1.04–1.08) (90).

The concentrations of RCS corresponding to the relative risks can be calculated using the following (linear) model equation that describes the exposure-response relationship:

$$lnRR = slope\ (\beta) \times exposure$$

In this equation lnRR is the natural logarithm (ln) of the relative risk (RR); the slope (β) is 0.05827, which is the natural logarithm of the OR of 1.06; and the exposure is expressed as the cumulative exposure to respirable quartz (mg/m^3-years) after 40 years of occupational exposure.

An HBC-OCRV (expressed as an average concentration) is obtained by dividing the cumulative exposure concentration by 40 (years). Applying the estimated relative risks in this equation, the committees estimated that the HBC-OCRVs of respirable quartz exposure for the EU correspond to a prohibition risk level or high risk level of 4 extra lung cancer deaths per 1 000 workers, for 40 years of occupational exposure, equals to 0.0363 mg/m^3, see also Table 9.

Because the HBC-OCRVs were estimated using a life-table analysis based on epidemiological data, the cancer risk values for the target risk level (or low risk level) and prohibition risk level (or high risk level) deviate from the assumed factor 100 difference between the two recommended cancer risk values, despite the fact that a linear model equation was used.

Table 9. Lung cancer excess lifetime risk associated with 40 years of occupational exposure to respirable quartz based on the data by Ge *et al.* (2020) (90).

Based on EU mortality rates	Truncated at 100 years
4/100 000 (target risk level / low risk level)	0.00038 mg/m^3
4/1 000 (prohibition risk level / high risk level)	0.0363 mg/m^3

The HBC-OCRVs are expressed as 8-hour TWA exposures and based on exposure data for respirable quartz (see also Annex VII). HSE (2002), OSHA (2016), ANSES (2019) and NFA (2021) reported that the risk estimates in studies with either exposures to primarily cristobalite or primarily quartz are similar. Therefore, there is no reason to differentiate according to the specific crystalline silica polymorphs (10, 117, 196, 226).

9.4.1 Remarks on the calculated HBC-OCRVs

The calculated HBC-OCRVs are reported as absolute values, however these values may be influenced by some underlying uncertainties in the calculations and assumptions made by the committees. For instance, for the risk calculations it was assumed that a worker is exposed to the same level of RCS during an entire working life of 40 years. In Chapter 4 the committees addressed the large variability in exposure levels, and the general decline in these exposure levels in the last 60 years. The assumption of the same exposure level across time may not fully capture the complexity of long-term exposure to RCS in relation to a chronic disease outcome such as lung cancer. Still, little is understood about the relative importance of intensity, duration, and timing of exposures to RCS in relation to occurrence of lung cancer. The pooled analysis by Ge *et al.* (2020) (90) uses a cumulative exposure metric which bundles duration with intensity. Exposure metrics for average exposure even removes the influence of duration, but both cumulative and average exposure metrics lack information regarding the time-varying intensity of exposure. So, cumulative exposure may be an attractive metric in terms of implementation and interpretation, compared to an average exposure metric, but does not take full advantage of the often available detailed work-history data with temporal resolution on the annual level (185, 249). Neophytou *et al.* (2018) therefore explored the relative contributions of intensity, duration, and timing of exposure to RCS on lung cancer. The authors conclude that both timing and intensity of exposure are factors that contribute to the overall relationship between RCS exposure and lung cancer (185).

Another assumption is that after a 40-year working life the workers maintain the accumulated exposure level they have gathered throughout their working life. Clearance of RCS particles takes place in the lungs through macrophages and via urine (see also Chapter 5), but to what extent and what that means for developing adverse health effects is still not fully elucidated.

Based on the statistical analyses presented by Ge *et al.* (2020) (90), the best fitting model was an unlagged model using cumulative exposure. However, it is unlikely that lung cancer can occur shortly after exposure. It generally takes 10 to 30 years to develop lung cancer. However, other recent occupational studies have applied no lag and lag-times varying between 5 to 25 years (89, 158, 239, 263). Liu *et al.* (2013) applied 0- (or unlagged), 5-, 10-, 15-, 20-, and 25-year lags and used minimised Akaike criterium to select the best fitting model. The 25-year lag had the lowest Akaike's criterium and was therefore considered to be the best fitting model, but results from analyses with unlagged, 15-, and 25-year lag-times showed no big

differences in the presented risk estimates (158). Other studies also reported little or no differences in presented risk estimates for unlagged and lag times applied (89, 239, 263). Vacek *et al.* (2011) even report reductions in the ORs for lag-times of 15 or 20 years. Unlagged and 10-year lag-time fitted the data well but gave similar results (263).

9.4.2 Comparison of calculated HBC-OCRVs with other recommended OELs

The current OEL for RCS in the Netherlands is 0.075 mg/m^3, for quartz, cristobalite and tridymite (68, 186). In Denmark and Sweden, the current OEL is 0.1 mg/m^3 for quartz and 0.05 mg/m^3 for cristobalite and tridymite (12, 186, 250). In Finland and Norway, the current OELs are 0.05 mg/m^3 for all three polymorphs (11, 186, 236). For the Netherlands the current OEL is based on the results of an American study among granite workers and silicosis as the critical health effect. For lung cancer no increased mortality or exposure-response relationship could be established (see also Annex III for more detailed information) (68). In the current DECOS-NEG evaluation of RCS, the committees recommend HBC-OCRVs for lung cancer of 0.0363 mg/m^3 and 0.00038 mg/m^3 as prohibition (or high) risk level and target (or low) risk level respectively, for the Netherlands and Nordic countries. NFA (2021) presented health-based risk estimates for lung cancer (expected excess lung cancer risk is 1:1 000 at 0.004 mg/m^3, 1:10 000 at 0.0004 mg/m^3 and 1:100 000 at 0.00004 mg/m^3) (226) that seem somewhat higher but are quite similar when taking the different risk levels into consideration. However, the NFA has based their evaluation and recommendation on other key studies (and defaults). A summary of this evaluation and that of others can be found in Annex III. In short, several organisations have recommended or established an OEL of 0.05 mg/m^3 for RCS (188, 196). Only the ACGIH has recommended a lower OEL of 0.025 mg/m^3 for quartz and cristobalite than in the current DECOS-NEG evaluation (4, 5). A few other organisations were unable to recommend an OEL: the SCOEL (2003) (232) could not identify a clear threshold for the development of silicosis, and the ATSDR (2019) (13) could not indicate a no effect level to establish a minimal risk level (MRL).

9.5 Conclusion and recommendation

The committees have estimated the HBC-OCRVs for lung cancer using data from the publication by Ge *et al.* (2020) (90). The committees have estimated that the HBC-OCRVs, which correspond to predefined (set by the Dutch authority) extra risk of developing cancer, for respirable quartz in the breathing zone, are as follows:

- 4 additional deaths of lung cancer per 100 000 workers (4×10^{-5}), for 40 years of occupational exposure, equals to 0.00038 mg/m^3 (target risk level or low risk level).
- 4 additional deaths of lung cancer per 1 000 workers (4×10^{-3}), for 40 years of occupational exposure, equals to 0.0363 mg/m^3 (prohibition risk level or high risk level).

These HBC-OCRVs are expressed as 8-hour TWA exposures of respirable quartz. There is evidence from epidemiological studies that quartz, cristobalite and tridymite have generally similar toxicity and carcinogenic potential (10, 196, 226, 245). The committees therefore recommend the same HBC-OCRVs for all three RCS polymorphs: quartz, cristobalite and tridymite.

9.6 Skin notation

A skin notation for a substance is recommended when data indicate a substantial contribution of dermal exposure to systemic adverse health effects, on which a health-based OEL is based. In the case of RCS, the primary route of exposure is inhalation, so no substantial dermal absorption is expected. Therefore, the committees do not recommend a skin notation.

9.7 Groups at extra risk

Individuals with underlying lung conditions, such as asthma, emphysema, or tuberculosis, may be more susceptible to adverse respiratory effects of RCS exposure. Furthermore, the risk of lung cancer due to exposure to RCS may be influenced by smoking (13). Therefore, smokers may be at extra risk as well.

10. Research needs

Although the association between exposure to RCS and health effects such as silicosis and lung cancer has been well established, there are still gaps in knowledge. For silicosis there are research needs concerning the onset and pathological pathways of silicosis because of exposures in modern industries, in particular artificial stone manufacturing. There have been numerous case reports of severe forms of silicosis, affecting relatively young workers, after relatively short work durations and with an aggressive disease progression. In addition, to improve early detection and more accurate diagnosis of silicosis or other RCS-related pulmonary disease, further development of highly sensitive and practical diagnostic methods is needed.

In addition, other health effects associated with RCS exposure, such as COPD, renal diseases, cardiovascular diseases, and autoimmune diseases need further research to establish quantitative exposure-response relationships adjusted for all major potential confounders. The relationship between RCS exposure and renal diseases probably also suffers from underreporting due to the lack of a biopsy for a good diagnosis and the non-specific clinical manifestations of the disease. For some specific types of cardiovascular diseases with lower lethality rates, the use of morbidity data to investigate the relationship with RCS exposure would be more appropriate.

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Annexes

I. Literature search

The literature search has been updated until June 2023 and has been carried out using PubMed and SCOPUS. The following keywords and combinations of keywords were used:

Keywords substance: CAS registry number, crystalline silica, quartz, cristobalite, tridymite, silica dust(s), quartz dust(s), cristobalite dust(s), tridymite dust(s)

Keywords occupational exposure: process(es), processing, manufacturing, factory, industry, mining, quarrying, worker(s)

Keywords health effects:

- [General toxicity] toxicity, occupational exposure, adverse health effects, health damage, dose-effect relationship, dose-response relationship, exposure-effect relationship, exposure-response relationship, hazard assessment, risk assessment, cardiovascular effects, ischemic heart disease, acute toxicity, chronic toxicity, acute effects, chronic effects, pulmonary effects, pulmonary function, pulmonary toxicity, nephrotoxicity, kidney effects, nephritis, nephrosis, renal disease, inhalation, long term exposure, short term exposure, lung disease, silicosis, silico-tuberculosis, pneumoconiosis
- [Carcinogenicity] cancer, carcinogenicity, tumourigenesis, cancer mortality; adenoma, carcinoma, occupational carcinogenesis

Keywords type of studies: cohort(s), epidemiological study, meta-analysis, meta-analyses, cross-sectional, case-control, case-referent, nested case-control, case-cohort, pooled analysis, pooled analyses, carcinogenicity study, animal study, animal experiment, epidemiological data, epidemiology, cohort analysis.

