ARBETE OCH HÄLSA
VETENSKAPLIG SKRIFTSERIE

Nr 2014;48(3)

Scientific Basis for Swedish Occupational Standards XXXIII

N-Methyl-2-pyrrolidone
Crystalline Silica, Quartz
Epichlorohydrin

Swedish Criteria Group for Occupational Standards
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The consensus reports in this volume are translated from Swedish. If there is any doubt as to the understanding or interpretation of the English version, the Swedish version shall prevail.

ISBN 978-91-85971-52-7 ISSN 0346-7821

UNIVERSITY OF GOTHENBURG

ARBETSMILJÖ VERKET
Swedish Work Environment Authority

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by Occupational and Environmental Medicine at Sahlgrenska Academy, University of Gothenburg. The series publishes scientific original work, review articles, criteria documents and dissertations. All articles are peer-reviewed.

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Arbete och Hälsa 2014;48(3)

University of Gothenburg,
SE-405 30 Gothenburg
http://www.amm.se/aoh

ISBN 978-91-85971-52-7
ISSN 0346–7821

Printed at Kompendiet Gothenburg

Preface

These documents have been produced by the Swedish Criteria Group for Occupational Standards, the members of which are presented on the next page. The Criteria Group is responsible for assessing the available data that might be used as a scientific basis for the occupational exposure limits set by the Swedish Work Environment Authority. It is not the mandate of the Criteria Group to propose exposure limits, but to provide the best possible assessments of dose-effect and dose-response relationships and to determine the critical effect of occupational exposure.

The work of the Criteria Group is documented in consensus reports, which are brief critical summaries of scientific studies on chemically defined substances or complex mixtures. The consensus reports are often based on more comprehensive criteria documents (see below), and usually concentrate on studies judged to be of particular relevance to determining occupational exposure limits. More comprehensive critical reviews of the scientific literature are available in other documents.

Literature searches are made in various databases, including KemI-Riskline, PubMed and Toxline. Information is also drawn from existing criteria documents, such as those from the Nordic Expert Group (NEG), WHO, EU, NIOSH in the U.S., and DECOS in the Netherlands. In some cases the Criteria Group produces its own criteria document with a comprehensive review of the literature on a particular substance.

As a rule, the consensus reports make reference only to studies published in scientific journals with a peer review system. This rule may be set aside in exceptional cases, provided the original data is available and fully reported. Exceptions may also be made for chemical-physical data and information on occurrence and exposure levels, and for information from handbooks or documents such as reports from NIOSH and the Environmental Protection Agency (EPA) in the U.S.

A draft of the consensus report is written in the secretariat of the Criteria Group or by scientists appointed by the secretariat (the authors of the drafts are listed in the Table of Contents). After the draft has been reviewed at the Criteria Group meetings and accepted by the group, the consensus report is published in Swedish and English as the Criteria Group's scientific basis for Swedish occupational standards.

This publication is the 33rd in the series, and contains consensus reports approved by the Criteria Group from June, 2012 through October, 2013. The consensus reports in this and previous publications in the series are listed in the Appendix (page 96).

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of October, 2013)

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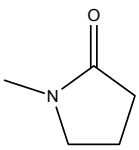
Consensus Report for N-Methyl-2-pyrrolidone

December 5, 2012

This consensus report is based in part on a criteria document from the Nordic Expert Group (61), as well as risk assessments carried out within the World Health Organization (WHO), International Program on Chemical Safety (IPCS) (22), EU Scientific Committee on Occupational Exposure Limits (SCOEL) (48), EU Scientific Committee on Consumer Safety (SCCS) (47) and US Environmental Protection Agency (EPA) (17). Complementary literature searches were carried out in November 2011 and in March and September 2012 on PubMed, Toxline and Web of Science. The Swedish Criteria Group has previously published a consensus report on N-methyl-2-pyrrolidone 1987 (33).

Chemical-physical data

CAS no	872-50-4
Synonyms	NMP, 1-methyl-2-pyrrolidone, N-methylpyrrolidone, N-methyl-α-butyrolactam, N-methyl-2-ketopyrrolidine
Empirical formula	C_5H_9NO
Structural formula	
Molecular weight	99.13 g/mol
Density	1.028 kg/dm^3 (25 °C)
Boiling point	202 °C
Melting point	24 °C
Vapour pressure	0.045 kPa (0.33 mm Hg) (25 °C)
Saturation concentration	446 ppm
Partition coefficient (log $K_{o/w}$)	-0.38
Conversion factors	1 ppm = 4.12 mg/m^3; 1 mg/m^3 = 0.24 ppm

N-Methyl-2-pyrrolidone (NMP) is a colourless-to-yellowish liquid with an unpleasant amine-like odour. The substance comprises a basic, polar molecule which is relatively stable, though some degradation (oxidation) occurs with

exposure to light and air. NMP is hygroscopic, fully miscible with water and soluble in a number of organic solvents, such as ethanol, diethyl ether, ethyl acetate, chloroform and benzene.

Use, occurrence, exposure

The substance is mainly used as a solvent in a range of different processes in the petroleum industry, in reaction media for the chemical production of polymers (e.g., polyvinyl chloride) and in stripping and cleaning procedures in the manufacture of microelectronic components. NMP is used as a substitute for dichloromethane in the removal of paint and graffiti (61). NMP is also used as a pharmaceutical vehicle and as a penetration enhancer for pharmaceuticals applied to the skin (24). The substance is also used as a binder in cosmetics, as a solvent in the preparation of pigments, dyes and inks, and in various pesticide products (61). NMP is not produced in Sweden but in 2008 ca 164 tonnes were imported, most of which was used as a raw material in the production of paints and paint removers (28).

With regard to levels in the workplace environment, some studies have measured concentrations during graffiti removal in Sweden (3, 4, 29). NMP levels of up to 25 mg/m^3 have been measured in the atmosphere during short term exposure and up to 5 mg/m^3 on average during an eight-hour working day (8-h TWA, 8-hours time-weighted average). In one study of occupational exposure in the microelectronics industry up to 6 mg NMP/m^3 were measured (7). The levels increased to 280 mg/m^3 (8-h TWA) when heated (80 °C) NMP was used. Measurements of NMP in a German adhesives plant showed levels of up to 85 mg/m^3 during short term exposure and up to 15.5 mg/m^3 over a working day (8-h TWA) (5). Measurements taken in two different industries in Japan showed levels that were lower than 3 mg/m^3 (8-h TWA) (39, 58).

NMP has been isolated from a marine fungus, *Clathria frondifera*, which shows that the substance can be produced naturally (42).

Uptake, biotransformation and excretion

Both human and animal studies show that NMP is absorbed rapidly when inhaled and when administered orally (6, 26, 43, 63, 64, 65). Several studies, in both animals and humans, show that NMP in liquid form is readily absorbed through the skin (23). The study regarded as the most suitable for assessing dermal absorption in humans (23) is that by Dick *et al*. (15) which measured dermal absorption of NMP in human skin *in vitro*. The rate of absorption of undiluted NMP was calculated as 10 mg/cm^2/hour. Extrapolation of data to 2000 cm^2 skin (equivalent to both hands and forearms) and 1 hour of exposure gave a dermal absorption of 20,000 mg. This uptake was estimated to be ca 10 times greater than the uptake with 8 hours of inhalation at the Swedish occupational exposure limit (200 mg/m^3). Other studies have shown a percutaneous absorption of ca 70% of the applied dose in both rats (200 mg, 10 cm^2 after 2 hours) (40) and humans (300

mg, 20 cm^2 after 6 hours) (32). Dermal exposure to NMP in liquid form can therefore result in significant absorption.

A significant dermal absorption has also been demonstrated in humans exposed to NMP in vapour form (6). Research volunteers (n = 16) were exposed to 80 mg NMP/m^3 for 8 hours, either via the skin and respiratory system or via the skin alone. The absorption of NMP was analyzed by measuring NMP and NMP metabolites in the urine. The dermal uptake of NMP vapour at rest was calculated as ca 42% of the total absorption (absorption by skin plus respiratory system). With moderate work (75 W, 6 x 10 minutes) total absorption increased by 41% and dermal absorption as a percentage of total absorption was somewhat lower, at 33%.

Animal studies have shown that NMP crosses the placenta in rats and that levels in foetal blood are the same as levels in the mother's blood after 6 hours (43).

Absorbed NMP is rapidly metabolized in both humans and rats. NMP is first metabolized to 5-hydroxy-NMP (5-HNMP) which in turn is metabolized further to N-methylsuccinimide (MSI) and finally to 2-hydroxy-N-methylsuccinimide (2-HMSI) (26, 64, 65). The same metabolic pathways are observed with both oral and dermal administration. In addition, Carnerup and co-workers have identified a further metabolite, 2-pyrrolidone, which is formed in small quantities (12, 13).

A human study showed a significant relationship between CYP2E1 mRNA levels and levels of 5-HNMP and 2-HMSI in urine. The same relationship could be demonstrated in rats by pretreating these animals with the CYP2E1 inhibitor diethylthiocarbamate. (32).

The half-lives of NMP, 5-HNMP, MSI and 2-HMSI in plasma from male participants in inhalation studies exposed to 10-80 mg NMP/m^3 for 8 hours were ca 4, 6, 8 and 28 hours, respectively, (6, 65). With dermal application of NMP (300 mg for 6 hours) in humans the plasma concentration of NMP reached a maximum 3 hours after exposure (62), which indicates that dermal absorption was delayed relative to inhalation absorption. There was a further delay of ca 4 hours when NMP was applied as an aqueous solution (5-50%) (1, 6, 27, 62).

NMP is mainly excreted in the urine, with only a small part (<4%) being eliminated through biliary excretion and exhalation (55). Inhalation studies with male research subjects exposed to 10-80 mg NMP/m^3 for 8 hours showed the following relative levels of NMP and its metabolites in urine: NMP 1-2%, 5-HNMP 60-68%, MSI 0.1% and 2-HMSI 31-37% (percentage of the total amount of excreted NMP and metabolites) (6, 65). A similar relative proportion of metabolites in urine was measured after oral administration of 100 mg NMP (63). 5-HNMP has also been identified as the main metabolite in rat urine (32 , 40, 56).

In a number of studies both NMP and its various metabolites have been proposed as biomarkers for NMP exposure. To sum up, the biggest disadvantages for NMP as a biomarker are its short half-life and low concentrations in urine. The metabolites 5-HNMP and 2-HSMI have been identified as the most promising biomarkers for work-related exposure (inhaled and dermal) because of their long half-lives and high concentrations in urine (6, 12, 13, 14, 26).

Toxic effects

Human data

In one study involving repeated exposure to NMP for 8 hours per day over 2 days, 10 out of 12 workers, most of whom were women, showed skin irritation and contact dermatitis (31). The work task consisted of dipping one end of a plastic casing in NMP (10 seconds) and then dipping the opposite end in NMP (10 seconds). After each dipping the surplus NMP was wiped off with a paper towel which was replaced after every tenth plastic casing or 20 dippings. Each worker treated ca 110 casings per hour over an 8-hour working day. There was no information on exposure levels. Protective equipment consisted of latex gloves but it was reported that these were not used regularly. The authors of the study point out that after the workers began wearing cotton gloves (which were changed every hour) under the latex gloves to avoid dampness, no further skin problems were reported (31). Another study showed irritative contact dermatitis in three workers who were exposed to NMP for the first time. The effects were explained by the hygroscopic properties of NMP (25). There are no studies which show that occupational exposure to NMP leads to sensitization.

Workers exposed to up to 280 mg/m^3 NMP (8-h TWA) in the manufacture of microelectronic components involving the use of hot (80 °C) NMP, reported severe eye irritation and headaches (7). The exposure levels were on average between 0.1 and 6 mg/m^3 (8-h TWA) with processes in which NMP was not heated, but even exposure to relatively low levels (ca 3 mg/m^3) was reported to cause headaches and chronic eye irritation. No conclusive data has been presented on the frequency of these effects. Because of methodological shortcomings in the study it has not been possible to establish any dose-response relationship.

In a study of 38 graffiti cleaners who worked an 8-hour shift in Stockholm's underground rail system and were exposed to a mixture of solvents, including NMP, an increased occurrence was observed of fatigue, headaches and symptoms related to effects on the respiratory system, eyes and skin, when compared with controls. As well as NMP the cleaning agent also contained glycol ethers (e.g., dipropylene- and propylene glycol methyl ether), toluene, xylene, 1,2,4-trimethylbenzene, limonene, nonane, octane, etc. Levels of NMP in the atmosphere measured over 15 minutes with various work tasks were on average 4.71 mg/mg^3 (SD ± 6.17, range 0.01-24.6). The Swedish occupational exposure limits for short term exposure (300 mg/m^3, 15 min) or for 8-hours exposure (200 mg/m^3) were not exceeded. Only trimethylbenzene levels exceeded the Swedish occupational exposure limit (170 mg/m^3) with short term exposure (maximum measured levels were ca 280 mg/m^3). Because of the mixed exposure it was not possible to establish a specific relationship between exposure to NMP and the symptoms exhibited (29).

Workers at a German adhesives plant who cleaned containers with the help of NMP reported irritation of the upper respiratory tract and eyes as well as headaches when exposed to 15.5 mg/m^3 (8-h TWA) with a 5-minute maximum exposure of 85 mg/m^3 NMP (5). A Japanese study of 15 workers who cleaned components with an NMP solution (>90%), examined clinical effects (urine and blood

status) and effects on motor and cognitive functions. Exposure, which was mainly via inhalation, was measured as ca 0.6-1 mg/m^3 (8-h TWA, 5 days). The authors reported no effects when compared with the control group (39).