The literature search has resulted in a literature database with almost 500 references. Given the overload on information, the variety in potential health end points, study settings and designs, the committees have made restrictions. This advisory report focused on previous evaluations by other organisations and epidemiological studies preferably published pooled and meta-analyses on the selected health outcomes for the risk analysis. As reported in the guidance (105), the committees prefer to rely on a pooled or meta-analyses as key study if available. A summary of relevant pooled analyses on lung cancer and silicosis is provided in Annex IV. To demonstrate the large amount of data available, an overview of individual epidemiological studies with quantitative data on crystalline silica is presented on the next pages. This overview also shows the large variety in study settings and potential co-exposures. Only studies that used quantitative data on RCS are included in this overview, so it is not a complete overview of all studies and data on RCS.

Table Ia. Overview of individual quantitative exposure-response studies.

Study name	Study location	Substance(s)	Type of industry	Remarks	Reference
Vermont granite workers	USA, Vermont	Granite	Opencast mining		(14, 63, 66, 95-97, 261, 263, 265)
South African gold miners	South Africa	Gold	Underground mining		(111-113)
Ontario hard rock miners	Canada, Ontario	Gold, uranium	Underground mining	21 mines; nickel/copper mines excluded	(179, 180, 264)
South Dakota gold miners	USA, South Dakota	Gold	Underground mining		(35, 243, 244)
Colorado miners	USA, Colorado	Molybdenum, lead, zinc and gold	Underground mining	Molybdenum largest mine, lead, zinc and gold only smaller operations	(144)
UK pottery workers	UK	Pottery	Processing		(57-59, 165)
Diatomaceous earth workers	USA, California	Diatomaceous earth	Opencast mining		(46-48, 89, 120, 184, 185, 202, 222)
American sand workers	USA, North America	Sand	Opencast mining	9 plants	(121, 164, 166, 219)
UK coal miners	UK	Coal	Underground mining		(170)
Scottish coal miners	UK, Scotland	Coal	Underground mining		(33, 169)
Chinese metal mines and pottery	China	Pottery, iron/copper, tin, tungsten	Processing, underground and opencast mining	9 pottery factories; 20 mines, 6 iron/copper mines, 4 tin mines, 10 tungsten mines	(51-56, 61, 102, 148, 157-159, 248, 269, 283)
UK sand workers	UK	Sand	Opencast mining		(30, 31)
American sand workers	USA	Sand	Opencast mining		(228, 246, 247)
Granite workers	Finland	Granite	Processing and opencast mining		(136, 140-142)
Hong Kong granite workers	China, Hong Kong	Granite	Opencast mining		(187)
Silicon carbide workers	Norway	Silicon carbide	Processing	Heating of quartz sand	(34, 88)
UK clay workers	UK	Clay	Processing		(160)

Table Ia. Overview of individual quantitative exposure-response studies.

Study name	Study location	Substance(s)	Type of industry	Remarks	Reference
Iron foundry workers	USA, Midwestern	Iron	Processing		(224)
Aluminium foundry workers	Sweden	Aluminium	Processing		(272)
Sweden iron foundry workers	Sweden	Iron	Processing		(7, 8, 87, 271)
Sweden iron miners	Sweden	Iron	Underground and opencast mining		(23, 24, 108)
Miners and stone workers	Sweden	Several	Processing, underground and opencast mining	Miners, well borers, dressing plant workers, and stone workers	(270)
South African gold miners	South Africa	Gold	Underground mining		(60, 138, 139)
Australian gold miners	Australia	Gold	Underground and opencast mining		(67)
German uranium miners	Germany	Uranium	Underground mining	Wismut-cohort	(64, 91, 146, 168, 239)
Miners and stone quarrying	Italy, Sardinia	Granite, coal, lead and zinc	Underground and opencast mining	Granite quarrying, coal, and metals mining	(36-38)
Ceramic and quarry workers	Germany	Several in ceramics, stone industry	Processing and opencast mining	Stone quarrying	(258)
Porcelain workers	Germany	Porcelain	Processing		(21, 22, 174, 181)
General population	Finland	Several	Processing, underground and opencast mining	Used Fin-JEM	(217)
Construction workers	The Netherlands	Construction	Processing		(256, 257)
South African gold miners	South Africa	Gold	Underground mining		(221)
American sand workers	USA	Sand	Processing and opencast mining	40 plants in 22 states	(220, 262)

II. Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ANCA	anti-neutrophil cytoplasmic antibody
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
ATSDR	Agency for Toxic Substances and Disease Registry
ATX	autotaxin
CEN	European Committee for Standardization
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ECHA	European Chemicals Agency
DECOS	Dutch Expert Committee on Occupational Safety
DFG	Deutsche Forschungsgemeinschaft
FEV_1	forced expiratory volume in 1 second
FT-IR	Fourier transform infrared spectrometry
FVC	forced vital capacity
HBC-OCRV	health-based calculated occupational cancer risk value
HBR-OEL	health-based recommended occupational exposure limit
HIV	human immunodeficiency virus
HR	hazard ratio
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IGF	insulin-like growth factor
IHD	ischaemic heart disease
IL	interleukin
IRR	incidence rate ratio
ISCO	International Standard Classification of Occupations
ISO	International Organization for Standardization
JEM	job-exposure matrix
LOD	limit of detection
MAK	Maximale Arbeitsplatz-Konzentration
MDHS	Methods for the Determination of Hazardous Substances
MRL	minimal risk level
MSHA	Mine Safety and Health Administration
NEG	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

NFA	National Research Centre for the Working Environment
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbons
PEL	permissible exposure limit
RCS	respirable crystalline silica
REL	recommended exposure limit
RERI	relative excess risk due to interaction
RNS	reactive nitrogen species
ROS	reactive oxygen species
RR	relative risk
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCOEL	Scientific Committee on Occupational Exposure Limits
SIR	standardised incidence ratio
SMR	standardised mortality ratio
TGF	transforming growth factor
TLV	threshold limit value
TNF	tumour necrosis factor
TWA	time-weighted average
VIS	colorimetric spectrophotometry
WHO	World Health Organization
XRD	X-ray diffraction

III. Occupational exposure limits and recommendations of health-based risk estimates

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
DECOS, Ministry of Social Affairs and Employment (1992); (68)	Quartz, cristobalite, tridymite	Silicosis	A dose-response relationship between exposure to respirable quartz and the relative risk in attaining silicosis and tuberculosis, as found in a proportional cohort mortality study (66). The results suggest that the cut-off point of exposure lies at 0.075 mg/ m^3 which could be designated as the NOAEL for silicosis. The results have been confirmed in a follow-up study using SMR and additional deaths (63). No dose-response or increased mortality for lung cancer was found.	0.075 mg/m^3 8-h TWA	*USA Vermont granite workers:* Davis *et al.* (1983) (66), Costello and Graham (1988) (63).	Previous report on RCS by DECOS.
ACGIH (2001); (2)	Quartz	Silicosis and fibrosis	ACGIH recommends a TLV-TWA of 0.05 mg/m^3 for the α-quartz form of crystalline silica. This is a reduction by a factor 2 of the previously recommended value of 0.1 mg/m^3. In the recognition that workers exposed to levels near 0.1 mg/m^3 can have undetected (by chest X-ray) fibrosis, as was demonstrated in an autopsy study among miners. This study by Hnizdo and Sluis-Cremer (1993) (113) showed that a large percentage of moderate to marked silicotics at autopsy were not detected radiologically. It is this concern for fibrosis of silicosis and the role of fibrosis as a risk factor for lung cancer, that caused ACGIH to recommend the lowering of the TLV from 0.1 mg/m^3 to 0.05 mg/m^3.	0.05 mg/m^3 8-h TWA	*USA Vermont granite workers:* Graham *et al.* (1991) (95). *South African gold miners:* Hnizdo and Sluis-Cremer (1993) (113). *Ontario hard rock miners:* Muir *et al.* (1989) (179). *USA South Dakota gold miners:* Steenland and Brown (1995) (244). *USA Colorado miners:* Kreiss and Zhen (1996) (144).	Withdrawn in 2006. ACGIH recognises that this value is based on epidemiological uncertainties in the measurements of historical exposures and in the detection of silicosis cases.

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
ACGIH (2001); (1)	Cristobalite	Fibrosis	Animal studies show that cristobalite produces a more severe response than quartz and that the fibrosis elicited was diffuse rather than nodular. Because only the respirable fraction of cristobalite dust is toxicologically significant, a TLV-TWA of 0.05 mg/m^3, measured as respirable particulate fraction, is recommended.	0.05 mg/m^3 8-h TWA		Withdrawn in 2006.
ACGIH (2001); (3)	Tridymite	Fibrosis and silicosis	Based on very limited animal toxicity data, tridymite appears to be the most biologically active form of crystalline silica in producing pulmonary fibrosis and silicosis. Data on human responses from occupational exposure to tridymite are not available. The same TLV-TWA as for quartz and cristobalite is recommended.	0.05 mg/m^3 8-h TWA		Withdrawn in 2006.
NIOSH (2002); (188)	Crystalline silica	Silicosis and lung cancer	Until improved sampling and analytical methods are developed for RCS, NIOSH recommends an exposure limit of 0.05 mg/m^3 as a TWA for up to a 10-h workday during a 40-h workweek. NIOSH also recommends substituting less hazardous materials for crystalline silica when feasible, using appropriate respiratory protection when source controls cannot keep exposures below REL, and making medical examinations available to exposed workers.	REL 0.05 mg/m^3 10-h TWA workday during a 40-h workweek		Current sampling and analytical methods do not meet the accuracy criterion needed to quantify exposures at concentrations below the NIOSH REL of 0.05 mg/m^3.

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
SCOEL (2003); (232)	Quartz, cristobalite, tridymite	Silicosis	Epidemiological studies show that the incidence of lung cancer is increased, especially in workers with silicosis. Therefore, to reduce the cancer risk, the first step must be the prevention of silicosis. The mechanism for the development of silicosis and lung tumours in man and animals exposed to crystalline silica is still unclear. A clear threshold for silicosis development cannot be identified. It was observed that the dose-response curve for silicosis appears to be sigmoidal and that maintenance of exposure below 0.05 mg/m^3 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.	No OEL was recommended.	Based on several publications; the following were considered particularly meaningful: *USA Vermont granite workers:* Davis *et al.* (1983) (66). *Ontario hard rock miners:* Muir *et al.* (1989a, 1989b) (179, 180). *USA South Dakota gold miners:* Steenland and Brown (1995a, 1995b) (243, 244). *South African gold miners:* Hnizdo and Sluis-Cremer (1993) (113). *UK pottery workers:* Cherry *et al.* (1998) (59).	*Working lifetime doses:* 0.05 mg/m^3 (reduces silicosis prevalence to 5%). 0.02 mg/m^3 (reduces silicosis prevalence to 0.25%).
ACGIH (2010) ACGIH (2022); (4, 5)	Quartz, cristobalite	-	ACGIH lowered the TLV for crystalline silica to 0.025 mg/m^3 in 2006.	TLV 0.025 mg/m^3		The TLV for tridymite has been withdrawn entirely, the current TLV is for quartz and cristobalite only. Update in 2022 did not alter TLVs for quartz or cristobalite.

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
OSHA (2016); (196)	RCS	Lung cancer, silicosis (also morbidity) NMRD and kidney disease	OSHA is setting its revised PEL at 50 µg/m^3 based on consideration of the body of evidence describing the health risks of crystalline silica as well as on technological feasibility considerations. OSHA used, for each key study, the exposure-response risk model(s) and regression coefficient from the model(s) in a life-table analysis that accounted for competing causes of death due to background causes and cumulated risk through age 85. Risk estimates were presented in terms of lifetime excess risk per 1 000 workers for exposure over an 8-h working day, 250 days per year, and a 45-year working lifetime. OSHA finds there to be suitable exposure-response data from many well-conducted studies that permit the agency to estimate quantitative risks for lung cancer, silicosis, NMRD and kidney disease mortality, and silicosis morbidity. OSHA found clearly significant risks at the previous PEL for RCS, with excess lifetime risk estimates for lung cancer, silicosis and NMRD mortality, and silicosis morbidity each being much greater than 1 death per 1 000 workers exposed for a working life of 45 years. At the revised PEL of 0.05 mg/m^3 RCS, these estimated risks are substantially reduced (but still more than 1 death per 1 000 workers).	PEL: 0.05 mg/m^3 8-h TWA Action level: 0.025 mg/m^3 8-h TWA	Lung cancer: *USA diatomaceous earth workers:* e.g., Checkoway *et al.* (1993, 1997, 1999) (46-48). *UK pottery workers:* Cherry *et al.* (1998) (59) McDonald *et al.* (1995) (165). *USA Vermont granite workers:* e.g., Attfield and Costello (2004) (14), Graham *et al.* (2004) (96), Costello and Graham (1988) (63). *North American sand workers:* e.g., Hughes *et al.* (2001) (121) McDonald *et al.* (2001, 2005) (164, 166). *UK coal miners:* e.g., Miller and MacCalman (2010) (170). *Pooled analysis 10 industrial cohorts:* Steenland *et al.* (2001) (245). Silicosis (mortality): *Pooled analysis 6 industrial cohorts:* 't Mannetje *et al.* (2002) (252).	OSHA excludes exposures in construction from this rule, exposure to crystalline silica remains below 0.025 mg/m^3 (TWA) under any foreseeable conditions. In addition, OSHA also excludes exposures that result from the processing of sorptive clays. Based on PEL of 0.05 mg/m^3 OSHA has estimated excess lifetime risks for 45 years of exposure (through age 85 years) for: Lung cancer mortality: 5 to 23 deaths per 1 000 workers. Silicosis mortality: 7 deaths per 1 000 workers. NMRD mortality (incl. silicosis): 44 deaths per 1 000 workers.

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
					NMRD: *USA diatomaceous earth workers:* Park *et al.* (2002) (202). Renal disease: *Pooled analysis three industrial cohorts:* Steenland *et al.* (2002) (242). Silicosis (morbidity): *USA South Dakota gold miners:* Steenland and Brown (1995) (244). *Scottish coal miners:* Buchanan *et al.* (2003) (33). *China tin miners:* Chen *et al.* (2001) (56). *China tin & tungsten miners, pottery workers*: Chen *et al.* (2005) (53) *South African gold miners:* Hnizdo and Sluis-Cremer (1993) (113).	Renal disease mortality: 32 deaths per 1 000 workers. Silicosis morbidity: 20–170 cases per 1 000 workers (depending on which study was used).

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
ANSES (2019); (10)	Quartz, cristobalite, tridymite	Not specified	ANSES concludes that the current 8-h OEL value of 0.1 mg/m^3 is not sufficiently protective. For protecting the occupational population, the expert committee (CES) specifically recommends: Revising the OELs for crystalline silica, given the identified health risks, without distinguishing between the different polymorphs of silica. Current OELs in France 0.1 mg/m^3 (8-h TWA) for quartz, and 0.05 mg/m^3 (8-h TWA) for cristobalite and tridymite.	No OEL recommended but the current OEL is not sufficiently protective	Based largely on the analyses by OSHA (2016).	Crystalline silica is in France acknowledged as a hazardous chemical but not as a carcinogen. In the presence of respirable dust containing one or more forms of crystalline silica and other non-silicogenic dust, an exposure index (EI) is defined which takes into account the exposure levels to each polymorph and to non-silicogenic respirable dust and must be less than 1.
ATSDR (2019); (13)	RCS	Silicosis	Silicosis occurs at the lowest estimated cumulative exposure levels reported. Silicosis is a serious adverse effect that has the potential to result in death due to respiratory failure or lung cancer. Given the serious nature of silicosis and the uncertainties associated with identification of a no effect level, no MRLs were derived for inhaled crystalline silica for any exposure duration.	Insufficient data for MRL derivation		
HSE (2020); (119)	RCS	Not specified	Not specified.	0.1 mg/m^3 8-h TWA	Not specified.	

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
NFA (2021); (226)	Quartz, other crystalline silica polymorphs	Lung cancer (and silicosis)	The report by OSHA (2016), including the background documents (2010 and 2013) was used as basis for the NFA evaluation. The NFA 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 NFA decided to use a non-threshold approach. This is in line with the mathematical equations used for risk calculations by OSHA. For silicosis no threshold could be established in epidemiological studies. The scientific literature on the health effects of quartz is extensive; therefore, the NFA focused on the studies included in the final assessment by OSHA (2016). One additional suitable study was identified. Note, the NFA literature search was completed before Ge *et al.* (2020) was published. Because the available quantitative exposure-response data for lung cancer is more extensive, transparent, and comparable than the available data for silicosis, the risk calculations are based on lung cancer. Risk calculations are based on four studies using log-linear models. Based on four epidemiological studies with almost 60 000 participants, the NFA estimates that	Expected excess lung cancer risk: 1:1 000 at 0.004 mg/m^3, 1:10 000 at 0.0004 mg/m^3, and 1:100 000 at 0.00004 mg/m^3	*USA Vermont granite workers:* Attfield and Costello (2004) (14). *USA sand workers:* Hughes *et al.* (2001) (121). *UK coal workers:* Miller and MacCalman (2010) (170). *China metal miners & pottery workers:* Liu *et al.* (2013) (158).	Primarily based on the evaluation by OSHA (2016). NFA disregards Steenland *et al.* (2001) (245) and Rice *et al.* (2001) (222) for the final risk calculations. The pooled analysis by Steenland *et al.* (2001) was left out because of concerns regarding the exposure assessment and statistical methods applied by the authors. The study by Rice *et al.* (2001) was left out of the final risk calculations because the authors used a linear model.

Table IIIa. OEL recommendations or regulations by national and international organisations.

Organisation (year); (ref.)	Type of silica	Critical effect	Motivation	Recommendation or regulation	Key references	Remarks
			occupational exposure to 0.038 mg/m^3 crystalline silica for 45 years will cause 10 excess lung cancer cases per 1 000 exposed workers. At 0.05 mg/m^3 this would correspond to 13 excess lung cancer cases per 1 000 exposed workers. NFA recommends adopting the same OEL for quartz, cristobalite and tridymite.			

ACGIH: American Conference of Governmental Industrial Hygienists, ANSES: French National Agency for Food, Environmental and Occupational Health & Safety, ATSDR: Agency for Toxic Substances and Disease Registry, DECOS: Dutch Expert Committee on Occupational Safety, HSE: Health and Safety Executive, MRL: minimal risk level, NFA: National Research Centre for the Working Environment, NIOSH: National Institute for Occupational Safety and Health, NMRD: non-malignant respiratory diseases, NOAEL: no observed adverse effect level, OEL: occupational exposure limit, OSHA: Occupational Safety and Health Administration, PEL: permissible exposure limit, RCS: respirable crystalline silica, REL: recommended exposure limit, SCOEL: Scientific Committee on Occupational Exposure Limits, SMR: standardised mortality ratio, TLV: threshold limit value, TWA: time-weighted average.

Table IIIb. Classification on carcinogenicity by national and international organisations.