When six research volunteers were exposed to 10, 25, and 50 mg/m^3 NMP over 8 hours, no acute nasal changes were observed in the form of swelling of mucous membranes (measured using acoustic rhinometry), nor any effects on FEV_1, vital capacity and forced vital capacity measured with a spirometer. Responses to a questionnaire about subjective symptoms related to smell and irritation of the nose, eyes or respiratory tract revealed no feelings of discomfort or irritative effects. Two research subjects reported a smell of acetone at 50 mg/m^3 but this was not described as unpleasant (65).

Van Thriel and co-workers (54) carried out a comprehensive exposure study of 16 healthy young male volunteers in order to examine any chemosensory effects of NMP under conditions similar to occupational exposure. The research subjects were exposed to 10, 40, and 80 mg/m^3 for 8 hours, once a week, every second week, for 8 weeks. To maximize any chemosensory effects a peak exposure scenario was also included, with a basal exposure of 25 mg/m^3 and 4 × 15-minute peaks of 160 mg/m^3 (the time-weighted average value measured was 72 mg/m^3). All exposure was carried out with or without physical activity, which consisted of 6 × 10-minute sessions on a bicycle ergometer (75 watt) during the 8 hours of exposure. The results showed that the research subjects were able to detect the smell of NMP which was reported to be somewhat unpleasant. No other symptoms associated with chemosensory effects were observed and no dose-response relationship (frequency of blinking, nasal airflow, breathing rate, mental concentration, etc.) was demonstrated. The authors concluded that NMP is a foul-smelling substance with no irritative properties, even at exposures of up to 160 mg/m^3 (54).

Animal- and in vitro-data

NMP shows weak acute toxicity in animals exposed to NMP orally, dermally or via inhalation, see Table 1. Studies have failed to show sensitization with dermal exposure of guinea pigs to NMP (E.I. du Pont de Nemours and Company 1976, referred to in (22)). The potential irritant effects of NMP on the skin and eyes have been tested in rabbits and the results have indicated low dermal irritation (0.5 ml undiluted NMP) and a moderate and brief irritant effect on the eyes (0.1 ml undiluted NMP) (2).

A number of inhalation studies with repeated exposure to NMP (in the form of aerosol or vapour) have been carried out but according to SCOEL (48) and IPCS (22) the studies by Lee and co-workers (30) and the studies by BASF (1992-1995) are regarded as the most reliable because they recorded sufficient details on methods and results to allow them to be used as a basis for risk assessment. This summary therefore focuses on these. The other studies are unpublished industrial reports that are not publicly available.

Table 1. Summary of acute toxicology data for NMP in animals (data from ref. 22 and 61)

Test	Effect/effect level
Oral LD_{50} (rats, mice, rabbits, guinea pigs)	3500 - 7900 mg/kg
Dermal LD_{50} (rats and rabbits)	2500 - 10,000 mg/kg
Inhalation LC_{50} (rats; whole body exposure)	≈1700 mg/m^3
Inhalation LC_{50} (rats; head and nose exposure)	>5100 mg/m^3
Primary eye irritation (rabbits)	Moderate reversible eye irritation
Primary skin irritation (rabbits)	Largely non-irritant

Lee and co-workers exposed CD-1 rats (whole body exposure) to 100, 500 or 1000 mg NMP/m^3, 6 hour/day, 5 days per week for 4 weeks. Exposure was mainly in the form of aerosol (>95% of droplets <10 μm). Exposure to the highest dose (1000 mg/m^3) resulted in excess mortality and treatment was discontinued after 10 days. Concentration-related lethargy and irregular breathing were observed with all doses and were reversible within 30-45 min with the two lower doses (100 and 500 mg/m^3). No histopathological changes were reported at these lower exposure levels (30).

The same group also carried out a 2-year study with CD-1 rats (whole body exposure, 120 rats of each sex and for each dose level) exposed to 0, 40, or 400 mg NMP/m^3 for 6 hours/day, 5 days per week, in the form of vapour. Haematological, histopathological, and blood- and urine-chemical analyses were carried out after 1, 3, 6, 12, 18 and 24 months. After 18 months male rats exposed to 400 mg/m^3 showed higher haematocrit values and higher serum levels of alkaline phosphatase than the control group. This difference was not observed after 24 months of exposure. On the other hand, body weight was somewhat reduced (6%) in male rats. At 400 mg/m^3 male rats produced large volumes of urine and the urine was dark yellow in both male and female rats (30).

BASF carried out a number of inhalation studies in the 1990s which have been quoted in the IPCS and SCOEL reports on NMP (22, 48). As the reports from BASF are not freely available the assessment below is based on summaries by IPCS and SCOEL. Male and female rats (head exposure only, 10 rats of each sex and for each dose level) exposed to 10-10,000 mg NMP/m^3 in the form of aerosol 6 hours/day, 5 days per week for 2, 4 or 13 weeks. The 13-week study from 1994 can be found as an industry report in ECHA's database and is reported here. The results and conclusions are difficult to assess as they were not fully reported. Wistar rats were exposed to 0, 500, 1000 or 3000 mg/m^3 using the same exposure strategy as above. Exposure to 3000 mg/m^3 caused irritation of the airways and lungs, reduced testicular weight (15%) with associated histopathological changes, mild systemic toxic effects comprising reduced body weight (10%, males, day 33), mild hepatotoxicity and changes in haematological parameters.

Exposure to 1000 mg/m^3 caused transient weight loss as well as irritation of the nasal passages. A NOAEL of 500 mg/m^3 was reported for both male and female rats. Further studies with full body exposure of rats to 1000 mg NMP/m^3 in the form of aerosol (same exposure strategy as above) with small (~ <4 µm) or large (~ >5 µm) droplets and at different humidities (10-70% RH) showed that the toxic effects were stronger with larger droplets and higher humidities. This was observed as higher mortality and more severe organ damage in, for example, the spleen, lungs and bone marrow (22, 48).

As with the inhalation studies, a number of oral exposure studies have been carried out, but SCOEL (48) has concluded that only a gavage study by BASF in rats and three dietary studies in rats and mice by Malek, Malley and co-workers (34, 35, 36) report sufficient details of methodology and results to be used as a basis for risk assessment. The other studies are unpublished industrial reports that are not publicly available.

In a 28-day study in rats (10 rats of each sex) carried out by BASF in 1978, 0, 257, 514, 1028 or 2060 mg NMP/kg body weight/day, for 5 days per week, for 4 weeks was administered via stomach tube. Dose-related changes were observed, including tremors, restlessness, ruffled fur, reduced body weight gain and increased relative liver and kidney weights. Male rats exposed to 2060 mg/kg body weight/day showed reduced relative and absolute testicular weight with associated histopathological changes. A NOAEL (effect on testes) of 514 mg/kg body weight/day was reported (22).

Studies of oral exposure of rats [Crl:CD (SD)BR] to NMP via diet was carried out by NMP Producers Group (34, 35, 36) and included dosage levels up to 30,000 mg/kg feed for 28 days, 18,000 mg/kg feed for 90 days and 15,000 mg/kg feed for 2 years. The results show that NMP had a sedative effect, with a consequent decrease in body weight gain at higher dosage levels together with reduced food consumption. In the 2-year study male rats in the high-dose group showed a significantly increased frequency of severe progressive nephropathy (19%) accompanied by increased mortality (8%). Moreover, male rats in the high-dose group showed increased incidence of polyarteritis in the caecum, the mesenteric lymph nodes, and the testes. It was concluded that the kidney was the target organ in male rats, even though testicular degeneration and atrophy was repeatedly observed in the high-dose group. Female rats in the high dose group showed reduced levels of lymphocytes in the mesenteric lymph nodes. Dose-dependent but statistically non-significant effects were also observed in the lower dosage groups.

- In the 28-day study a NOAEL of 6000 mg/kg (429 mg NMP/kg body weight/day) was reported for males and 18,000 mg/kg (1548 mg NMP/kg body weight/day) for females, with weight reduction and effects on clinical-chemical parameters as end-points (34).
- The 90-day study reported a NOAEL of 3000 mg/kg (169 and 217 mg NMP/kg body weight/day, for males and females, respectively) with weight reductions and neurological changes as end-points (35).

- The 2-year study reported a NOAEL of 5000 mg/kg (207 and 283 mg NMP/kg body weight/day for males and females, respectively), with nephropathy and reduced lymphocyte levels, respectively, as end-points (36).

The studies carried out in B6C3F1 mice over 28 days, 90 days and 18 months showed fewer clear effects in terms of reduced body weight gain and feed consumption compared with those observed in rats. Centrilobular hypertrophy and increased liver weight were observed in male and female mice in the dosage group receiving 7500 mg NMP/kg feed for 90 days or 18 months and in male mice exposed to 1200 mg/kg for 18 months. Histopathological changes were observed in the kidneys of mice exposed to ≤7500 mg/kg for 28 days.

- In the 28-day study a NOAEL of 2500 mg/kg (720 mg NMP/kg body weight/day) was reported for males and a figure of 7500 mg/kg (2970 mg NMP/kg body weight/day) for females, with pathological changes in the renal tubules as the end-point (34).
- In the 90-day study a NOAEL of 1000 mg/kg (277 mg NMP/kg body weight/day) was reported, with increased liver weight as the end-point (35).
- In the 18-day study a NOAEL of 600 mg/kg (89 mg NMP/kg body weight/day) was reported for males and 1200 mg/kg (115 mg NMP/kg body weight/day) for females, with increased liver weight and hypertrophy of liver cells as end-points (36).

In 1983 Becci and co-workers carried out a sub-chronic exposure study with beagle dogs (8). The animals were exposed via diet to 0, 25, 79, or 250 mg NMP/kg body weight/day for 13 weeks. The results showed no statistically significant, dose-dependent effects that were regarded as toxicologically relevant.

Exposure to 0.01, 0.1, 1.0 or 5.0% (vol/vol), which is equivalent to 0.001, 0.01, 0.1 and 0.5 mol/l NMP in the medium for 4 or 24 hours, caused strong effects on oxidative and non-oxidative glucose metabolism in the rat muscle cell line L6. Exposure led to a dose-dependent inhibition of ATP and lactic acid formation in parallel with a stimulation of reactive oxygen species formation and oxygen consumption (60).

Campbell and co-workers studied the toxicity of NMP and the two metabolites MSI and 2-pyrrolidone as well as the final oxidation product succinimide. This was carried out using a Microtox assay that is based on the metabolic capacity of the marine microorganism *Vibrio fisheri*, which is measured after exposure. The authors concluded that MSI was the most toxic of the substances tested, with an EC_{50} of 1.2 g/l (0.012 mol/l) (11).

Genotoxicity

A number of *in vitro* studies have been carried out to determine whether NMP has any genotoxic properties. Research in bacterial systems and mammalian cell lines

shows only negative results with respect to mutagenicity. Cytotoxic effects in *Salmonella typhimurium* exposed to high doses of NMP were reported by Wells and co-workers (57). However, it has been shown that NMP can induce aneuploidy (an uneven number of chromosomes) in *Saccharomyces cerevisiae* at high doses (7.6-23 g/l, equivalent to 0.08-0.23 mol NMP/l) (37, 38, 59).

Two *in vivo* studies carried out with NMRI mice and hamsters exposed orally to doses of NMP up to 3800 mg/kg body weight, showed no mutagenic effects (micronuclei or chromosome aberrations) (16).

Carcinogenicity

A 2-year inhalation study in CD-1 rats exposed to 0, 40, or 400 mg/m^3 NMP for 6 hours/day, 5 days/week, in the form of vapour showed no carcinogenic effects (30). Histopathological studies were carried out on kidneys, bone marrow, lymph nodes, spleen and lungs. A 2-year study in rats [Crl:CD (SD)BR] exposed to 0, 1600, 5000 and 15,000 mg NMP/kg feed (equivalent to 0, 66.4, 207 and 678 mg NMP/kg body weight/day for males and 0, 87.8, 283 och 939 mg NMP/kg body weight/day for females) with histopathological studies (44 tissues), showed no dose-dependent carcinogenic effects (36). A 2-year study in B6C3F1 mice exposed to 0, 600, 1200 or 7200 mg NMP/kg feed (equivalent to 8, 89, 173 and 1089 mg NMP/kg body weight/day for males and 0, 115, 221 and 1399 mg NMP/kg body weight/day for females) with histopathological studies (44 tissues), reported a significant increase in the incidence of hepatocellular adenoma and carcinoma in males in the dose group with 7200 mg NMP/kg feed (12 out of 50 animals and 13 out of 50 animals, respectively, compared with 5 out of 50 and 4 out of 50, respectively, in the control group) in parallel with an increase in the number of hepatocellular foci. The same effect was observed in females in the same dose group (7 out of 50 animals and 3 out of 50 animals, respectively, compared with 2 out of 50 and 0 out of 50, respectively, in the control group) but the increase was regarded as not exceeding the historical background variation. The authors suggested that the tumours were not formed via a genotoxic mechanism but as a result of increased cell proliferation in the liver (36). This was based in part on data on centrilobular hypertrophy in males in the high-dose group.

No epidemiological studies of carcinogenicity have been found in the literature.