Organisation (year); (ref.)	Type of silica	Motivation	Classified as carcinogen
DECOS, Ministry of Social Affairs and Employment (1992); (68)	RCS, free silica	In animal experimentation it is shown that long-term exposure to quartz dust by inhalation or intratracheal instillation induces lung cancer in rats, but not in hamsters and probably also not in mice. Quartz is not genotoxic. It may be concluded that free silica is an epigenetic carcinogen to rats.	Yes
HCN, Committee on the Evaluation of the Carcinogenicity of Chemical Substances (1998); (103)	Quartz	The committee endorses IARC's conclusion that there is sufficient evidence for the carcinogenicity in humans of inhaled quartz from occupational sources. The strongest evidence for a causal relationship between exposure to quartz and an excess lung cancer risk was derived from studies on granite workers. Although negative epidemiological studies were encountered. The committee concludes that inhaled quartz is carcinogenic to man and mediates its carcinogenicity by a non-stochastic genotoxic mode of action, which implicates the existence of an exposure level of quartz below which the cancer risk can be considered nil.	Yes
DFG (2000); (71)	RCS	It may be concluded from the available epidemiological data that exposure to quartz or cristobalite is associated with an increase in the relative lung cancer risk. There are no epidemiological studies of the effects of tridymite. The suggestion that properties of quartz dusts can influence their carcinogenic effects is also supported by the results of animal experiments. Administration of quartz to rats by inhalation or intratracheal instillation also led to the development of lung tumours. Therefore, quartz is classified as carcinogen category 1.	Yes Category 1 for quartz and cristobalite
ACGIH (2001); (2)	Quartz	ACGIH recommends a carcinogenicity notation of A2, suspected human carcinogen, in view of conflicting epidemiological evidence and because a search of the literature for studies of non-silicotic silica workers that show increased risk for lung cancer has been unsuccessful to date. The evidence of carcinogenicity in an animal model lacks strength because the rat, the only animal in which carcinogenicity has been observed, is recognised as a poor predictor of dust effects in humans. The implication is that the presence of fibrosis in silica workers is required for there to be an increased risk for lung cancer. The A2 notation is appropriate since it appears that a threshold exposure that protects against fibrosis also will protect against lung cancer.	Yes category A2
ACGIH (2001); (1, 3)	Cristobalite and tridymite	Insufficient data available to recommend carcinogenicity notations.	No

Table IIIb. Classification on carcinogenicity by national and international organisations.

Organisation (year); (ref.)	Type of silica	Motivation	Classified as carcinogen
NIOSH (2002); (188)	RCS	NIOSH has reviewed the studies considered by IARC and ATS, and NIOSH concurs with the conclusions of IARC (1997) and the ATS (1997). These conclusions agree with NIOSH testimony to OSHA, in which NIOSH recommended that crystalline silica be considered a potential occupational carcinogen [54 Fed. Reg.* 2521 (1989)]. Further research is needed to determine the exposure-response relationship between lung cancer in non-smokers and occupational silica dust exposure and to determine why lung cancer risks appear to be higher in workers with silicosis. The cellular mechanisms for development of lung cancer after crystalline silica exposure have been explored in many experimental studies and are not yet fully understood.	Yes
SCOEL (2003); (232)	RCS	The data indicates that the relative lung cancer risk is increased for persons with silicosis. At present there are no studies available which provide an explanation of the mechanism by which lung tumours develop and the possible role of silicosis.	Yes
IARC (1997, 2012); (123, 124)	RCS	The IARC working group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs. In 2012, IARC retained the Group 1 classification for crystalline silica, concluding that there is sufficient evidence in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite, which causes cancer of the lung. There is sufficient evidence in experimental animals for the carcinogenicity of quartz dust.	Yes Group 1
OSHA (2016); (196)	RCS	OSHA concludes that the data provide ample evidence that exposure to RCS increases the risk of lung cancer among workers. - Lung cancer likely results from both genotoxic and non-genotoxic mechanisms that arise during early cellular responses as well as during chronic inflammation from exposure to crystalline silica. - There is no convincing data to demonstrate that silicosis is a prerequisite for lung cancer. - Experimental studies in rats, relevant to humans, provide supporting evidence for carcinogenicity. - Any threshold for an inflammatory response to RCS is likely several times below the final PEL of 0.05 mg/m^3. Thus, OSHA finds that RCS increases the risk of lung cancer in humans, even in the absence of silicosis, and that lung cancer risk can be increased by exposure to crystalline silica at or below the new OSHA PEL of 0.05 mg/m^3.	Yes

Table IIIb. Classification on carcinogenicity by national and international organisations.

Organisation (year); (ref.)	Type of silica	Motivation	Classified as carcinogen
ANSES (2019); (10)	RCS	Currently not recognised as a carcinogen under French Labour Code. ANSES recommends recognition of work involving exposure to crystalline silica dust as carcinogenic processes, transposed into French law.	No
ATSDR (2019); (13)	RCS	Compared to other occupational lung carcinogens, such as asbestos, the reported association between 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 provide the strongest support for the carcinogenicity of crystalline silica in the lung. These studies show increased risks of lung cancer in crystalline silica workers, with risks exhibiting dependence upon cumulative exposure. A Chinese study indicates that exposure to crystalline silica is associated with lung cancer in the absence of silicosis.	Yes
NTP Report on Carcinogens 15th revision (2021); (194)	RCS	RCS was first listed in the 6th Annual Report on Carcinogens in 1991 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals; the listing was revised to *known to be a human carcinogen* in the 9th Report on Carcinogens in 2000.	Yes

ACGIH: American Conference of Governmental Industrial Hygienists, ANSES: French National Agency for Food, Environmental and Occupational Health & Safety, ATS: American Thoracic Society, ATSDR: Agency for Toxic Substances and Disease Registry, DECOS: Dutch Expert Committee on Occupational Safety, DFG: Deutsche Forschungsgemeinschaft, HCN: Health Council of the Netherlands, IARC: International Agency for Research on Cancer, NIOSH: National Institute for Occupational Safety and Health, NTP: National Toxicology Program, OSHA: Occupational Safety and Health Administration, PEL: permissible exposure limit, SCOEL: Scientific Committee on Occupational Exposure Limits, RCS: respirable crystalline silica.

IV. Summary of relevant epidemiological data

Lung cancer - Summary of relevant pooled analyses investigating the exposure-response relation between RCS and lung cancer.

Table IV1a. Study population characteristics and study selection.

Study; (ref.)	Design and setting	Population description	Studies included	Notes
Ge *et al.* (2020); (90)	Pooled analysis. Mortality data. *14 case-control studies:* Europe (n = 13; Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, the UK) and Canada (n = 1).	16 901 lung cancer cases and 20 965 control subjects.	14 population and hospital-based case-control studies. See Table E1 in the supplementary material of Ge *et al.* (2020) for an overview of included case-control studies.	SYNERGY project See also Annex V for more details on SYNERGY.
Steenland *et al.* (2001); (245)	Pooled analysis. Mortality data. 10 industrial cohort studies: Australia (n = 1), China (n = 3), Finland (n = 1), South Africa (n = 1), and the USA (n = 4).	Pooled cohort of 65 980 workers (44 160 miners and 21 820 non-miners) with 1 072 lung cancer deaths (663 miners and 409 non-miners). Only the Chinese cohort on pottery, tin and tungsten mines included non-exposed workers (32% of the Chinese workers).	10 industrial cohort studies in: diatomaceous earth (47), gold mining (67, 111, 243), sand industry (246), granite industry (63, 142), metal mining (n = 2, tin and tungsten) (51), pottery (51). 5 cohort studies were updated for mortality since latest publications: USA gold mining (243), Finland granite industry (142), China pottery (51), and China metal mines (tin and tungsten) (51). 1 cohort study was newly developed for this pooled analysis: US sand industry (246). 7 cohort studies had updated follow-up, quantitative exposure measures by job and calendar period or were developed for this pooled analysis:	IARC multicentre study 13 cohorts with quantitative exposure data identified, 3 cohort studies excluded due to confidentiality issues (167), data unavailability (221), or incompatible data (59). Coal mines were excluded, due to low silica content in dust and different surface properties. Foundries were also excluded, due to co-exposures to PAH and others.

Table IV1a. Study population characteristics and study selection.

Study; (ref.)	Design and setting	Population description	Studies included	Notes
			Australia and USA gold mining (67, 243), USA and Finland granite industry (63, 142), USA sand industry (246), China pottery (51), and China metal mines (tin and tungsten) (51).	

IARC: International Agency for Research on Cancer, PAH: polycyclic aromatic hydrocarbons.

Table IV1b. Study methodology.

Study; (ref.)	Exposure	Exposure data	Exposure assessment	Exposure metrics	Limitations	Notes
Ge *et al.* (2020); (90)	Quartz (RCS)	Lifetime occupational histories of all subjects. 23 640 historical personal respirable quartz measures available.	Exposure measurements (n = 23 640) from ExpoSYN database were combined with exposure ratings from a general population JEM (Dom-JEM), to create the SYN-JEM. SYN-JEM is a quantitative JEM using ISCO (version 1968) for classifications of jobs.	All exposure estimates in mg/m^3. Cumulative exposure (mg/m^3-years) category; (no. of cases/controls per exposure category): > 0–0.39; (1 113/1 128) 0.4–1.09; (1 221/1 120) 1.1–2.39; (1 231/1 122) ≥ 2.4; (1 358/1 118). Average exposure estimates not indicated.	No data on other RCS exposures than quartz. No exposure measurements before 1960, exposure levels assumed to be constant on same level as 1960.	
Steenland *et al.* (2001); (245)	RCS	Original data obtained for each cohort study. 6 cohort studies had complete occupational history in the plant available. 1 cohort study had lifetime occupational history available. China cohort study on pottery and metal mines (n = 3) only one job title was available for each worker. > 2 100 000 exposure measurements available	Original data obtained for each cohort study. Gravimetric total dust, respirable dust or particle count were converted to mg/m^3 (conversion factors study specific).	All exposure estimates in mg/m^3. Cumulative exposure (mg/m^3-years) in quartiles for each cohort (no. of deaths/workers) [data derived from 't Mannetje *et al.* (2002) (253)]: *USA diatomaceous earth* (n = 749/2 342): Q1: 0.38 Median: 1.05 Q3: 2.48 Maximum: 62.71. *Finland granite industry* (n = 418/1 026): Q1: 0.84 Median: 4.63 Q3: 15.42 Maximum: 100.98. *USA granite industry* (n = 1 762/5 408):	Various sampling methods, exposure measures, time periods, and conversion factors used	Most workers were exposed to respirable quartz. Except in diatomaceous earth industry, most workers were exposed to respirable cristobalite. See also Tables 1–2 from 't Mannetje *et al.* (2002) (253) for detailed information on the exposure data in

Table IV1b. Study methodology.

Study; (ref.)	Exposure	Exposure data	Exposure assessment	Exposure metrics	Limitations	Notes
		[stationary (predominantly) and personal measurements].		Q1: 0.14 Median: 0.71 Q3: 2.19 Maximum: 50.00. *USA sand industry* (n = 860/4 027): Q1: 0.03 Median: 0.13 Q3: 0.52 Maximum: 8.27. *China pottery* (n = 1 592/9 017): Q1: 3.89 Median: 6.07 Q3: 9.44 Maximum: 63.15. *China tin mining* (n = 956/7 858): Q1: 2.79 Median: 5.27 Q3: 5.29 Maximum: 83.09. *China tungsten mining* (n = 4 549/28 481): Q1: 3.47 Median: 8.56 Q3: 29.79 Maximum: 232.26. *South Africa gold mining* (n = 1 009/2 260): Q1: 3.22 Median: 4.23 Q3: 5.35		the pooled analysis.

Table IV1b. Study methodology.

Study; (ref.)	Exposure	Exposure data	Exposure assessment	Exposure metrics	Limitations	Notes
				Maximum: 9.28. *USA gold mining* (n = 1 925/3 348): Q1: 0.10 Median: 0.23 Q3: 0.74 Maximum: 6.20. *Australia gold mining* (n = 1 3512 213): Q1: 6.25 Median: 11.37 Q3: 17.31 Maximum: 50.22. Total median cumulative exposure: 4.27 mg/m^3-years. Average exposure estimates (mg/m^3) in quartiles for each cohort study (no. of deaths/workers). *USA diatomaceous earth* (n = 749/2 342): Q1: 0.11 Median: 0.18 Q3: 0.46 Maximum: 2.43. *Finland granite industry* (n = 418/1 026): Q1: 0.39 Median: 0.59 Q3: 1.29 Maximum: 3.60.		

Table IV1b. Study methodology.

Study; (ref.)	Exposure	Exposure data	Exposure assessment	Exposure metrics	Limitations	Notes
				USA granite industry (n = 1 762/5 408): Q1: 0.02 Median: 0.05 Q3: 0.08 Maximum: 1.01. *USA sand industry* (n = 860/4 027): Q1: 0.02 Median: 0.04 Q3: 0.06 Maximum: 0.40. *China pottery* (n = 1 592/9 017): Q1: 0.18 Median: 0.22 Q3: 0.34 Maximum: 2.10. *China tin mining* (n = 956/7 858): Q1: 0.12 Median: 0.19 Q3: 0.49 Maximum: 1.95. *China tungsten mining* (n = 4 549/28 481): Q1: 0.15 Median: 0.32 Q3: 1.28 Maximum: 4.98.		

Table IV1b. Study methodology.

Study; (ref.)	Exposure	Exposure data	Exposure assessment	Exposure metrics	Limitations	Notes
				South Africa gold mining (n = 1 009/2 260): Q1: 0.15 Median: 0.19 Q3: 0.22 Maximum: 0.318. *USA gold mining* (n = 1 925/3 348): Q1: 0.02 Median: 0.05 Q3: 0.10 Maximum: 0.24. *Australia gold mining* (n = 1 3512 213): Q1: 0.25 Median: 0.43 Q3: 0.65 Maximum: 1.55. Total median average exposure: 0.19 mg/m^3.		

ISCO: International Standard Classification of Occupations, JEM: job-exposure matrix, RCS: respirable crystalline silica.

Table IV1c. Statistical methods.

Study; (ref.)	Statistical analyses	Covariates	Limitations	Notes
Ge *et al.* (2020); (90)	Logistic regression for exposure-response relations and joint effects of silica exposure and smoking on lung cancer. Lag times 0, 5, 10, 15 and 20 years applied. Thin-plate regression spline analyses to explore shape of exposure-response relationship. Excess lifetime cumulative risk of lung cancer death.	Smoking (lifetime history available), age, sex, study, smoking cessation since interview/diagnosis, ever employment in list A jobs.	Silicosis status (yes/no) available for 50% of the study population, with n = 108 silicosis cases.	Stratified analyses for cancer risks (with cancer subtypes) associated with cumulative exposure categories. Multiplicative and additive interactions tested.
Steenland *et al.* (2001); (245)	Conditional logistic regression for exposure-response relations using a pooled nested case-control analyses. Matched for race (USA studies), sex, date of birth (± 5 years) and study. Case-control ratio 1:100. Lag times 0, 5, 10, 15 and 20 years applied. Log-linear restricted cubic spline to explore shape of exposure-response relation. Excess lifetime cumulative risk of lung cancer death.	Age, calendar period, study.	Majority of studies had no data on smoking. Other confounders, like radon in underground mines. Most studies had no data on silicosis morbidity.	Focus on internal exposure-response analyses. Heterogeneity tests and subanalyses with silicosis.

Table IV1d. Health assessment.

Study; (ref.)	Health assessment	Health outcome	Notes
Ge *et al.* (2020); (90)	Self-reports of physician-diagnosed silicosis, collected in 4 centres by in-person or next-of-kin interviews.	Lung cancer (n = 16 901) and lung cancer subtypes (adenocarcinoma (n = 4 752), squamous cell carcinoma (n = 6 503), and small cell carcinoma (n = 2 730).	Silicosis status available for 50% of the study population (n = 18 931), of which only 108 silicosis cases. Unclear how lung cancer and subtype was established, no details in publication.
Steenland *et al.* (2001); (245)	Derived from the individual cohort studies.	Lung cancer (n = 1 072 lung cancer deaths).	No data on silicosis morbidity in most studies, therefore effect of silicosis on lung cancer could not be analysed.

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
Ge *et al.* (2020); (90)	No data.	ORs (95% CI) for lung cancer using cumulative exposure in mg/m^3-years: > 0–0.39: 1.15 (1.04–1.27) 0.4–1.09: 1.33 (1.21–1.47) 1.1–2.39: 1.29 (1.17–1.42) ≥ 2.4: 1.45 (1.31–1.60) *Test for trend:* p < 0.01. ORs (95% CI), no. of cases for lung cancer in subjects without silicosis. ORs adjusted for study, age group, sex, smoking (pack-years), list A job: Not exposed: 1.0 (ref), 6 091 > 0–0.39: 1.22 (1.07–1.40), 665 0.4–1.09: 1.50 (1.31–1.71) 1.1–2.39: 1.48 (1.30–1.69) ≥ 2.4: 1.42 (1.25–1.63) *Test for trend*: p < 0.01.	Estimated excess lifetime risk (above background) through age 80 assuming 45 year working life (20–65 years) using European lung cancer mortality rates for 2008: Exposure levels based on current international recommended exposure limits: 0.025 mg/m^3: 0.2% or 2/1 000 workers. 0.05 mg/m^3: 0.45% or 4.5/1 000 workers. 0.1 mg/m^3: 0.96% or 9.6/1 000 workers.	ORs (95% CI), no. of cases for lung cancer by smoking status: *Never smoked:* Not exposed: 1.0 (ref), 1 121 > 0–0.39: 1.17 (0.85–1.57), 60 0.4–1.09: 1.07 (0.78–1.43), 59 1.1–2.39: 1.02 (0.75–1.36), 60 ≥ 2.4: 1.40 (1.03–1.86), 69 *Test for trend*: p < 0.01 Excluding not exposed: p = 0.02. *Former smokers:* Not exposed: 1.0 (ref), 3 696 > 0–0.39: 1.07 (0.92–1.25), 366 0.4–1.09: 1.37 (1.18–1.59), 433 1.1–2.39: 1.35 (1.16–1.57), 441 ≥ 2.4: 1.47 (1.27–1.70), 496 *Test for trend*: p < 0.01 Excluding not exposed: p < 0.01. *Current smokers:* Not exposed: 1.0 (ref), 7 161 > 0–0.39: 1.19 (1.03–1.39), 687 0.4–1.09: 1.33 (1.15–1.55), 729 1.1–2.39: 1.29 (1.11–1.50), 730 ≥ 2.4: 1.39 (1.20–1.62), 793 *Test for trend*: p < 0.01 Excluding not exposed: p = 0.07.	

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
				ORs (95% CI), no. of cases/controls for lung cancer, testing for *interactions* between RCS exposure and smoking: *Never smoked, not exposed:* 1.0 (ref), 1 121/5 900 *Never smoked, ever exposed:* 1.02 (0.87–1.19), 248/1 253 *Ever smoked, not exposed:* 6.37 (5.91–6.87), 10 857/10 577 *Ever smoked, ever exposed:* 8.72 (8.0–9.52), 4 675/3 235 *P-value multiplicative interaction:* < 0.01. *Relative excess risk due to interaction*: 2.34 (1.85–2.83).	
Steenland *et al.* (2001); (245)	Coefficient average exposure for exposure-response trend [standard error (SE)] in mg/m^3: *USA diatomaceous earth:* 0.1459 (0.2883) *South Afrika gold mining:* 7.789 (2.761) *USA gold mining:* 0.0181 (0.0252)	Coefficient cumulative exposure for exposure-response trend, 15-year lag-time (SE) in mg/m^3-years: *USA diatomaceous earth:* 0.0500 (0.0219) *South Afrika gold mining:* 0.2099 (0.0909) *USA gold mining:* 0.0058 (0.1453)	Based on spline model with 15-year lag-time estimated excess lifetime risk (above background) through age 75, assuming 45-year working life (20–65 years) using national mortality rates: *China:* 1.1% (95% CI 0.1–2.3%)		Coefficients for log-linear model (log RR = ßX). Results (coefficients for exposure-response trend) show considerable heterogeneity by study especially for cumulative exposure and average exposure.