Effects on reproduction

Human data

A 23-year-old laboratory technician was exposed to NMP through her work during the first 20 weeks of her pregnancy, in particular in week 16 of her pregnancy when she cleaned up spilled NMP During the 4 days following this exposure she experienced a feeling of discomfort, headache and nausea, and in week 25 signs of delayed foetal development were noticed. She gave birth to a stillborn baby in week 31. There was no information on how much NMP the mother was exposed

to, and even though it is uncommon to have a miscarriage at this stage it was concluded that it could not be ascertained whether NMP was the causative factor (10, 52).

Animal data

The effects of NMP exposure on reproduction have been investigated in several studies in which exposure was mediated via inhalation or by oral or dermal administration. The majority of studies were carried out in rats and the results from these studies, found in publicly accessible databases (e.g., PubMed), have been summarized together with established NOAEL- and LOAEL-values in Table 2a, b and c.

The studies of repeated exposure carried out by Malley and co-workers showed that exposure to high levels of NMP (15,000 mg/kg feed) led to reduced testicular weight and histopathological changes, including degeneration and atrophy (36). Toxicokinetic studies in rats with radioactively labeled NMP detected high levels in the testes and at other sites (49, 55). A fertility study by Fries and co-workers showed no effect on testicular morphology nor on sperm count in Mol:Wist rats exposed to 618 mg/m^3 NMP for 90 days (19). In another study male Imp:WIST rats were exposed orally to 0, 100, 300 or 1000 mg NMP/kg body weight/day for 10 weeks and mated with non-exposed females to examine the effects on fertility and foetal development. The results showed that 1000 mg/kg/day made the male rats infertile. Histopathological studies showed severe necrotic changes in the epithelial cells in the vas deferens. A 300 mg/kg/day dose did not affect fertility in male rats but did reduce the viability of their offspring (50).

NMP has been shown to pass through the placenta in pregnant rats, with comparable levels in the blood of foetuses and mothers (43). It has been reported that NMP does not cause reproductive toxicity or maternal toxicity in rats (Charles River CD) exposed via inhalation to up to 360 mg/m^3, 6 h/day on days 6-15 of pregnancy (30). Mol:Wist rats exposed to 680 mg/m^3 NMP vapour for 6 h/day on days 4-20 of pregnancy showed increased preimplantation loss compared with the control group. Delayed bone formation was observed in the foetuses, in the cranium, cervical vertebrae, sternum, etc.(20). The same research group exposed Mol:Wist rats to NMP (622 mg/m^3, 6 h/day, days 7-20 of pregnancy) and observed effects on cognitive development in offspring, including increased latency in the Morris water maze and operant delayed spatial alternation (Skinner boxes) during weaning. No maternal toxicity was observed (21). Crl:CD (SD)BR rats exposed to up to 478 mg NMP/m^3 via inhalation showed no effects on the number of pregnancies, nor on the size or viability of the litter. A somewhat lower foetal weight was observed in the high dose group compared with the control group (up to 12%) (53). In the same study some reduction was seen in response to noise by mothers in the highest dose group.

Table 2a. Summary of the effects of NMP on reproduction via inhalation exposure (whole body exposure) in animals.

Animal species/type of study	Expo. (mg/m^3)	Toxic effects		NOAEL, LOAEL (mg/m^3)	Ref.
		Foetus/young	Parent Mother/Father		
Subchronic tests					
Male rats, 6 h/d, 7 d/wk, 90 d	618		No effect on testes and sperm	Reproductive toxicity: NOAEL = 618	19
Developmental toxicity tests					
Rats, 6 h/d, d 6-15 of pregnancy	100	No effect	Lethargy and irregular breathing during the first 3 d of expo.	Reproductive toxicity: NOAEL = 360 Maternal toxicity: LOAEL = 100	30
	360	No effect	Lethargy and irregular breathing during the first 3 d of expo.		
Rats, 6 h/d, d 7-20 of pregnancy	622	Reduced body weight, cognitive effects	No effect	Reproductive toxicity: LOAEL = 622 Maternal toxicity: NOAEL = 622	21
Rats, 6 h/d, d 4-20 of pregnancy	680	Increased preimplantation loss, delayed bone formation, reduced foetal weight	No effect	Reproductive toxicity: LOAEL = 680 Maternal toxicity: NOAEL = 680	20
Rats, 6 h/d, d 6-20 of pregnancy	125	No effect	No effect	Reproductive toxicity: NOAEL = 250 Maternal toxicity: NOAEL = 125	45
	250	No effect	Reduced body weight gain		
	500	Reduced foetal weight	Reduced body weight gain and feed consumption		
Fertility tests					
Rats, 6 h/d, 7 d/wk*	41	No effect	No effect	Reproductive toxicity: NOAEL = 206 LOAEL = 478 Reproductive and maternal toxicity: NOAEL = 206 LOAEL = 478	53
	206	No effect	No effect		
	478	Reduced body weight (F_1)	Reduced response to noise (P_0)		

Expo. = exposure, NOAEL = No observed adverse effect level, LOAEL = Lowest observed adverse effect level, d = day/days, h = hours, wk = week
*two-generation study, F_1 = the first generation, P_0 = parental generation

Table 2b. Summary of reproductive effects of NMP after oral (gavage) and dermal exposure of animals.

Animal species/type of study	Expo. (mg/kg/d)	Toxic effects		NOAEL, LOAEL (mg/kg/d)	Ref.
		Foetus	Parent Mother/Father		
Oral exposure					
Developmental toxicity tests					
Rats, d 6-20 of pregnancy	125	No effect	No effect	Reproductive toxicity: NOAEL = 125 LOAEL = 250 Maternal toxicity: NOAEL = 250 LOAEL = 500	44
	250	Reduced foetal weight	No effect		
	500	Increased resorption, reduced foetal weight, and external, internal and skeletal malformations	Reduced body weight gain and feed consumption		
	750	Increased resorption, reduced foetal weight and viability, and external, internal and skeletal malformations	Reduced body weight gain and feed consumption		
Fertility tests					
Rats, 5 d/wk, 10 wk	100	No effect	No effect	Reproductive toxicity: NOAEL = 100 LOAEL = 300 Paternal toxicity: NOAEL = 300 LOAEL = 1000	50
	300	Reduced viability	No effect		
	1000	-	Infertility (males)		
Rats, 5 d/wk, 9 wk	150	Reduced survival (3 wk)	Reduced body weight gain	Reproductive toxicity: LOAEL = 150 Maternal toxicity: LOAEL = 150	51
	450	Reduced survival (3 wk)	Reduced fertility and body weight gain		
	1000	Reduced foetal viability.	Reduced fertility and body weight gain		
Dermal exposure					
Developmental toxicity tests					
Rats, d 6-15 of pregnancy	500	No effect	No effect	Reproductive and maternal toxicity; NOAEL = 500 LOAEL = 1100	9
	1100	Massive resorption, reduced foetal viability and foetal weight	Reduced body weight gain		
	2500	-	Lethal (100%)		
Rats, d 6-15 of pregnancy	75	No effect	No effect	Reproductive and maternal toxicity: NOAEL = 237 LOAEL = 750	9
	237	No effect	No effect		
	750	Increased resorption, delayed bone formation	Reduced body weight gain		

Expo. = exposure, NOAEL = No observed adverse effect level, LOAEL = Lowest observed adverse effect level, d = day/days, wk = week/weeks

Table 2c. Summary of reproductive effects of NMP metabolites after oral (gavage) exposure of animals.

Metabolite/ Animal species	Expo. (mg/kg/d)	Toxic effects		NOAEL, LOAEL (mg/kg/d)	Ref.
		Foetus	Mother		
5-HNMP					
Rats, d 6-20 of pregnancy	250, 500, 750, 1000	No effect	No effect	Reproductive toxicity: NOAEL = 1000 Maternal toxicity: NOAEL = 1000	46
MSI					
Rats, d 6-20 of pregnancy	500	No effect	No effect	Reproductive toxicity: NOAEL = 500 LOAEL = 750 Maternal toxicity: NOAEL = 500; LOAEL = 750	46
	750	Delayed bone formation, internal malformations	Reduced body weight gain and feed consumption		
	1000	Reduced foetal weight, external and internal malformations	Reduced body weight gain and feed consumption		
	1250	Reduced foetal weight, increased resorption, external and internal malformations	Reduced body weight gain and feed consumption		
2-HSMI					
Rats, d 6-20 of pregnancy	250	No effect	No effect	Reproductive toxicity: NOAEL = 1500 Maternal toxicity: NOAEL = 250 LOAEL = 500	46
	500	No effect	Reduced body weight gain and feed consumption		
	1000	No effect	Reduced body weight gain and feed consumption		
	1500	No effect	Reduced body weight gain and feed consumption		

Expo. = exposure, NOAEL = No observed adverse effect level, LOAEL = Lowest observed adverse effect level, d = day

In a study by Sitarek and co-workers female rats (Wistar rats) were exposed by gavage, 5 days/weeks to 0, 150, 450 or 1000 mg NMP/kg body weight/day, 2 weeks before mating and during mating, pregnancy and lactation (total ca 9 weeks). The females were mated with non-exposed males and the toxic effects on reproduction were studied. For the two highest doses exposure resulted in a significantly lower fertility index (percentage of females who became pregnant 71.4 and 68.2%, respectively, compared with 91.7% for the control group). Exposure to NMP at all doses resulted in a significantly lower viability index (per-

centage survival of young after 4 days, were 86.4, 71.6, and 0%, respectively, compared with 94% for the control group), reduced survival of newborn rats during the first 3 weeks after birth (78.2, 43.4 and 0%, respectively, compared with 96.1% for the control group) and lower body weight gain during days 0-20. The reduction in body weight gain for mothers showed a dose-response relationship, with 87.7, 75.6 and 40.7% relative body weight gain for the three doses, compared with 100% for the control group (51).

Saillenfait and co-workers have carried out three studies in which they examined the effects on development of NMP and the three metabolites 5-HNMP, MSI and 2-HMSI in Sprague-Dawley rats exposed via inhalation (45) or oral administration (44, 46), see Tables 2a, b and c. In the inhalation study pregnant females were exposed (whole body) to 0, 125, 250 or 500 mg NMP/m^3, 6 h/day on days 6-20 of pregnancy. Reduced foetal weight (5%) was observed at 500 mg/m^3 and mothers showed reduced body weight gain (23%, day 6-13) which was associated with reduced feed consumption (8%, day 6-21) at the same but not at lower doses. The study with oral administration (gavage, 0, 125, 250, 500 or 750 mg NMP/kg body weight/day on days 6-20) showed reduced body weight gain (25 and 50%, respectively) and reduced feed consumption (8 and 15%, respectively) in pregnant rats given 500 and 750 mg/kg/day, respectively (44). Effects on the foetus were observed with the 250 mg/kg/day dose and higher and consisted of increased resorption, reduced foetal weight, and external, internal and skeletal malformations. Exposure to the three NMP metabolites at up to 1500 mg/kg/day on days 6-20 of pregnancy showed that 5-HNMP was toxic neither to the foetus nor the mother and that 2-HSMI was only toxic to the mother (reduced body weight gain and feed consumption) at the doses tested (46). The metabolite MSI caused a dose-dependent increase in delayed bone formation, external and internal malformations, and increased resorption at the 750 mg/kg/day dose and higher. Effects on the mother were observed at this same dose and consisted in reduced body weight gain and feed consumption. The authors concluded that none of the three metabolites was a more potent teratogen than NMP.

A dermal exposure study carried out by Becci and co-workers in the 1980s observed increased foetal resorption at the dose 750 mg NMP/kg body weight/day (exposed on days 6-15) in pregnant Sprague-Dawley rats. The same dose resulted in reduced body weight gain in mothers (9).

Flick and co-workers studied the reproductive toxicity of NMP and its three metabolites (5-HNMP, MSI and 2-HMSI) in an *in vitro* culture system comprising whole rat embryos. The embryos were exposed *in vitro* to up to 0.06% NMP (vol/vol), equivalent to 0.006 mol/l in the medium, and up to 0.44% (vol/vol) of 5-HNMP, MSI or 2-HSMI on days 9.5-11.5 of pregnancy. The results showed that exposure to NMP (≤0.03%/0.003 mol/l) and 5-HNMP (≤0.10%) caused foetal injuries comprising abnormalities of the cranium, abnormal development of the second visceral arch and delayed anterior neuropore closure. On this basis the authors concluded that NMP and 5-HNMP can be classified as weak teratogens and that 2-HMSI and MSI have no teratogenic properties (18).

Poet and co-workers used PBPK- and benchmark dose-modelling to calculate the point of departure (POD) as the area under the blood concentration-time curve (AUC) for NMP in the blood (41). The calculations were mainly based on two experimental inhalation studies in rats (45, 53). Reduced weight of foetuses and newborn was regarded as the critical effect. It was calculated that the POD value was equivalent to inhalation exposure to 1977.6 mg/m^3 (8 h/day, 5 days/week) (41). It should be pointed out that this calculation of equivalence includes the questionable assumption that rats and humans have similar sensitivity to NMP at the same internal concentrations, i.e., they differ only in terms of toxicokinetics. It can be noted that Sallenfait *et al*. (45) observed reduced foetal weight in rats at 500 mg/m^3 (NOAEL 250 mg/m^3).

The two companies BASF and GAF, which also produce NMP, have carried out several further studies which examined the toxic effects of NMP on animal reproduction. As these reports are difficult to access, this review of them is based on information and results presented as industrial reports in ECHA's database for NMP. The results and conclusions are difficult to assess as they were not fully reported.