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
	Australia gold mining: 0.5539 (0.3139) *USA granite industry:* 0.3824 (0.9417) *Finland granite industry:* 0.3523 (0.2588) *USA sand industry:* 4.432 (1.590) *China tungsten mining:* 0.1724 (0.0573) *China pottery:* 0.2436 (0.3333) *China tin mining:* 0.9417 (0.023) *Pooled average exposure*: 0.047 (0.023) *Model likelihood:* 4.4, 1 df *Heterogeneity test:* P < 0.0001. *Pooled categorical ORs average exposure (95% CI):* < 0.07: 1.0 (ref) 0.07–0.21: 1.4 (1.1–1.7) 0.21–0.41: 1.6 (1.3–2.0) 0.41–1.36: 1.6 (1.2–2.0) > 1.36: 1.7 (1.2–2.3) *Model likelihood:* 22.6, 4 df.	*Australia gold mining:* 0.0161 (0.0120) *USA granite industry:* 0.0146 (0.0285) *Finland granite industry:* 0.0080 (0.0102) *USA sand industry:* 0.1774 (0.1153) *China tungsten mining:* 0.0095 (0.0022) *China pottery:* 0.0037 (0.0164) *China tin mining:* 0.0358 (0.0078) *Pooled cumulative exposure, 15-year lag-time:* 0.010 (0.002) *Model likelihood:* 21.4, 1 df *Heterogeneity test:* p = 0.02. *Pooled cumulative exposure, no lag-time:* 0.008 (0.002) *Model likelihood:* 17.3, 1 df *Heterogeneity test:* p = 0.008. *Pooled categorical ORs cumulative exposure no lag-time (95% CI):* < 0.4: 1.0 (ref) 0.4–2.0: 1.0 (0.85–1.3) 2.0–5.4: 1.3 (1.1–1.7)	*USA:* 1.7% (95% CI 0.2–3.6%) *Finland:* 1.3% (95% CI 0.1–2.9%) Differences due to differing background lung cancer rates (range 3–6%) or all cause death rates.		Heterogeneity across studies assessed by comparing log likelihoods for model with 10 interaction terms versus model without interaction terms. Models with duration of exposure or log duration of exposure did not fit the data well, model likelihood 0.2 and 0.5 (1 df) respectively. The spline model (relatively unconstrained, allowing any cubic curve between knots) for the log of cumulative exposure with 15-year lag-time shows a reasonably monotonic increase in risk with increasing cumulative exposure.

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
		5.4–12.8: 1.5 (1.2–1.9) > 12.8: 1.6 (1.3–2.1) *Model likelihood:* 21.0, 4 df. *Pooled categorical ORs cumulative exposure 15-year lag-time (95% CI):* < 0.4: 1.0 (ref) 0.4–2.0: 1.0 (0.83–1.3) 2.0–5.4: 1.3 (1.0–1.6) 5.4–12.8: 1.5 (1.2–1.8) > 12.8: 1.5 (1.2–1.9) *Model likelihood:* 17.3, 4 df. *Coefficient exposure-response trend using log cumulative exposure, 15-year lag-time (SE) in mg/m^3-years:* *USA diatomaceous earth:* 0.0887 (0.0538) *South Afrika gold mining:* 0.6665 (0.3359) *USA gold mining:* 0.0388 (0.0775) *Australia gold mining:* 0.1937 (0.1154) *USA granite industry:* 0.1121 (0.0496) *Finland granite industry:* 0.0489 (0.0698)			

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
		USA sand industry: 0.0312 (0.0568) *China tungsten mining:* 0.0297 (0.0257) *China pottery:* 0.0764 (0.0362) *China tin mining:* 0.0784 (0.0341) *Pooled log cumulative exposure, 15-year lag-time*: 0.062 (0.015) *Model likelihood:* 18.8, 1 df *Heterogeneity test*: p = 0.34. *SMRs for lung cancer by cohort study (95% CI), no. of lung cancer deaths:* *USA diatomaceous earth:* 1.3 (1.0–1.6), 77 *Finland granite industry:* 1.4 (1.0–2.0), 38 *USA granite industry:* 1.2 (1.0–1.3), 124 *USA sand industry:* 1.6 (1.2–1.9), 85 *China pottery:* 1.1 (0.84–1.4), 68 *China tin mining:* 2.1 (1.7–2.6), 97			

Table IV1e. Results pooled analyses.

Study; (ref.)	Association using average exposure	Association using cumulative exposure	Excess lifetime risk	Confounding and interaction	Notes
		China tungsten mining: 0.63 (0.53–0.75), 135 *South Africa gold mining:* not indicated, 77 *USA gold mining:* 1.2 (1.0–1.4), 156 *Australia gold mining:* 1.8 (1.5–2.1), 135 *Total population:* 1.2 (1.1–1.3), 992 *SRR for lung cancer morbidity (95% CI), exposed vs non-exposed. China study cohorts only:* *China pottery:* 2.8 (1.6–4.8) *China tin mining:* 1.5 (0.98–2.4) *China tungsten mining:* 0.92 (0.63–1.3)			

CI: confidence interval, OR: odds ratio, RCS: respirable crystalline silica, SE: standard error, SMR: standardised mortality ratio, SRR: standardised rate ratio.

Silicosis – Summary of relevant pooled analyses investigating the exposure-response relation between exposure to RCS and silicosis

Table IV2a. Study population characteristics and study selection.

Study; (ref.)	Design and setting	Population description	Studies included	Notes
't Mannetje *et al.* (2002); (252)	Pooled analysis. Mortality data. 6 industrial cohort studies in Australia (n = 1), Finland (n = 1), and the USA (n = 4).	Pooled cohort of 18 364 workers; 170 deaths in total, 150 deaths with underlying silicosis, 20 deaths with unspecified pneumoconiosis.	6 industrial cohort studies in: Diatomaceous earth industry (47), Gold mining (67, 243), Sand industry (246), Granite industry (63, 142). 1 cohort study was newly developed for this pooled analysis: USA sand industry (246). 5 cohort studies had updated follow-up, quantitative exposure measures by job and calendar period, or were developed for this pooled analysis: Australia and USA gold mining (67, 243) USA and Finland granite industry (63, 142) USA sand industry (246).	Linked to the pooled analyses by Steenland *et al.* (2001) on lung cancer (245). 4 industrial cohort studies, included in Steenland *et al.* (2001), were excluded for this pooled analysis because of differential definition in coding of silicosis (n = 3) (51), or no deaths with silicosis as underlying cause (n = 1) (67).

Table IV2b. Study methodology.

Study; (ref.)	Exposure(s)	Exposure data	Exposure assessment and metrics	Limitations	Notes
't Mannetje *et al.* (2002); (252)	RCS	Original data obtained for each cohort study. 5 cohort studies had complete occupational history in the plant available. 1 cohort study had lifetime occupational history available. > 12 200 exposure measurements available.	All exposure estimates in mg/m^3. Gravimetric total dust, respirable dust or particle count were converted to mg/m^3 (conversion factors study specific).	Silicosis possibly underreported due to registered under other causes of death. Various sampling methods, exposure measures, time periods, and conversion factors used.	Most workers exposed to quartz, except in cohort of diatomaceous earth mostly exposed to cristobalite. See also 't Mannetje *et al.* (2002) (253) for details on quantitative exposure assessment.

RCS: respirable crystalline silica.

Table IV2c. Statistical methods.

Study; (ref.)	Statistical analyses	Covariates	Limitations	Notes
't Mannetje *et al.* (2002); (252)	Standard life-table analyses using 10 categories of cumulative exposure. Poisson regression to calculate rate ratios with lowest exposure category as reference adjusted for covariates. Conditional logistic regression for exposure-response analyses using a pooled nested case-control. Matched for race (USA studies), sex, date of birth (± 5 years) and study. Case-control ratio 1:100. Lag times of 0, 5, 10, 15 and 20 years applied. Cubic spline to explore shape exposure-response relations. Excess lifetime cumulative risk of silicosis death.	Age, calendar period, study.	Differences in biological activity of different types of RCS dust could not be taken into account. Not possible to adjust for potential confounders, like smoking.	Apart from differences between quartz, cristobalite or tridymite, other physical characteristics (freshly cleaved or coated) may also play a role in its biological activity. Heterogeneity between studies tested.

Table IV2d. Health assessment.

Study; (ref.)	Health assessment	Health outcome	Notes
't Mannetje *et al.* (2002); (252)	Original data obtained for each cohort study.	Silicosis (ICD-9: 502) and unspecified pneumoconiosis (ICD-9: 505).	Not unlikely that silicosis is underreported, because it was coded as tuberculosis or chronic obstructive pulmonary disease.

ICD: International Classification of Disease.

Table IV2e. Results pooled analyses.

Study; (ref.)	Associations with average exposure	Associations with cumulative exposure	Excess lifetime risk	Confounding & interaction	Notes
't Mannetje *et al.* (2002); (252)	Nested case-control analysis relative risk models, rate ratio for increase of one unit of each exposure measure (95% CI): Average exposure over working period (mg/m^3): 2.77 (1.80–4.26). *Model likelihood*: 19.9, 1 df.	Mortality rate ratios (95% CI) adjusted for age (4 categories), calendar period (8 categories), study (6 categories) by categories of cumulative exposure (mg/m^3-years) using Poisson regression: 0–0.99: 1.00 (ref) 0.99–1.97: 3.39 (1.42–8.08) 1.97–2.87: 6.22 (2.56–15.12) 2.87–4.33: 9.40 (3.71–23.80) 4.33–7.12: 13.69 (5.04–37.18) 7.12–9.58: 22.64 (7.88–65.10) 9.58–13.21: 23.97 (8.05–71.32) 13.21–15.89: 40.25 (13.25–122.3) 15.89–28.10: 25.11 (8.09–77.91) > 28.10: 63.63 (19.87–203.8). Nested case-control analysis using conditional logistic regression, cases and controls were matched for age, sex date of birth and	Estimated excess lifetime risk (above background) through age 75, assuming 45 year working life (20–65 years) using national mortality rates: Assuming cumulative exposure of 0.10 mg/m^3 (4.5 mg/m^3-years) 13 deaths from silicosis per 1 000 workers. Assuming cumulative exposure of 0.05 mg/m^3 (2.25 mg/m^3-years) 6 deaths from silicosis per 1 000 workers.	Nested case-control analysis using conditional logistic regression, cases and controls were matched for age, sex date of birth and study. Relative risk models, rate ratio for increase of one unit of each exposure measure (95% CI): Heterogeneity was tested through adding interaction terms between study and exposure. Log cumulative exposure (log mg/m^3-days) by study: *USA diatomaceous earth:* 2.08 (1.23–3.52) *Finland granite industry:* 2.76 (1.37–5.57) *USA granite industry:*	Cut-points of cumulative exposure categories were chosen by dividing cumulative exposure levels of the silicosis deaths in deciles. Median average exposure of the silicosis deaths was 0.26 mg/m^3, compared to 0.07 mg/m^3 for the total cohort. No statistically significant heterogeneity was observed between the studies, only little differences in model with and without interaction terms for study (-2LL = 6.6, 5 df, p = 0.25). Heterogeneity between

Table IV2e. Results pooled analyses.

Study; (ref.)	Associations with average exposure	Associations with cumulative exposure	Excess lifetime risk	Confounding & interaction	Notes
		study. Relative risk models, rate ratio for increase of one unit of each exposure measure (95% CI): Cumulative exposure (mg/m^3-years): 1.04 (1.03–1.06) *Model likelihood:* 30.9, 1 df. Log cumulative exposure (log mg/m^3-days): 2.08 (1.71–2.53) *Model likelihood*: 73.2, 1 df.		1.76 (1.30–2.38) *USA sand industry:* 1.63 (1.03–2.57) *USA gold mining:* 3.57 (1.90–6.69) *Australia gold mining:* 2.31 (1.34–3.97). Heterogeneity by age was tested through stratification by age and including age-exposure interaction terms. Log cumulative exposure (log mg/m^3-days) by age: < 65 years: 2.70 (1.90–3.84) ≥ 65 years: 1.81 (1.44–2.29).	studies could not be explained by time since last exposure. Adding interaction term age-exposure yielded p = 0.07. Adding lag-time (5, 10, 15, and 20 years were considered) did not improve model fit. Applying cubic spline with 5 knots did not improve model fit over log cumulative exposure model (-2LL = 1.7, 4 df, p = 0.63).

CI: confidence interval

V. SYNERGY exposure data

Table Va. Characteristics of ExpoSYN database of exposure measurements, underlying the exposure estimates in SYN-JEM [adapted from Table 3 from Peters *et al.* (2012) (210)].

Total no. RCS measurements	148 911	
Type of polymorph (%)	Quartz (93%) Cristobalite (2%) Tridymite (<1%) Unspecified (4%)	
Time period measurements	1951–2009	
Reason for measurements (%): Survey Inspection Compliance Unknown	 17 743 (12%) 49 419 (33%) 7 710 (5%) 74 039 (50%)	
No. of measurements: Personal Stationary	 34 017 114 894	
No of measurements per country:	Total no. of measurements	No. of personal measurements [a] (n = 23 640):
Canada	8 449	2 384
Denmark	318	-
Finland	6	-
France	9 921	4 995
Germany	115 009	8 419
Italy	2 793	373
The Netherlands	687	519
Norway	1 292	-
Poland	331	-
Romania	508	-
Slovakia	806	-
Sweden	897	1 838
UK	7 894	5 112

[a] Adapted from supplementary material Table S2 from Peters *et al.* (2016) (212).
JEM: job-exposure matrix, RCS: respirable crystalline silica.

VI. Evaluation on the carcinogenic mechanism of respirable crystalline silica

Evaluation by the Subcommittee on the Classification of Carcinogenic Substances, a subcommittee of the DECOS, on the mechanism for carcinogenicity of RCS.

Summary findings on genotoxicity

Mutagenicity

No data are available on mutagenicity in humans who were exposed to RCS particles.

In an animal experiment, subchronic inhalation of cristobalite (mass median aerodynamic diameter 1.3 µm, 3 mg/m^3) induced a 4-fold increase[1] of the *hprt* gene mutant frequency in alveolar cells of exposed rats [13 weeks after the start of the exposure (134)]. This was accompanied by a 19-fold increase in lung burden (µg silica/lung). A single intratracheal instillation of 100 mg alpha-quartz/kg bw induced around a 10-fold increase in *hprt* gene mutant frequency in alveolar type II cells (measured seven months after the instillation) (76). A similar instillation of 10 and 100 mg alpha-quartz/kg bw induced a 4-fold increase (10 mg/kg) and an 18-fold increase (100 mg/kg) in *hprt* gene mutant frequency in alveolar type II cells (measured 15 months after the instillation) (75). The subcommittee noted the high dose applied in both studies and that no data were reported on lung burden. The subcommittee also noticed that all *hprt* gene studies were non-guideline studies, used a small number of animals and no positive control was included. A single intratracheal instillation of 1.2 mg DQ12 or 2.4 mg quartz dust in rats induced 0.7 and 2.1% p53 mutant positive cells respectively (234). All animal studies showed an increase in inflammatory markers.

In an *in vitro* experiment, exposure of Muta™Mouse lung cell line to quartz (mean particle size 1.59 µm; 100 µg/ml) induced no increase in mutant frequency in *lacZ* and *cII* transgenes (132).

Clastogenicity

In a cross-sectional study among Turkish ceramic workers (n = 99), an increase in DNA breakage, micronucleus frequency and oxidative damage was shown after exposure to silica-rich dust (mean concentration 3.6 mg/m^3) (9). In a cross-sectional study in Italy among pottery, ceramic and marble manufacturing and stone quarry workers (n = 135) an increase in oxidative DNA damage for workers that were exposed to a complex mixture, including silica was shown. No increase was reported for workers that were exposed to silica alone (205). In a Turkish retrospective cohort study among sand workers (n = 50), the investigators reported an increase in micronucleus frequency in isolated nasal epithelial cells and peripheral blood cells of non-smoking workers who were exposed to quartz and cristobalite particles at concentrations of 0.25 mg/m^3 and higher (69). A cross-

[1] All increases mentioned in this Annex are statistically significant and dose-dependent and are compared to controls (unexposed workers/animals or untreated cells).

sectional study in India among male workers (n = 50) exposed to silica in stone crushing units, reported an increase in total chromosomal aberrations and sister-chromatid exchanges (238). None of the human studies reported information on inflammatory markers.

Single intratracheal instillations of quartz particles (Min-U-Sil 5; total dose applied, 0–22.5 mg) in rats increased the number of micronucleated alveolar macrophages, accompanied with an increase in inflammatory markers. No clear dose-response was observed (151).

In three *in vitro* assays, increases in micronuclei frequency per 1 000 cells were observed (including dose-response trend) in mammalian cells exposed to non-coated quartz particles (156, 183, 282). Another *in vitro* assay showed an increase in sister chromatid exchanges in human lymphocytes and monocytes for tridymite (no dose-response trend), but not for quartz (200). In two other *in vitro* assays, no increase in micronuclei frequency was observed; in both tests, exposure was confirmed by the presence of cytotoxicity (65, 100).

Indicator tests

In one Turkish cross-sectional study among foundry and pottery workers (n = 52) who were exposed to respirable dust and quartz (mean concentration: 0.72 mg/m^3 at time of blood sampling), an increase in DNA strand breakage is reported in isolated lymphocytes. No information on inflammatory markers is reported (19).

In one animal experiment, rats received DQ12 quartz (0 or 2 mg) by a single intratracheal instillation (137). After three days, primary lung epithelial cells were isolated; the percentage of cells with increased DNA strand breaks was increased. These observations were accompanied with an increase in the number of neutrophils, macrophages and other inflammatory markers in the bronchoalveolar lavage fluid.

A number of *in vitro* comet assays has been performed, most of which showed increased DNA damage (DNA strand breaks and oxidative DNA damage) in cultured mammalian and human cells, which were exposed to (non-coated) crystalline silica particles (Min-U-Sil 5 quartz, DQ12 quartz, alpha-quartz; geometric mean diameter ranging between 1.1 and 5 µm; concentrations applied: up to 200 µg/cm^2). Within the concentration ranges, also loss of cell viability or increase in cytotoxicity was reported. Four studies showed an increase in DNA double strand breakage (H2AX phosphorylation assay) after exposure to quartz (mean particle size 1.59 µm; 100 µg/ml) or Min-U-Sil 5 (nominal diameter 1.6 µm, 5 µg/cm^2) (178, 277, 278, 280).

Inflammation and oxidative stress

In human and mammalian *in vitro* cell systems, crystalline silica particles caused oxidative stress and an increase in extracellular and intracellular formation of reactive oxygen species (ROS) (70, 92, 137, 178, 277, 280). Also, in rats *in vivo*, a statistically significant increase in oxidative stress was observed, which was accompanied by an increase in inflammatory markers (26).