In 1993 BASF studied the effects of NMP on reproduction in rabbits and included an inhalation study and a dermal exposure study. In the inhalation study pregnant rabbits were exposed (nose/head) to up to 1000 mg/m^3 NMP (mix of vapour/aerosol) 6 h/day on days 7-19 after insemination. The highest dose produced no maternal toxicity or effects on fertility but there was an increased incidence of skeletal abnormalities (extra 13th rib) in foetuses. A NOAEL of 500 mg/m^3 was established for foetal toxicity and 1000 mg/m^3 for maternal toxicity. In the dermal application study, in which pregnant rabbits were exposed to up to 1000 mg NMP/kg body weight/day as a 40% aqueous solution (6 h/day for days 7-19 after insemination), no toxic effects were observed in the female rabbits. Teratogenic effects were only observed at 1000 mg/kg body weight/day and, in this study too, included the development of a 13th rib. A NOAEL of 300 mg/kg body weight/day was established for foetal toxicity and 1000 mg/kg body weight/day for maternal toxicity.

In 1991 GAF carried out studies in which it dosed pregnant rabbits perorally with 0, 55, 175 or 540 mg/kg body weight/day on days 6-18 after insemination. Dosing with 175 or 540 mg/kg/day caused reduced body weight gain in the mothers. Teratogenic effects were only observed at the highest dose and included postimplantation loss, altered foetal morphology and increased incidence of cardiovascular and cranial malformations. A NOAEL of 175 mg/kg body weight/day was established for foetal toxicity and 55 mg/kg body weight/day for maternal toxicity.

Dose-effect-/dose-response-relationships

The acute toxicity of NMP is relatively low, see Table 1. Dose-response relationships for toxic effects after inhalation exposure in humans are summarized in

Table 3, and after inhalation exposure and oral exposure in animals in Tables 4 and 5, respectively.

Studies with human research subjects indicate that NMP is weakly irritant or non-irritant with inhalation exposure (up to 160 mg/m^3) (54, 65). Studies of occupational exposure indicate that NMP can cause varying degrees of irritation, especially with exposure to high doses of NMP in vapour form (340 mg/m^3) (5, 7) or with skin exposure (25, 31). Workers experienced skin problems after 2 or several days of exposure, while research subjects were exposed for one day (65) or had one-day exposures with a 2-week gap between each (54). In these studies the research subjects were exclusively men whereas the group of workers studied included women. Another possibility that might be significant is that a damp workplace environment, or alternatively a closed environment, might contribute to irritant contact dermatitis. Such conditions might make studies carried out in exposure chambers irrelevant in establishing exposure limits.

No studies reporting that NMP causes sensitization have been found in the literature.

Inhalation studies in rats show that exposure to 100 mg NMP/m^3 results in transient lethargy and irregular breathing. Exposure of female rats at the same level for 6 h/day on days 6-15 of pregnancy had no effect on the foetuses (30). Reduced body weight in newborn animals was observed in a two-generation study in rats exposed to 478 mg NMP/m^3. The dose induced maternal toxicity in the form of reduced response to noise (53). Reduced body weight and effects on cognitive functions were observed in the offspring of rats exposed to 622 mg NMP/m^3, on days 7-20 of pregnancy. No maternal toxicity was seen at this dose (21).

A reduced survival rate for rat offspring was observed 3 weeks after birth, in parallel with reduced body weight gain (12%) for mothers exposed orally to 150 mg NMP/kg body weight/day (51). Exposure of rats to 250 mg NMP/kg body weight/day, on days 6-20 of pregnancy resulted in reduced foetal weight. At the 500 mg NMP/kg body weight/day dose an increased number of resorptions and skeletal, external and internal malformations was also observed. (44). At the higher dose maternal toxicity was seen in the form of reduced body weight gain (25%) and feed consumption (8).

The authors of two studies involving the oral exposure of rats and mice to NMP commented that males appeared to be more sensitive to NMP than females. In both studies this was possibly related to gender differences in the metabolism of NMP (34,36).

Conclusions

There is insufficient data to establish a critical effect for NMP in occupational exposure. On the basis of animal research the critical effect of NMP is transient CNS effects (irregular breathing, drowsiness). This has been observed with inhalation of 100 mg NMP/m^3.

Irritant contact dermatitis has been reported with occupational exposure to NMP in liquid form.

NMP is toxic to reproduction in animals. Reduced survival of newborn rats was observed with an oral dose of 150 mg/kg body weight/day. With inhalation exposure reduced body weight of offspring as well as some maternal effects were observed at 478 mg/m^3. Malformations and cognitive effects have been observed at somewhat higher exposure levels.

NMP is efficiently absorbed both via the respiratory tract and the skin (also in vapour form) and skin uptake can be substantial.

Table 3. Dose-effect-/dose-response-relationships in humans exposed to NMP via inhalation.

Exposure situation	8-h TWA, mg/m^3 (range)	Number individuals	Effects	Ref.
Occupational exposure, manufacture of microelectronic components where hot (80 °C) NMP is used in certain processes	< 0.12	6	No reported effect.	7
	(2.9-6.2)	5	Discomfort due to unpleasant smell. Chronic headache after full working day.	
	66 (62-70)	4	Discomfort and eye irritation after 30 seconds of exposure.	
	280 (200-340)	3	Immediately intolerable.	
Exposure chamber, 8 hours	10, 25, 50	6	No effect on the eyes, nose, or airways at any exposure level.	63
Occupational exposure, bottling of adhesive products	1.8 (0.9-2.8)	4	No effect on the eyes, nose, or airways.	5
Occupational exposure, cleaning containers with NMP	8.5 (3.4-15.5; max 85 for 5 minutes)	3	A worker with short term exposure to 85 mg/m^3 reported irritation of the upper airways and eyes, as well as headache.	5
Exposure chamber, 8 hours with or without physical activity	10, 40, 80, 72*	16	No chemosensory effects. Unpleasant smell at the two higher doses.	54
Occupational exposure, cleaning of components (5 days).	(0.6-1.0)	14	No effect on clinical, motor or cognitive parameters.	39

8-h TWA = 8-hours time-weighted average value
*Basic exposure 25 mg/m^3 + 4 x 160 mg/m^3 for 15 minutes.

Table 4. Dose-effect-/dose-response-relationships in animals exposed to NMP via inhalation.

Exposure (mg/m^3)	Animal species	Exposure time	Number of animals	Effects	Ref.
100, 500, 1000	Rats	6 h/day, 5 days/wk, 4 wk	15/sex/ group	Transient lethargy and irregular breathing, no histopathological findings at the two lowest exposure levels. Death, lethargy, irregular breathing, histopathological findings showing bone marrow hypoplasia, atrophy and lymphoid organ necrosis at the highest dose.	30
40, 400	Rats	6 h/day, 5 days/wk, 2 yr	120/sex/ group	At 400 mg/m^3 reduced body weight (6%) was observed in male rats, while dark-coloured urine and large urine volumes were seen in both sexes, though without any effect on the kidneys.	30
100, 360	Rats	6 h/d, days 6-15 of pregnancy	25 females/ group	No effect on the foetus at any exposure level. Lethargy and irregular breathing in mothers on days 1-3 at both exposure levels.	30
618	Rats	6 h/day, 7 days/wk, 90 days	12 males	No effect on testes and sperm	19
622	Rats	6 h/day, days 7-20 of pregnancy	18 females	Cognitive development effects in offspring, no maternal toxicity.	21
680	Rats	6 h/day, days 4-20 of pregnancy	28 females	Increased preimplantation loss, delayed bone formation, reduced foetal weight, no maternal toxicity.	20
41, 206, 478	Rats	6 h/day, 7 days/wk, 14 wk*	10 males 20 females/ group	Reduced body weight up to weaning (F_1) and reduced response to noise (P_0) observed at the highest dose 478 mg/m^3.	53
125	Rats	6 h/day, days 6-20 of pregnancy	20 females	No effect on foetuses or mothers.	45
250			20 females	No effect on foetuses, reduced body weight gain in mothers.	
500			25 females	Reduced foetal weight, reduced body weight gain and food consumption in mothers.	

h = hours, wk = week/weeks
*two-generation study

Table 5. Dose-effect-/dose-response relationships in animals with oral (via gavage or feed) exposure to NMP.

Exposure, males/females (mg/kg body weight/day)	Animal species	Exposure time	Number of animals	Effects	Ref.
25, 79, 250	Beagle dogs	90 days	6/sex/group	No effect at any exposure level.	8
149/161	Rats	28 days	5/sex/group	No effect.	34
429/493			5/sex/group	No effect.	
1234/1548			5/sex/group	No effect in females, reduced body weight and effects on clinical-chemical parameters in males.	
2019/2268			5/sex/group	Reduced body weight and effects on clinical-chemical parameters and on bone marrow in both sexes. Testicular degeneration.	
130/180	Mice	28 days	5/sex/group	No effect.	34
720/920			5/sex/group	No effect.	
2130/2970			5/sex/group	No effect in females, effect on kidneys in males.	
2670/4060			5/sex/group	Kidney effects in both sexes.	
169/217 433/565 1057/1344	Rats	90 days	20-26/sex/ group	At the two highest dose levels reduced body weight gain in both sexes and neurological effects in males.	35
277	Mice	90 days	10/sex/group	No effect.	35
619			10/sex/group	No effect in females, increased liver weight in males.	
1931			10/sex/group	Increased liver weight and hypertrophy in both sexes.	
66.4/87.8 207/283 678/939	Rats	2 years	62/sex/group	At the highest dose level reduced body weight gain in both sexes and nephropathy in males.	36
89/115	Mice	18 months	50/sex/group	No effect.	36
173/221			50/sex/group	No effect in females, increased liver weight in males.	
1089/1399			50/sex/group	Increased liver weight and hypertrophy in both sexes.	

Table 5. Continued.

Exposure, males/females (mg/kg body weight/day)	Animal species	Exposure time	Number of animals	Effects	Ref.
125	Rats	Days 6-20 of pregnancy	22 females	No effect.	44
250			24 females	Reduced foetal weight, no effect in mothers.	
500			25 females	Foetal malformations, reduced body weight gain in mothers.	
750			25 females	Reduced foetal viability and malformations, reduced body weight gain in mothers.	
100	Rats	5 days/week, 10 weeks +1 week during mating	24 males	No effect.	50
300			23 males	Reduced foetal viability, no effect in fathers.	
1000			22 males	Infertility.	
150	Rats	5 days/week, 9 weeks (before, during and after pregnancy)	26 females	Reduced survival in offspring (3 weeks postnatally), and reduced body weight gain in mothers.	51
450			28 females	Reduced survival in offspring (3 weeks postnatally), and reduced fertility and body weight gain in mothers.	
1000			22 females	Reduced foetal viability and reduced fertility and body weight gain in mothers.	

Potential conflicts of interest

Gunnar Johanson (member) has declared that he was involved in SCOEL's evaluation of N-methyl-2-pyrrolidone and the consensus resolution on recommended occupational exposure limits for the EU.

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Consensus Report for Crystalline Silica, Quartz

December 31, 2012

This consensus report is based on a document on crystalline silica published by WHO in 2000 (39) and on a monograph on silica from IARC (The International Agency for Research on Cancer) (72). Certain parts of the report are based on an overview of current knowledge issued by the Swedish Work Environment Authority 2011 (11). There is a substantial volume of scientific literature on crystalline silica and its health risks. In this report the literature concerning cancer and crystalline silica focuses on articles published after IARC's 1997 cancer classification and on articles of special interest (e.g., Swedish studies).

The search term "silicosis" yielded 7456 articles from PubMed (November 2011), with the earliest published studies dating back to the 1920s. The consensus report includes a description of those silicosis studies that are quoted as critical studies in CICAD's document from 2000 (39), as well as a number of subsequent epidemiological studies. The search term ”tridymite” retrieved 42,831 articles from PubMed and ”cristobalite” 42,913 articles (November 2011), the majority of which were studies of materials. Relevant studies of health effects have been included.

The report does not cover quartz-based nanomaterials.

Chemical-physical data

Quartz, CAS no:	14808-60-7
Cristobalite, CAS no:	14464-46-1
Tridymite, CAS no:	15468-32-3
Chemical formula:	SiO_2
Synonyms:	crystalline silicon dioxide
Mol. weight:	60.09 g/mol
Density:	2.6 g/ml (α-quartz)
	2.3 g/ml (cristobalite)
	2.3 g/ml (tridymite)
Melting point:	1610 °C (α-quartz)
Boiling point:	2230 °C (α-quartz)
Solubility:	Insoluble in water
Colour:	White or colourless

Occurrence, use

Silica (silicon dioxide) is a compound of silicon and oxygen. Crystalline silica in the form of quartz is a common mineral in the earth's crust and occurs, for example, in rock forms such as granite and gneiss. Quartz can be transformed into other crystalline forms, such as cristobalite and tridymite. These forms occur naturally at low levels but can be produced during industrial processes at high temperatures and high pressures, for example, when diatomaceous earth (diatomite, kieselguhr) is heated, in the manufacture of ceramics and silicon carbide, in foundry processes, or in other processes involving high temperatures. Silica is also found in an amorphous form, a more disordered structure which occurs naturally, for example, in opal, biogenic silica (in living matter), and kieselguhr. Amorphous silica is also produced synthetically and is used in products such as fillers or anti-caking agents (Swedish Chemicals Agency, Information on substances 2013: http://apps.kemi.se/flodessok/floden/kemamne_eng/kiseldioxid_eng.htm, (39)).

Diatomaceous earth (kieselguhr) consists of amorphous silica (65-90%). When kieselguhr (diatomite) is heated it is gradually converted to the crystalline forms tridymite, cristobalite, and quartz; the proportion of cristobalite can be relatively high.

The three crystalline structural types, quartz, cristobalite, and tridymite, occur in both alpha and beta forms. The high temperatures involved in their formation mean that the minerals initially exist in the beta form. When the minerals cool they are converted to the alpha form. The alpha form is therefore the one that occurs under normal conditions and the form that is commonly considered (39). In scientific publications quartz dust is normally referred to as ”silica dust” and the type of crystalline silica is not usually mentioned.

Sampling and analysis of α-quartz and cristobalite

The sampling of respirable dust is carried out by pumped sampling with use of a pre-separator for respirable dust (68); separation of the respirable fraction is carried out in accordance with international standards (49). The lowest quantifiable concentration in the measurement of respirable dust can be 0.08 mg/m^3 during sampling over a full 8-hour shift and at a flow rate of 2.5 l/min; the equivalent when sampling for 4 hours is 0.2 mg/m^3 (16).

The respirable fraction of quartz is sampled on a membrane filter. The sample is ashed in a low temperature oven, suspended in ethanol, and transferred to a silver filter. α-Quartz is determined by x-ray diffractometry (70, 99, 103). A typical limit of quantification could be 2 µg/sample, with a measurement uncertainty of up to ±25% at 2.0 – 19 µg and ±15% at 20 – 400 µg (17). For sampled air volumes of 600 and 1200 litres, respectively, from 4 and 8 hours sampling, respectively, at a flow rate of 2.5 l/min, the quantifiable concentrations are 0.0033 and 0.0017 mg/m^3, respectively. For cristobalite in air a quantifiable amount per sample could

be 5 µg (18), and therefore the lowest quantifiable concentrations in air for 4 and 8 hours sampling, respectively, would be 0.008 and 0.004 mg/m^3, respectively.

Exposure

Exposure to quartz is one of the most common forms of occupational exposure. In an international appraisal of occupational exposure, quartz was listed as the substances to which the greatest proportion of workers were exposed (48). It has been estimated that more than 3 million workers in Europe are exposed to quartz during their work, of whom around 85,000 are based in Sweden (76). Exposure to forms of crystalline silica other than quartz, e.g., cristobalite and tridymite, can occur in certain areas of occupation. Studies carried out in American foundries have demonstrated, for example, high levels of cristobalite in dust samples (74).

Exposure to quartz occurs during work involving soil and land and in the handling and use of products that contain quartz. Examples include agriculture, mining, stonemasonry, steel industry work, glass- and abrasive products-manufacturing, porcelain and ceramics work, building work (demolition, bricklaying, concrete- and casting-work) and sandblasting, see Table 1 (39, 72, 86). Exposure to quartz often involves dust with variable quartz content.

In the 1930s silicosis, pneumoconiosis, and lung disease caused by long term exposure to quartz dust were recognized as occupational diseases in Sweden (135). Stricter control of air levels of quartz was introduced and major efforts were made to reduce quartz levels in the workplace; the incidence of silicosis subsequently fell in Sweden (1).

A thesis on silicosis in Swedish industry was published in Sweden in the 1940s. A quarter of iron ore mineworkers, sand blasters, brick layers in steelworks, and workers in steel foundries had silicosis. The disease was most common in those who worked in the mining or crushing of quartz (25). The silicosis project "Silicosis in Sweden", which was started in the 1960s, tried to identify those occupational areas with an especially high risk of silicosis, e.g., where silicosis appeared after a particularly short period of time or where the disease reached an advanced stage during the period examined. Those occupations in which the highest risks were identified were the manufacture of scouring powders, rock and tunnel blasting, mining, sand blasting, iron foundry work, porcelain factory work, stonemasonry work, certain jobs in steel works and smelting plants, and the manufacture of silica gel (56). See Table 2 for dust levels in various industries, data from 1974.

Table 1. Examples of occupations where workers can be exposed to crystalline silica, quartz.

Industry/activity	Specific occupational tasks and sectors	Materials
Agriculture	Ploughing, harvesting, use of machinery	Soil
Mining operations	Drilling, loading, crushing	Rock, stone, ore
Quarrying/rock processing	Rock crushing, sand and gravel processing, blasting, slate- and stone-cutting work	Sandstone, granite, flint, sand, gravel, slate, kieselguhr
Building work	Blast cleaning of buildings and structures. Construction work, road- and tunnel-work, excavation and ground work, bricklaying, working with concrete, demolition work	Rock, earth, stone, concrete, mortar, plaster
Glass- and glass fibre-production	Processing of raw materials, installation and repair of fire-proof ceramic materials	Sand, crushed quartz, fireproof ceramic materials
Cement manufacture	Processing of raw materials	Clay, sand, limestone, kieselguhr
Grinding work	Silicon carbide production, abrasives production	Sand, sandstone
Ceramics work, including work with bricks, tiles, sanitary ware, porcelain, fireproof material, enamel	Mixing, moulding, glazing, enamel work, finishing	Clay, shale, flint, sand, kieselguhr
Ironworks and steelworks	Manufacture of fireproof materials and repair of furnaces	Fireproof materials
Foundries	Foundry work	Sand

Measurement using personal monitors began in Sweden in 1968. In 1990 exposure to respirable quartz dust was on average around 10-fold lower than in 1970 (see Table 3). In 2005 exposure levels were similar to those in 1990 (around 1/3 of the occupational exposure limit). Around 7% of all measurements made during this period exceeded the occupational exposure limit of 0.1 mg/m^3 (personal communication from Nils Plato, Unit of Occupational Medicine, Karolinska Institutet, May 2012).

Obligatory measurements of quartz exposure were reported to Swedish Work Environment Authority during the period 2002-2011. These are summarized in Table 4 which shows how many measurements have equalled or exceeded the Swedish occupational exposure limit of 0.1 mg/m^3. The equivalent Norwegian figures indicate that 34% of measurements equalled or exceeded that country's occupational exposure limit (0.1 mg/m^3) over the period 2007-2009. During the periods 2001-2003 and 2004-2006, 16% and 7% of measurements, respectively, equalled or exceeded the occupational exposure limit (126).

Table 2. Dust and quartz levels in different industries. Measurements of exposure to total dust, proportion of fine fraction, quartz level in fine fraction, and fine-grained quartz. Modified from ref. (56).

Activity	Number Samples (n)	Dust concentration (mg/m^3) (AM)	Fine fraction < 5 µm (weight%)	Quartz concentration (weight%)	Fine-grained quartz* (mg/m^3)
Mining industry, underground work	249	5.9	21	7	0.087
Quartz industry	65	4.5	38	46	0.79
Quarrying industry	381	19	27	18	0.92
Rock crushing plant	226	24	22	21	1.1
Construction work	70	12	17	17	0.34
Ferroalloys plant	16	23	26	5	0.29
Steelworks	195	17	0.24	0.09	0.37
Iron foundries	821	20	27	12	0.63
Porcelain factories	46	7.1	39	9	0.25
Glass industry	52	13	29	8	0.31
Abrasives manufacture (abrasive paper/cloth)	9	8.0	38	42	1.3
Plaster/polishing materials	5	2.8	29	46	0.36
Lime and dolomite production	11	51	25	2	0.26
Cement manufacture	32	61	18	4	0.44
Clinker production	21	22	24	8	0.42
Roof felting manufacture	14	72	20	4	0.57
Manufacture of scouring powder	9	19	41	47	3.6
Blasting	67	39	12	44	2.1
Kieselguhr mining/handling	4	28	34	4	0.38

AM = arithmetic mean.
*The estimation of fine-grained quartz is based on a consideration of dust content, fine fraction, and quartz content. The occupational exposure limit for fine-grained quartz at the time was 0.2 mg/m^3.

Table 3. Average levels of respirable quartz in mg/m^3 (workplaces in Sweden).*

Industry	1970	1990
Mining	0.1	0.025
Quarrying industry	0.92	0.045
Road building work	0.34	0.03
Iron casting	0.63	0.035
Ceramics manufacture	0.19	0.024
Housing construction work	0.28	0.03

*Data from Nils Plato, Unit of Occupational Medicine, Karolinska Institutet. Data from 1990 based on a total of 1000 measurement values (number from 1970 unknown). Information on particle size distribution and ranges are not available.

Table 4. Compilation of obligatory measurements of quartz using personal monitors reported to Swedish Work Environment Authority during the period 2002-2011 (personal communication from Jouni Surakka, Swedish Work Environment Authority, June 2012).

Year:	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[2]
% measurements ≤OEL[1]	6.5	8.7	6.5	8.4	9.5	7.5	8.1	6.0	10.0	9.0
Number of measurements ≤OEL	27	58	59	74	77	71	64	37	60	24
Total number of measurements	414	665	782	879	808	936	784	616	597	265

[1] Occupational exposure limit (OEL) = 0.1 mg/m^3.
[2] It is probable that not all measurement reports from 2011 have been entered into the database.

There are indications that the levels of quartz are increasing in certain workplace environments, e.g., because of new methods and materials being used in some occupational areas (27, 85). Globally, silicosis caused by stone dust is still a major problem (86). One example of a relatively new form of occupational quartz exposure is the sand blasting of denim fabric for the fashion industry. This has recently caused a silicosis epidemic amongst young people in Turkey. Workers without adequate protective equipment have been exposed to very high levels of quartz and have quickly developed lethal silicosis (3, 4, 13, 79). Another example involves workers who had been grinding a kitchen and bathroom material in Israel. A total of 25 persons who had worked for around 20 years grinding the material CaesarStone®, containing 93% quartz, were diagnosed with silicosis (on the basis of occupational history, x-ray results, and biopsies) (81). An increased occurrence of special x-ray changes typical of silicosis (type r according to the ILO-classification, see below) has been observed in coal miners in the US (Virginia, West Virginia, Kentucky). It has been speculated that this may be due to an increase in the quartz content of coal dust resulting from changes in mining technology, as well as higher production rates and an increase in working hours (85).

A report from 2005 contains dust data from the construction industry in 2004 (9). Sampling was carried out using personal monitors and in some cases stationary monitors as well. The measurements were made at 20 work sites where demolition and reconstruction work was being carried out in kitchens or bathrooms, so-called renovation-reconstruction-extension work, as well as other workplaces. The results showed that occupational exposure limits for inhalable dust were exceeded in 53% of the measurements. The OEL was exceeded in 65% of the measurements for total dust, 15% for respirable dust, and 64% for respirable quartz. The highest measured value for quartz was 0.91 mg/m^3 (Swedish occupational exposure limit 0.1 mg/m^3). Grinding work with clinker bricks and flooring at a shopping centre resulted in 0.07 mg/m^3 respirable quartz, the demolition of internal concrete walls 0.17 mg/m^3 respirable quartz, the removal of rubble with

a BobCat on the same work site 0.12 mg/m^3 respirable quartz (9). 0.03 mg/m^3 was measured during the demolition of an area of housing surrounded by other buildings.

Exposure measurements made in the US (1980-1992), covering 255 industries, showed that 48% of these industries exceeded the permitted exposure level for quartz of 0.1 mg/m^3 (54). In a Swedish exposure study, which included 11 foundries, 23% of the measurements exceeded 0.05 mg/m^3. A total of 435 exposure measurements were carried out. The geometric mean for quartz was 0.028 mg/m^3 (0.003-2.1 mg/m^3) (6). Quartz levels in the Swedish foundries fell sharply from 1968 to 1980, mainly for particular occupational groups (furnace and ladle renovators), and then remained relatively constant between 1980 and 2006. Exposure levels (geometric mean) are estimated at 0.072 (1968-1974), 0.050 (1975-1979), and 0.028 mg/m^3 (2005-2006) (7).

Studies with personal breathing zone samples amongst farmers in North Carolina, USA, showed high levels of respirable quartz. The average quartz content in the respirable fraction was 35%. The highest exposure to respirable silica was measured during sweet potato transplanting (3,9 ± 2,1 mg/m^3). The study revealed large variations in respirable dust exposure which were to a significant degree related to the type of agricultural activity and the dampness of the soil (12).

Uptake, biotransformation, elimination

The main pathway for uptake is inhalation. The particles can reach the lung alveoli and can be stored in the lungs. How far these particles penetrate into the bronchial system depends on their size: particles larger than 5 µm lodge higher up in the airways but smaller particles can reach the alveoli. IARC writes that particles which reach the bronchioles and alveoli are eliminated more slowly, interact with macrophages, and increase the risk of lung damage. Quartz particles with an aerodynamic diameter below 10 µm are, according to IARC, probably the most harmful to humans (72). According to CICAD our knowledge about how quartz is transported away from the lungs (the kinetics) is still unclear (39). An article from 1976 showed that patients with silicosis had up to 15-20 g silica in their lungs, compared with the normal figure of < 0.2 g (151).