Considerations on the carcinogenic mode of action

- *Lung overload*. Lung overload is defined as a failure of alveolar macrophage mediated lung clearance following exposure to high concentrations of particles, thereby triggering accumulation of particles in the deep lung and subsequent inflammatory responses. There is some evidence that lung overload can occur in humans and therefore, it must be assumed that the rat model identifies potential carcinogenic hazards to humans (25).
- *Evidence from epidemiological studies.* Although it was previously assumed that the risk for lung cancer after exposure to RCS was higher for workers with silicosis than for workers without silicosis (suggesting an inflammatory mechanism leading to lung cancer) recent studies suggest that the risk for lung cancer is similar for workers with and without silicosis (90).
- *Uptake in cells*. Extensive cellular uptake of DQ12 quartz has been reported, leading to induced DNA strand breaks and oxidative DNA damage. Reducing the cellular uptake also decreases cytotoxicity and DNA strand break formations (231).
- *Genotoxicity of generated reactive oxygen species.* Reactive species generated by RCS, directly, as well as via the cellular response, can translocate into the nucleus to potentially damage DNA.
- *Uptake in nucleus*. Although uptake in the cytoplasm has been reported, there is currently no evidence that RCS can enter the nucleus (27, 154).
- *Formation of inflammation-induced reactive oxygen species*. *In vivo* and *in vitro* studies show that RCS generate a cellular response resulting in an increase in oxidative stress, accompanying oxidative DNA damage.
- *Formation of radicals on surface*. It is demonstrated that RCS can form reactive radicals on their surface which enhanced cellular signalling, cell proliferation, and ROS production in fibroblasts (216).
- *Genotoxicity via intracellular signalling*. Recent studies found that RCS particles in contact with the cell membrane can induce DNA breakage following mitochondrial depolarisation and an innate inflammatory response (278). Recently, translocation of endonuclease G from the mitochondria to the nucleus was postulated as a new mode of action of DNA damage (281).

Conclusion on the carcinogenic mode of action

It is indisputable that exposure to RCS causes tumours and that a genotoxic mechanism of action is involved. The genotoxicity data summarised above show an increased mutation frequency in *p53* and *hprt* genes, DNA breakage and micronucleus formation. The question is whether indirect and/or direct genotoxic mechanisms are involved.

Various *in vitro* and *in vivo* studies show an increase in inflammatory markers after exposure to RCS. In addition, carcinogenic effects in animals are consistently accompanied by inflammation. In humans, lung cancer occurring after crystalline silica exposure is often, although not obligatory, accompanied with the

inflammation-endpoint silicosis, where it should be noted that in the absence of silicosis inflammation can still be present. Inflammation and ROS generated as a result are considered as phenomena with a threshold, i.e., with an indirect mode of action. The subcommittee considers it likely that these contribute significantly to the observed genotoxic damage.

Recent studies found that RCS particles can activate intracellular signalling pathways leading to the formation of DNA breaks, which would present another potential indirect mechanism.

Direct-acting genotoxic carcinogens include substances that (either in their unchanged form or as reactive metabolites) interact directly with DNA, causing damage (adducts, single- and double-strand breaks) (106).

There is currently no evidence that RCS particles themselves directly interact with DNA to induce these genotoxic effects; RCS have not shown to be able to enter the nucleus (although the subcommittee notes, that data on intracellular translocation of crystalline silica are limited). However, the subcommittee considers genotoxic carcinogens that generate ROS also as direct genotoxic carcinogens, given the genotoxicity of the produced ROS (106). The subcommittee notes that ROS can be formed on the surface of crystalline silica particles, thus far there is no evidence that these ROS contribute to the observed genotoxic effects of RCS.

The DECOS Subcommittee on the Classification of Carcinogenic Substances concludes, that the carcinogenic potential of RCS results primarily from genotoxicity by indirect mechanisms, related to damage of lung cells with consequently inflammation and a tumour-promoting inflammatory micro-environment. Involvement of a direct genotoxic mechanism involving particle-generated ROS, however, cannot be excluded.

DECOS Subcommittee on Classification of Carcinogenic Substances for the evaluation of the genotoxicity of RCS

Members

- Prof. dr. H.P.J. te Riele, Professor of molecular biology, VU University Amsterdam, and Netherlands Cancer Institute, Amsterdam, *chairman (until December 31, 2023)*
- Dr. R.W.L. Godschalk, Genetic toxicologist and molecular epidemiologist, Maastricht University
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* Structurally consulted experts are consulted throughout the advisory process because of their expertise. These experts and also observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

VII. Risk calculations using life-table analyses

Study selection

For the calculation of health-based occupational risk values the committees selected the study by Ge *et al.* (2020), which uses data from the SYNERGY project. See Annex IV for a more extensive summary of the publication by Ge *et al.* (2020) (90).

The SYNERGY project is a pooled analysis of case-control studies on the joint effects of known occupational lung carcinogens (asbestos, chromium, nickel, PAH and RCS) and smoking in the development of lung cancer. For the pooled analyses 14 case-control studies in Europe (Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, and the UK) and Canada were selected. For the SYNERGY project an occupational exposure database was created, called ExpoSYN. Data on occupational exposures from national exposure databases and research institutes from Europe and Canada were collected and entered into the ExpoSYN database using a structured protocol. A job-exposure matrix (JEM) was developed, called SYN-JEM, using job ratings from a semi-quantitative general population JEM (Dom-JEM), and individual exposure measures from the ExpoSYN. With the result that quantitative exposure estimates could be assigned to all the participants in the SYNERGY project (210-212).

See also Annex V for more detailed information about the underlying exposure data in the SYNERGY project.

Data sources

Information on the average population size and number of deaths from all causes and from lung cancer in 5-year age categories for the Dutch population during 2000–2014 were obtained from Statistics Netherlands (240). The all cause and lung cancer mortality rates from the European Union were obtained from Eurostat 2008 (86).

The exposure-response relationship between RCS and lung cancer has been derived using data from the SYNERGY study, as described by Ge *et al.* (2020) (90).

Calculations

Based on the predicted exposure-response curve calculated in the pooled analysis by Ge *et al.* (2020) (90), we estimated the RCS exposure level that is expected to result in 4 additional cases of lung cancer death after 40 years of occupational exposure, either per 1 000 (4×10^{-3}) or 100 000 (4×10^{-5}) workers.

The concentrations of RCS corresponding to the relative risks, can be calculated using the following linear model equation that describes the exposure-response relationship:

$$\ln RR = \text{slope } (\beta) \times \text{exposure}$$

lnRR is the natural logarithm (ln) of the relative risk (RR); the slope (β) is 0.05827, and the exposure is expressed as the cumulative exposure to RCS (mg/m^3-years) after 40 years of occupational exposure.

The concentration of RCS that corresponds to the threshold values of 4 additional cases of lung cancer per 1 000 and 100 000 exposed workers, respectively, were estimated using an iterative algorithm.

Occupational exposure to RCS has been assumed to occur from age 20 up until age 60. Excess risk calculations were truncated at the age of 100 years, assuming deaths occurring beyond this age are unlikely to be related to occupational exposure to RCS.

All analyses were conducted using R version 4.2.3.

Results

Table VII shows the estimated RCS exposure levels corresponding to the different excess lifetime risks of lung cancer, truncated at 100 years, and based on mortality rates for the EU.

Table VII. Lung cancer excess lifetime risk associated with 40 years of occupational RCS exposure.

Based on EU mortality rates	Truncated at 100 years
4/100 000	0.00038 mg/m^3
4/1 000	0.0363 mg/m^3

Risk calculations and reporting

- Dr. Lützen Portengen, Institute for Risk Assessment Sciences, Utrecht University
- Dr. Susan Peters, Institute for Risk Assessment Sciences, Utrecht University

VIII. The committees

Dutch Expert Committee on Occupational Safety (DECOS)

The membership of the DECOS for the evaluation of RCS

- Prof. dr. F.G.M. Russel, Professor of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, chairman
- Dr. H. Bouwmeester, Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- Dr. ir. W. Fransman, Senior Scientist, TNO, Zeist
- Prof. dr. I. Kreis, Retired Physician-Epidemiologist, Royal College of Surgeons, London, the UK
- Dr. E.D. Kroese, Toxicologist, TNO, Zeist
- Dr. A.L. Menke, Toxicological Pathologist, TNO Metabolic Health Research, Leiden
- Dr. M. Rooseboom, Principal Toxicologist, Shell Product Stewardship, Shell Global Solutions International B.V., The Hague
- Dr. G.B.G.J. van Rooy, Occupational Medicine Specialist, Arbo Unie Expert Centre for Chemical Risk Management, and Radboud UMC Outpatient Clinic for Occupational Clinical Toxicology, Nijmegen
- Prof. dr. L.A. Smit, Professor of One Health and Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht

*Structurally consulted expert**

- Dr. S. Peters, Associate Professor/Epidemiologist, Institute for Risk Assessment Sciences, Utrecht

*Observers**

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Scientific secretariat

- Dr. D. Boers, Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in relevant areas. Transparency regarding possible conflicts of interest is important. For each substance to be evaluated, the members are asked about their potential conflicts of interest. See also www.healthcouncil.nl for more information about the procedures of the Health Council and its Committees.

* Structurally consulted experts are consulted throughout the advisory process because of their expertise. These experts and also observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

The Nordic Expert Group (NEG)

The membership of the NEG committee for the evaluation of RCS

- Prof. dr. G. Johanson, Professor of Occupational Toxicology and Risk Assessment, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, chairman
- Dr. M.D. Bugge, Lead Head Physician, National Institute of Occupational Health, Oslo
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*The Nordic Expert Group – appointment and interests procedur*es

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* Structurally consulted experts are consulted throughout the advisory process because of their expertise. These experts and also observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

IX. Previous NEG criteria documents

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Carcinogens, Approaches for the setting of occupational exposure limits (OELs) for	2022;56(2)*
Cardiovascular disease, Occupational chemical exposures and	2020;54(2)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chloramines, Inorganic	2019;53(2)*
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
Hearing impairment, Occupational exposure to chemicals and	2010;44(4)*
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene, Thermal degradation products in the processing of plastics	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Silicon carbide	2018;52(1)*
Skin exposure to chemicals, Occupational	2018;52(3)*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Unusual working hours, Occupational chemical exposures in combination with	2023;57(2)*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

*: in English, remaining documents are in a Scandinavian language.
D: collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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