A couple of older articles describe the elimination of quartz (77, 78). Small quartz particles that have reached the alveoli can be phagocytosed and are transported to the lymph nodes before being carried to the kidneys via the blood. Some particles can be slowly dissolved in the body and subsequently eliminated via the urine. Urine samples from mineworkers have shown 2.5-fold higher levels of silicon than those from a non-exposed control group. Intake of silicon through the diet can also affect the silicon content of urine. In postmortems on 29 mineworkers accumulations of quartz were observed in the lungs and lymph nodes. Concentrations were 2.4 times higher in the lymph nodes than in the lungs (144). Accumulations of quartz have also been observed in lymph nodes around the lung tissue of rats exposed daily to quartz for two years (94).

Biological exposure monitoring

A review article from 2006 examined the literature on biological exposure monitoring. Quartz particles or silicon in BAL (bronchoalveolar lavage), serum, or urine indicate exposure. The effects of quartz particles in phagocytic cells can reflect early effects and inflammation before fibrosis appears. A number of biomarkers are proposed in this article: CC16 (in serum), TNF-alpha (from monocytes), IL-8 (from monocytes), reactive oxygen species (ROS, from neutrophils), 8-isoprostanes (in serum), antioxidant levels and glutathione, glutathione peroxidase, glutathione S-transferase, and PDGF (in serum). The authors believe that these biomarkers should be able to identify those individuals who are particularly sensitive (e.g., individuals with TNF-alpha polymorphism) (58). However, later studies show that the Nalp3 inflammasome and the proinflammatory cytokine IL-1β play central roles in quartz-induced inflammation (28, 47, 67).

In a study from 2010 silicosis patients were compared with healthy research subjects who were exposed to quartz (62 silicosis patients, 24 research subjects exposed to quartz, 19 who were not exposed). Serum levels of the cytokine TNF-alpha were significantly higher in healthy individuals exposed to quartz and in silicosis patients than in those who were not exposed (123).

The formation of collagen fibres is part of the process that leads to silicosis. Hydroxyproline is an important component of collagen and its concentration has been measured in the lungs of 29 deceased mineworkers. Hydroxyproline concentration showed good correlation with the radiological assessment but not with the pathological assessment (144). Significantly higher hydroxyproline concentrations have also been observed in the urine of individuals with silicosis than in the urine of those not exposed to quartz. On the other hand, individuals with suspected silicosis (ILO 1980, category 0/1) did not have significantly higher concentrations than controls. The authors concluded that the concentration of hydroxyproline in the urine cannot be used for early detection of silicosis but might possibly be used to evaluate the progression of silicosis that has already been detected (97).

A study of individuals diagnosed with silicosis after exposure to quartz during the sandblasting of denim fabric found a significant positive correlation between the serum concentration of lactate dehydrogenase (LDH) and the degree of x-ray changes in the lungs as well as with impairment of lung function (44). The authors do not recommend LDH as a diagnostic test for silicosis but do propose that LDH can be a biomarker which indicates the extent of lung parenchymal changes.

Toxic effects

Mechanisms of toxicity and tumour development

When quartz is processed fresh surfaces are created and silicon radicals can be generated on the fracture surfaces. Minerals and inorganic compounds can reduce (e.g., aluminium salts) or increase (e.g., dust from coal mines) the biological

activity of quartz and affect the toxicity in a complex manner. This can be difficult to predict (46, 118). The highest risk of adverse health effects, e.g., lung cancer, appears to be associated with exposure to very small and dry, newly generated particles (39, 72, 93). An appraisal of experimental and epidemiological literature has revealed that the risk is lower for exposure to particles that are "aged" or are contaminated with, for example, an aluminium-containing mineral (69).

There are several studies which have investigated how quartz can cause cytotoxicity. Mechanistic studies indicate that a number of cellular processes can lead to toxicity, inflammation, and immunological changes (59). These include effects on the production of pulmonary surfactant, receptor-mediated binding and toxicity in alveolar macrophages, increased production of free radicals, and lysosomal damage. None of these pathways exclude other mechanisms and they can act together (83).

Surface reactivity, cytotoxicity, and the morphological transformation of kieselguhr were studied in SHE cells. The samples that were examined were untreated kieselguhr (amorphous silicon dioxide), kieselguhr heated up to 900 °C and 1200 °C, and a commercial product (Chd) containing cristobalite (heated during the manufacture of the product), as well as Chd-f, a fraction of finer material (<10 μm) separated from Chd. X-ray diffraction showed that kieselguhr heated to 900 °C was mainly in the amorphous form whereas heat treatment at 1200 °C converted the material to the crystalline form cristobalite. A study of the ability to release free radicals showed that the finer fraction (<10 μm) released the most radicals, followed by kieselguhr heated to 1200 °C. The authors concluded that the ability of kieselguhr to transform cells *in vitro* can be linked to heat treatment and the formation of oxygen radicals. The finer fraction, <10 μm, seems to be the most toxic (50).

Studies have shown that the inflammatory response and the development of pulmonary fibrosis after quartz exposure is dependent on the receptor Nalp3 (28, 47). Quartz is recognized by the Nalp3 receptor and this leads to the release of interleukin-1 beta from macrophages. The Nalp3 receptor is thought to play an important initial role in the inflammation process which can lead to the development of, for example, silicosis. Genetically modified mice lacking the Nalp3 receptor developed less inflammation. Quartz was administered to the animals via intranasal instillation (20 mg/ml, 50 μl, on days 0 and 14) and inflammation and fibrosis in the lung were studied from 3 months after the first treatment. Wild type mice that had undergone the same level of exposure developed major inflammatory changes whereas mice lacking the Nalp3 receptor experienced significantly less inflammation (inflammation score) and granuloma formation as well as less collagen deposition (28).

Diseases such as silicosis and other pneumoconioses have been linked to increased levels of antibodies, immune complexes, and overproduction of immunoglobulins, particularly IgG. Chronic exposure to quartz and the development of silicosis can lead to a chronic stimulation of the immune system through quartz-induced damage to macrophages in the lungs. This leads to an elevation of in-

flammatory cytokinin levels, e.g., interleukin-1 and TNF-alpha, which in turn stimulate other cells and increase the inflammatory response. In addition, increased levels of oxygen radicals can contribute to immune system activation (107).

In its latest evaluation of human carcinogens IARC writes that impaired particle clearance, leading to macrophage activation and inflammation, is an established carcinogenic mechanism for quartz dust (134).

MARCO receptors (macrophage receptor with collagenous structure) on macrophages in the lungs bind quartz particles and mediate their uptake *in vitro*. When exposed to quartz, genetically modified mice lacking this receptor developed more marked lung inflammation and silicosis when compared with wild type mice. Macrophages from MARCO-/-mice also showed a reduced uptake of quartz particles, indicating impaired clearance of quartz. In addition, MARCO-/-mice had higher levels of cytokinins and inflammatory cells than wild type mice. The authors conclude that the MARCO receptor is an important factor in the clearance of quartz (137).

As discussed below (Mutagenicity, genotoxicity) the genotoxicity of quartz has been investigated in a number of studies. A review article from 2011 differentiates between indirect (secondary) and direct (primary) genotoxicity and discusses their role in cancer development. It is maintained that indirect genotoxicity, which is assumed to be caused by inflammation, is the one that is important for the development of cancer, as it can occur at moderate exposure levels. In direct genotoxicity quartz has a direct effect on DNA but in experimental studies very high levels of exposure are required and the authors believe this mechanism is improbable. According to the authors inflammation is the driving force behind the genotoxicity observed *in vivo*, which leads to cancer (22).

Human data

Silicosis

Silicosis is one of the oldest known occupational diseases. It was described as early as the 1700s by Carl von Linné who gave the disease the Swedish name: “Orsasjukan”. In English-speaking countries the disease has been known by names such as such as miners' phthisis and grinder's asthma. One of the early epidemiological studies of silicosis, published in 1900, concerned 30 deaths from silicosis amongst quartz workers in Nevada, USA (14). Silicosis is a potentially fatal disease from which thousands of people die each year throughout the world. Silicosis occurs in a variety of forms and stages, ranging from mild and symptom-free to rapidly progressing with breathing difficulties and high mortality. The disease is an inflammatory process which leads to fibrosis in the lungs. Unlike other forms of lung fibrosis it begins in the upper parts of the lungs and involves the development of nodules with a characteristic appearance under the microscope. Acute or fulminant silicosis is a variant that can develop after very high-level exposure and involves rapid disease progression (13, 106, 113). In acute silicosis the alveoli become filled with a fluid which contains lipid-rich protein residues from cells in the respiratory tract (so called alveolar lipoproteinosis, which can be seen under

a microscope) and reactive oxygen species can be formed (57). Two large clusters of acute silicosis in the USA have been described. One is from the beginning of the 1930s when, in order to supply water to a power plant at Hawk´s Nest in West Virginia, Union Carbide had a tunnel built through a mountain with a very high quartz content (≥90%) in 1930-1932. A total of 3000 persons worked in the tunnel; about half of them only worked there occasionally. No measures were taken to reduce dust levels and the workers had no respiratory protection. The data on how many died is very unclear. A conservative ("necessarily speculative but consistently conservative") estimate is that more than 700 men died from acute silicosis while working on the project and during a five-year period after the tunnel work was completed. In addition, approximately 2000 more workers were exposed to high levels of quartz but were not followed up (36). In the second cluster (from the start of the 1990s) 100 workers developed acute silicosis from sand blasting in Texas (141). However, silicosis normally develops gradually over many years and can be first clinically diagnosed only after many years of exposure. The progression of the disease can cease when exposure stops but can also progress even in the absence of further exposure. It is generally thought that the cumulative (gradually accumulating) dose is the important factor in the development of the disease (86).

Many studies have examined exposure to quartz and the rates of illness or death from silicosis in various occupational cohorts. More recent relevant studies are summarized below along with the critical studies in CICAD's report (39). The Criteria Group has chosen to describe studies with radiologically based diagnosis of silicosis separately from studies based on death from silicosis since the outcome is different: the risk of contracting the disease and the risk of dying from the disease.

The International Labour Organization (ILO) has a standardized classification system for the changes in chest radiographs that are used, for example, in diagnosing silicosis. The guidelines were updated in 2011 (73). The system uses, for example, four categories (0, 1, 2 and 3) that are based on profusion of small opacities, where 0 indicates an absence of opacities or opacities less than for category 1. There are 12 subcategories[1]. Examples of categorization are 0/1, 1/0, 1/1, etc., where the first figure denotes the category which best matches the x-ray image and the second figure indicates the subcategory that has been considered as an alternative; for example, 0/1 signifies that there are no or very small opacities and that category 1 has been considered as a possible alternative. Category 1/0 denotes that the x-ray image has been classed as category 1 after carefully considering category 0; category 1/1 means that the x-ray-image has been classed as category 1 and that no other category has been considered (73). The classification also includes designations of the shape and size of the opacities. Studies have

[1] ILO-categories:

Categories	0			1			2			3		
Subcategories	0/-	0/0	0/1	1/0	1/1	1/2	2/1	2/2	2/3	3/2	3/3	3/+

shown that sensitivity can be low in radiological examination. Postmortems on granite workers in Vermont, USA, showed that a large proportion of those workers without silicosis symptoms and showing no positive radiological results nevertheless had silicosis (141). Radiological studies combined with postmortem results showed that amongst South African gold mine workers only 20-40% of silicosis cases were diagnosed by x-ray examinations (ILO-classification 1/1). This was particularly noticeable when the workers' exposure to quartz dust was low (63). Nevertheless, studies have shown that ILO-classification of silicosis is more reliable and more sensitive than routine radiological assessment (5). Another reason why radiological diagnosis of silicosis is unreliable is that different conclusions can be reached when an x-ray image is assessed by different people or by the same person on different occasions. In addition, changes in lung x-ray results corresponding to the ILO-classification ≥0/1 are observed in the general population which is considered not to have been exposed to dust in the workplace environment. In a literature review (eight studies) by Meyer *et al*. the occurrence of opacities (ILO ≥1/0) was found to vary between 0.2% and 12% in control groups/the general population. The total pooled prevalence was 5.3% (95% CI 2.9–7.7%). The authors believe there is a background level of such x-ray changes in the general population. The reason for the changes is unclear. The authors point out that in order to avoid the large variation in classification between studies it is important to have well matched control groups, so as to establish a base level for opacities, and for x-ray images to be interpreted blind (92). To sum up, the specificity of radiological diagnosis using ILO-classification is normally high (around 95%, i.e., 5% false positives) (92) but even though the sensitivity is improved when this classification is compared with the routine assessment, two studies conclude that it is still limited (63, 141). In the references below the terms used by the authors, e.g., "silicosis" and "signs of silicosis", have been reproduced wherever possible.

The Swedish silicosis register was established in 1953 but had been collecting notifications of silicosis since 1931. In 1979 the silicosis register was replaced by ISA (Informationssystemet om arbetsskador; The Swedish Information System on Occupational Accidents and Work-related Diseases) (149). Statistics from the Swedish Cause of Death Register (Dödsorsaksregistret) show that the number of deaths from silicosis in Sweden was highest in the 1970s but fell in the 1980s. In 2000 nine men and four women died from silicosis; all were aged over 65 (www.kemiguiden.se, Dödsorsaksregistret). A report from The Swedish Work Environment Authority (Arbetsmiljöverket) (10) mentions that of the Swedish deaths from pneumoconiosis in 2007, four cases were related to quartz exposure (all were men aged over 85).

Studies that mainly describe silicosis diagnosed on the basis of radiological changes

A cohort study looked at 2235 South African gold mine workers who began employment before 1938. Measurements showed that dust in the mine contained 30% quartz. A total of 313 (14%) workers developed silicosis (ILO-category ≥1/1) during the follow-up period 1968-1971 to 1991. For the majority (57%) of the silicosis cases the disease developed after the end of employment and at an average age of 59 (64).

An article from 1978 describes 6 Swedish cases of silicosis caused by kieselguhr after a relatively short exposure time (2-20 years, median 4 years); diagnosis was mainly by x-radiography. According to the authors it was tridymite and cristobalite exposure in particular that caused silicosis from working with kieselguhr. By 1978 there had been no cases of kieselguhr-silicosis registered since 1958 (19).

A study from 2005 examined Dutch building workers for signs of silicosis. A group of 1335 workers were examined for silicosis in 1998 using mobile x-radiography; 0.8% showed signs of silicosis (ILO-classification ≥ 1/1). Four years later, in 2002, 96 of the workers were studied using a newer data tomography technique (high-resolution computed tomography) which revealed signs of silicosis in 9% of the workers; most of these had not been found in the previous study. The cumulative average exposure to quartz was estimated at 5.7 mg/m^3 x years. The authors state that, at similar exposure levels, the risk of contracting silicosis is lower for building workers than for other workers exposed to quartz. According to the authors this could be attributed to the effect of other particles in the building work dust, e.g., iron and aluminium, substances that can alter the toxicity of quartz. The authors estimated a lifetime silicosis risk of > 5% for Dutch building workers with high levels of quartz exposure. Exposure was measured for 34 building workers who worked with concrete and mortar or were involved in demolition or building site clearance. In 55% of samples the Dutch exposure limit for respirable quartz (0.075 mg/m^3) was exceeded. Materials in the dust which gave the highest exposure levels were limestone/sandstone, bricks, mortar, and concrete (138).

A study from 2004 examined the incidence of silicosis amongst 520 workers (aged 40 years or older) in a South African gold mine. 101 individuals in the group were found to have tuberculosis and nine workers were taking tuberculosis medication. The aim was to study the dose-response relationship with quartz dust. The average exposure level for respirable dust was 0.37 mg/m^3 and for quartz 0.053 mg/m^3. The incidence of silicosis (ILO-classification ≥ 1/1) was 18-20%. Those exposed to quartz were divided into five exposure categories: 0-0.8, 0.8-0.99, 0.99-1.24, 1.24-1.48, and 1.48-3.08 mg/m^3 x years. The prevalence of silicosis in these groups was 12, 9, 22, 28, and 47%, respectively (taken from figure 2 in the article). Using logistic regression analysis a significant relationship was observed between silicosis and the length of employment, average exposure, and cumulative exposure. The authors of the study believe that the workers developed silicosis despite being exposed to quartz concentrations below the exposure limit of 0.1 mg/m^3 and are of the opinion that this exposure limit does not protect

against silicosis. South African law requires that workers with both silicosis and tuberculosis should be transferred and so this cross sectional study probably underestimated the incidence of silicosis amongst these gold mine workers (38).

The EPA in the US estimated (using benchmark-dose methodology and data from Hnizdo and Sluis-Cremer 1993 (64), ILO-classification ≥ 1/1, see Table 8a) that the risk of developing silicosis at an environmental exposure level of 0.008 mg quartz/m^3 (based on high levels in heavily polluted city air in the USA) over 70 years (lifetime exposure) was 2.4% for healthy individuals (141). However, the authors of the report believe that city air differs from the air in mines both as regards particle size (larger particles in city air) and particle surfaces (more newly generated particles in mine air). There are reports of silicosis cases in groups that have not been occupationally exposed, e.g., people exposed to dust storms in the Himalayas and Bedouins in the Negev desert in Israel. In these studies signs of silicosis were observed in both postmortems (e.g., quartz particles <3 μm in nodules in the lungs) and in x-radiographic examinations. A total of 395 individuals in northern China exposed to dust storms (average dust concentration: 8.3–22 mg/m^3) were compared with a control group of 88 individuals (average dust concentration: 1.1–2.3 mg/m^3). Twenty eight individuals (7.1%) exposed to dust storms had silicosis, compared with none in the control group. No data on quartz concentrations was found (121).

A study of the incidence of silicosis at the Kiruna mine in 1931-1977 was published in 1986. During this period 144 cases of silicosis were identified. The concentrations of respirable quartz were estimated at 0.8 mg/m^3 (total dust 35-45 mg/m^3) in the 1960s, falling to less than 0.05 mg/m^3 by the end of the 1970s. Silicosis occurred only in underground workers. The cumulative incidence was 18% in 1921-1930 but fell to 2% in 1951-1960. In 34 cases (24%) the disease had progressed. Seven (5%) of the employees with silicosis had confirmed tuberculosis and 17 (12%) had suspected tuberculosis (x-ray observation). Tuberculosis was more common amongst those with progressive silicosis. Mortality was higher in those with stage II and III silicosis and in all stages (I-III) in those with tuberculosis. The authors conclude that, with an unchanged dose-response relationship for those who began working in the mine in the 1980s, there should be a cumulative incidence rate of 0.2% (1 case of silicosis per 500 workers). Since the 1960s only one case of stage I silicosis has been diagnosed (75). The classification I, II, III is in accordance with a system which was approved at a conference in Johannesburg in 1930 and which has been used in Sweden (for stage I x-ray images show a spread of spot-like opacities up to a pinhead in size; stage II is characterized by opacities up to the size of a pea and stage III by opacities that have merged to form large continuous blocks (2)).

A total of 134 male residents (aged 40 or over) in a mining town (the mined metals were molybdenum, lead, zinc, and gold) in Colorado, USA, were studied. One hundred were mine workers exposed to crystalline silica and 34 were non-exposed controls. Crystalline silica comprised 12% of the total dust. 32% of the exposed workers had silicosis (ILO-classification ≥ 1/0). Men with lower exposure

levels tended to be slightly older, to smoke slightly more, and to have a shorter exposure time when compared with those with the higher exposure levels. Those with an average exposure ≤0.05 mg/m^3 quartz, had a 10% prevalence (”silicosis rate”) for silicosis, those with an average exposure > 0.05-0.1 mg/m^3 had a prevalence of 23%, and those with an average exposure > 0.1 mg/m^3 had a prevalence of 49% (82). Amongst mine workers with a cumulative quartz exposure of 2 mg/m^3 x years 20% had silicosis and amongst those with an exposure > 2 mg/m^3 x years 63% had silicosis. On the basis of cumulative quartz exposure 94 of the 100 quartz-exposed mine workers were allocated to four subgroups: >0-1 mg/m^3 x years (n = 32), >1-2 mg/m^3 x years (n = 38), >2-3 mg/m^3 x years (n = 18), and >3 mg/m^3 x years (n = 6). The prevalence of silicosis (ILO-classification ≥ 1/0) in these subgroups was 12.5, 26.3, 55.6, and 83.3%, respectively. The study estimated the dose-response relationship for silicosis using three exposure indices. The number of years of exposure was calculated from occupational history and the cumulative dust exposure index was calculated using gravimetric dust exposure data. Cumulative dust and quartz exposure was also assessed on the basis of occupational history. The dust index was converted to a quartz estimate in order to compare with analyses based on the quartz index. The prevalence of silicosis amongst the 100 workers was 15% for those with < 20 years exposure, 30% amongst those with 20-29 years exposure, and 47% amongst those with > 30 years exposure. Using a logistic regression model the silicosis risk for an average exposure of 0.05 mg/m^3 was calculated as 9% after 25 years work (with a 20-year follow-up the risk increased to 36%) and as 50% after 45 years work (82).

Checkoway and colleagues have studied the relationship between respirable crystalline silica and non-malignant lung diseases and lung cancer mortality in the kieselguhr industry in several articles (32, 33, 71, 105). Dust from kieselguhr contains cristobalite. In the study from 2002 (105) 2342 workers employed for at least 1 year (1942-1994) at a plant in California were assessed. The average time of exposure was 7.4 years; a few workers were followed up after the end of their employment (4%). The level of crystalline silica varied between 1 and 25%. A total of 70 workers (3%) had a silicosis classification (ILO-classification ≥ 1/0). 67 workers had died from a lung disease other than cancer. The authors found a dose-response relationship between the risk of death from lung disease and exposure to crystalline silica. It was estimated that at a level of 0.05 mg/m^3 there was an extra risk of 54/1000 workers (5%) for 45 years of exposure and at 0.1 mg/m^3 the risk was 100/1000 workers. Using a regression model it was calculated that for 45 years of exposure there was an increase in the risk of contracting silicosis (ILO-classification ≥ 1/0) to 16/1000 workers (1.6%) at an average exposure of 0.01 mg/m^3, 7.5% at 0.05 mg/m^3, and 14% at 0.1 mg/m^3 (105).

Rosenman and colleagues studied 1072 workers in the iron foundry industry in the USA. Average exposure time was 19.2 years and for the overwhelming majority of participants (90%) the follow-up time from the start of employment was less than 30 years. There were 28 cases of silicosis (2.9%, ILO-classification ≥ 1/0) more than half of which were pensioned off workers. Amongst workers

with an average exposure of <0.05 mg/m^3, 0.8% had silicosis, while the prevalence was 0.3% for workers with an average exposure of 0.05-0.15 mg/m^3, 4.9% for workers exposed to >0.15–0.45 mg/m^3, and 6.3% for exposure to > 0.45 mg/m^3. The risk of silicosis increased with employment time, cumulative quartz exposure, type of work task, and smoking. A quartz exposure of 0.05 mg/m^3 over 20 years should mean that around 1% of those exposed would contract silicosis and over 40 years around 2% should be affected. If quartz exposure was 0.1 mg/m^3 around 2% should contract silicosis after 20 years exposure and around 3% after 40 years (114).

Quartz exposure and respiratory disease were studied in 440 granite workers in Spain (111). A total of 77 workers (18%) had diagnosed silicosis (ILO-classification ≥ 1/1). 73 of these had been exposed to more than 3.5 mg/m^3 x years (the occupational exposure limit for cumulative exposure recommended by OSHA, i.e. 0.1 mg/m^3 over 35 working years). A significant dose-response relationship was observed between quartz exposure and the odds ratio for contracting silicosis. For average exposures to quartz the odds ratio was 1.0 for 1.2 mg/m^3 x years, 2.8 (0.78–10) for 4.9 mg/m^3 x years, 10 (3.3–31) for 8.8 mg/m^3 x years, and 31 (10–96) for 19 mg/m^3 x years. Tuberculosis and asthma were also reported amongst the workers. Lung function tests revealed 18 cases (4.3%) with $FEV_1/FVC < 70\%$.

A study from 1995 investigated the relationship between quartz exposure and silicosis. The aim was to try to identify a NOAEL- and LOAEL-level (the highest dose level tested that produced no adverse effect and the lowest dose tested that produced an adverse effect, respectively) for silicosis based on epidemiological studies (112). NOAEL varied from 0.007 to 0.1 mg/m^3 and LOAEL from 0.008 to 0.25 mg/m^3. The authors concluded that the large variation could be due to many factors, such as the surface properties and particle size of quartz from various mines, the definition and x-radiographic classification of silicosis cases, methods for estimating exposure and risks, background concentrations of airborne crystalline silica, etc. The study included several epidemiological studies which contained quantitative information on quartz exposure and the risk of silicosis (see Table 5). The values were not statistically based but were estimated on the basis of demonstrating that the risk of silicosis was higher than that caused by background exposure. For studies where the variations in exposure were given, the value at the mid-point was used. Six studies were included, two of which used statistical models to determine the relationship between exposure and risk.

Table 5. Review articles/Meta-analyses/Studies of pooled data (silicosis and/or lung cancer). Studies in **boldface** are referred to in this report.

Reference	Studies
Finkelstein 2000 (silicosis & lung cancer) (53)	**Hnizdo and Sluis-Cremer 1993**; Ng and Chan 1994; **Steenland and Brown 1995; Kreiss and Zhen 1996; Rosenman *et al.* 1996**; Miller *et al*. 1998; Hughes *et al*. 1999.
Rice and Stayner 1995 (silicosis) (112)	Davis *et al*. 1983; **Hnizdo and Sluis-Cremer 1993**; McDonald and Oakes 1983; Muir *et al*. 1991; Rice *et al*. 1986.
t Mannetje *et al*. 2002 (silicosis) (136)	***Checkoway *et al.* 1997**; Koskela *et al*. 1994; Costello *et al*. 1988**; Steenland *et al.* 2001**; **Steenland *et al.* 1995**; De Klerk *et al*. 1998.
Steenland 2005 (silicosis & lung cancer) (127)	*Silicosis**: Checkoway *et al.* 1997**; Koskela *et al*. 1994; Costello *et al*. 1988; **Steenland *et al.*** 2001; **Steenland *et al.* 1995**; De Klerk *et al*. 1998. Lung cancer: **Checkoway *et al.* 1997**; Koskela *et al*. 1994; Costello and Graham 1988; **Steenland *et al.* 2001**; Chen *et al*. 1992; Hnizdo *et al*. 1997; Steenland *et al*. 1995; De Klerk and Musk 1998.
Steenland *et al*. 2001 (lung cancer) (129)	**Checkoway *et al.* 1997**; Koskela *et al*. 1993; Costello *et al*. 1988; Steenland *et al*. 2000; Chen *et al*. 1992; Hzindo *et al*. 1997; Steenland *et al*. 1993; De Klerk *et al*. 1998.
Lacasse *et al*. 2009 (lung cancer) (84)	**Checkoway *et al.* 1997**; **Steenland and Sanderson 2001**; Brown and Rushton 2005; Pukkala *et al*. 2005; Ulm *et al*. 1999; Bruske-Hohlfeld *et al*. 2000; Cocco *et al*. 2001; **Chen *et al.* 2007**; Westberg and Bellander 2003; Hughes *et al*. 2001; **McDonald *et al.* 2005; Cassidy *et al.* 2007**.
Erren *et al*. 2009 (lung cancer) (51)	Armstrong *et al*. 1979; Puntoni *et al*. 1988; Mehnert *et al*. 1990; Amandus and Costello 1991; Dong *et al*. 1995; Finkelstein 1995; Meijers *et al*. 1996, Checkoway *et al*. 1999; Mastrangelo *et al*. 1988; Lagorio *et al*. 1990; Sherson *et al*. 1991.

*Same cohorts.

A cohort of 3330 gold mine workers from South Dakota who had worked for at least 1 year between 1940 and 1965 was followed up until 1990. A total of 170 cases of silicosis were observed (on the basis of silicosis as the underlying cause of death, silicotuberculosis, lung tuberculosis or pneumoconiosis, and/or x-ray images classed as ILO-category ≥ 1/1). The median quartz level was 0.05 mg/m^3 and the average employment time was 9 years. The average follow-up period was 37 years. The concentration of quartz in total dust was calculated as 13%. The risk of silicosis was calculated as 1% for workers with a cumulative exposure of less than 0.5 mg/m^3 x years. The risk increased to 68-84% for the highest cumulative exposure category, 4 mg/m^3 x years (128).

A study from 2000 investigated the dose-response relationships between quartz, silicosis, and lung cancer (53). The investigation was based on a detailed perusal of articles on the relationship between silicosis and quartz exposure. In the various studies the risk of developing silicosis (ILO-classification ≥ 1/1) for a cumulative exposure of 2 mg/m^3 x years ranged from 0.4 to 11% and for 4 mg/m^3 x years from 1.2 to 53%. The authors estimated the cumulative risk of silicosis at around 5% for 2 mg/m^3 x years and around 50% for 4 mg/m^3 x years (based on the as-

sumption of a non-linear dose-response relationship for silicosis, where the risk increases more rapidly at higher cumulative doses) (53).

A cohort of 5115 quartz-exposed ceramics production workers in Stoke-on-Trent, England, was studied. Access to x-ray images was obtained for 83% of the cohort. For non-malignant respiratory diseases the SMR (standardized mortality ratio) was calculated as 2.0 (95% confidence interval, CI 1.6–2.7), using Stoke-on-Trent residents as reference. In a subcohort of 1080 selected workers with > 10 years employment, 64 workers (5.9%) had at least one x-ray image classed as ILO ≥ 1/0. The prevalence of small opacities increased with increasing exposure to quartz and the increase was greater amongst smokers (37), see Table 6.

Studies that mainly describe mortality in silicosis

In a report from 1998 the Centers for Disease Control and Prevention (CDC) in America have investigated all cases of death from silicosis amongst younger people in the USA between 1968 and 1994. The report showed that 207 deaths from silicosis were registered during this period for individuals aged 15-44. The construction and manufacturing industries were the ones most frequently recorded (28% each) but no deaths were linked to mining work. This stands in contrast to deaths in the older age group, > 65 years, where manufacturing accounted for 46%, mining work for 21%, and the construction industry for 10%. Common occupations for 25 young people who died within a year of the start of exposure, between 1985 and 1994, were machine operators for the crushing, milling, and mixing of rock materials, as well as painters and building workers. CDC states in the report that the exposure of these individuals to quartz was probably high and intensive. One of the reasons was sand blasting, and NIOSH has recommended a ban on the use of quartz-containing sand as an abrasive blasting agent (30). In Sweden there is a ban on using quartz-containing material as an abrasive blasting agent in manual dry blasting (8).

Mortality in silicosis was studied in 7729 Swedish mine workers (61) who had worked at least one year between 1923 and 1996. Mortality between 1952 and 2001 was examined with the help of the Cause of Death Register. The median cumulative exposure for all mine workers was 0.9 mg/m^3 x years. The cause of death for 58 workers was silicosis; for these workers the median cumulative

Table 6. Prevalence of silicosis (ILO-classification ≤ 1/0) and cumulative exposure to quartz and smoking (37).

Cumulative exposure (mg/m^3 x years)	Non-smokers	Smokers
< 2	0	0
2-3.9	0.9	1.8
4.0-5.9	2.9	6.3
≤ 6.0	9.3	16.3

exposure was 4.8 mg/m^3 x years. A dose-response trend was observed for cumulative exposure. For a cumulative dose of 0-0.9 mg/m^3 x years the silicosis mortality rate per 100,000 person years was 19; for 1-2.9 mg/m^3 x years, it was 33; for 3-4.9 mg/m^3 x years, 117; for 5-6.9 mg/m^3 x years, 129; for > 7 mg/m^3 x years, 140, after adjustment for age and year of birth. The authors concluded that an increased risk of fatal silicosis seemed to appear at exposure levels of around 3 mg/m^3 x years.

The relationship between quartz exposure and the silicosis mortality rate was studied using pooled data from six cohorts in a case-control study (136). 18,364 workers were involved in the study, 170 of whom had died from silicosis. Death from silicosis was defined as silicosis or unspecified pneumoconiosis being the underlying cause of death (150 and 20 deaths, respectively). The authors believe that the definition is specific but not sensitive as death from silicosis may have been attributed to other causes of death, such as tuberculosis or COPD (chronic obstructive pulmonary disease). The authors therefore believe that the definition probably leads to an underestimation of the number of deaths caused by silicosis. The average age of death from silicosis was 69 years (range 32-91 years). Sixteen individuals (9%) had died within one year of leaving their employment but 15 of these had long exposure time which, according to the authors, points to chronic silicosis rather than acute silicosis. The average exposure time was 28 years and the median cumulative exposure was 7.2 mg/m^3 x years (compared with 10 years and 0.62 mg/m^3 x years for the cohort as a whole). The median exposure was 0.26 mg/m^3 for those who had died, compared with 0.07 mg/m^3 for the cohort as a whole. The risk of death from silicosis at 0-0.99 mg/m^3 x years was calculated as 4.7/100,000 person years and 234/100,000 person years at > 28 mg/m^3 x years. The risk of death from silicosis at 0.1 mg/m^3 (45 years lifetime exposure) was calculated as 1.3% and at 0.05 mg/m^3 as 0.6%. The authors believe that an occupational exposure limit of around 0.1 mg/m^3 neither protects against contracting silicosis nor against death from silicosis (136).

A review article from 2005 examined available dose-response data for silicosis and lung cancer with quartz exposure. The increased risk of death or of contracting these diseases by the age of 75 was compared for exposure to 0.1 mg/m^3 respirable crystalline silica for 45 years (lifetime exposure). The risk of contracting silicosis (ILO-class 1/1 or higher) was estimated as 47-77% from three studies and the risk of death from silicosis as 1.9% (0.8-2.9%) from six studies. The risk of death from lung cancer was estimated as 1.7% (0.2-3.6%) from ten studies (127).

Lung cancer

In 1997 IARC classified quartz as a Group 1 carcinogen (carcinogenic to humans). Quartz had previously been classified by IARC as a Group 2A carcinogen (probably carcinogenic to humans) (72). The new classification was based on results from epidemiological studies where simultaneous exposure to other carcinogenic agents was low. IARC concluded: "There is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite

from occupational sources" (72). NIOSH (National Institute for Occupational Safety and Health, USA) and NTP (National Toxicology Program, USA) have also classified quartz as carcinogenic. However, IARC noted that quartz was not carcinogenic in certain studies and that this may have been related to particular properties of quartz or external factors which affected its biological activity. In 2009 IARC confirmed its earlier conclusion that quartz is a Group 1 carcinogen (134).

As mentioned above it has been shown in many studies that the biological effect of quartz can be explained by its surface activity, principally its ability to form reactive oxygen species and cause oxidative stress, but also by the activation of Nalp3 och IL-1β by quartz particles (86). The surface activity can be modified by a number of different substances, e.g., other minerals, which should be able to affect the risk of developing lung cancer in various workplace environments. Lung cancer caused by crystalline silica via the mechanism of inflammation is discussed in a review article from 2011 by Borm *et al*. (22). This mechanism is driven by inflammatory cells (macrophages and neutrophils) which are recruited to the inflammatory areas around the quartz particles. The chronic inflammation that arises can lead to oxidative stress and DNA-damage/genotoxicity. At the same time cell proliferation can be stimulated, contributing to the development of cancer (22).

The risk of lung cancer linked to quartz exposure is difficult to study because the occurrence of simultaneous exposure to other agents that can cause lung cancer and affect lung cancer frequency. The situation varies, depending on the workplace environment, and can also be influenced by smoking (so called confounding).

Cancer studies mainly published after IARC's evaluation of 1997

A study from 1997 examined mortality from lung cancer in Swedish silicosis patients (admitted to hospital for silicosis between 1965 and 1983). The analysis included 1052 men with silicosis. The risk of cancer/mortality was calculated using the standardized incidence ratio (SIR) and the standardized mortality ratio (SMR), defined as the relationship between the observed number and the expected number of cancer cases or deaths for all silicosis patients combined. The total cancer risk was increased, SIR=1.5 (confidence interval, 95% CI 1.3–1.7). The risk of respiratory cancer (cancer of the respiratory organs) was increased, SIR=2.8 (95% CI 2.0–3.8), as was the risk of lung cancer SIR=3.1 (95% CI 2.1–4.2). Mortality from lung cancer was also increased, SMR=2.9 (95% CI 2.1–3.9) (23). The authors considered the results to be in line with earlier studies which showed an increased risk of lung cancer in silicosis patients.

Lung cancer and exposure to quartz were studied in Swedish workers at iron ore mines in Kiruna and Malmberget. A total of 8804 men employed between 1923 and 1998 (working both above and below ground) were included in the cohort. The measurements showed that the average concentration of quartz in the dust to which the workers were exposed was 2.5%. An increase in the relative risk of lung

cancer was observed in workers at the Kiruna mine (compared with the general population), standardized incidence ratio (SIR)=1.5 (95% CI 1.2–1.8). Underground work was associated with a relative risk of 1.4 (SIR=1.6, 95% CI 1.3–2.0). An increased lung cancer risk was also observed at exposures < 2 mg x years/m^3 (15). A statistically significant relationship between cumulative quartz exposure and lung cancer was not observed. The authors concluded that mine workers at the Kiruna mine had an elevated risk of lung cancer due to quartz exposure. The authors pointed out the difficulty in assessing the quality of certain measurement data and that information on smoking habits was lacking. According to the authors this should not affect the results as the mine workers and the general population had similar smoking habits. The elevated risk of lung cancer in workers in the Malmberget mine was thought to be due to both quartz and radon exposure (the radon levels at Malmberget were much higher than at the Kiruna mine) (15).

A major European collaboration aimed at investigating the role of occupational exposure in lung cancer development found a relationship between quartz exposure and the risk of lung cancer. The study made adjustments for possible confounding factors, including smoking (29). 2852 cases of lung cancer were included in the study, as well as 3104 controls. The proportion of smokers (including former smokers) was higher amongst the cancer cases (90%) than the controls (64%). The odds ratio for lung cancer and quartz exposure after adjustment for smoking was 1.4 (1.1–1.7) (29). There was a trend towards increased risk of lung cancer with increasing cumulative exposure and duration of exposure.

A study from 2007 looked at Chinese mine and ceramics workers. The aim was to separate the effects of quartz from other risk factors. A total of 511 lung cancer cases and 1879 controls were included in the study. A dose-response relationship was observed for the carcinogenic effect of quartz when adjustments were made for smoking. This relationship disappeared when the analysis was adjusted for other risk factors (radon, arsenic, and PAH). The authors concluded that the study did not support the hypothesis that exposure to quartz was causally linked to an increased risk of lung cancer and that other risk factors, such as radon, arsenic, PAH, asbestos, diesel exhaust gases, and smoking, influenced the risk of lung cancer (35) The authors stated that: the job with the highest exposure to quartz (median 4.8 mg/m^3 x years, in tungsten mines) also involved high exposure to radon; jobs with moderate quartz exposure (in tin mines and during ceramics work the median exposure was 2.6 and the cumulative exposure was 2.1 mg/m^3 x years) also involved high exposure to PAH (ceramics work) and arsenic (tin mines). No increase in lung cancer risk was observed for the job with the lowest exposure (median 0.2 mg/m^3 x years), regardless of whether adjustments were made (35).

One study analysed various histological types of lung tumours in lung cancer patients at two French university hospitals (1997-2006). A significant relationship was observed between adenocarcinoma in the lung and previous exposure to quartz, amongst other substances, but this was not observed for other histological types (104).

Birk *et al*. studied mortality in a German cohort from the porcelain industry between 1985 and 2005. No increase in mortality from lung cancer was found, SMR=0.7 (95% CI 0.56–0.89) (20). According to the authors this was one of the largest cohorts of porcelain workers and included 8200 men and 9300 women. The authors believed that exposure to quartz dust in this study (over the period 1985-1987) was more relevant to modern industrial conditions than many previous studies. The weaknesses in the study, as pointed out by the authors, were that the cohort was relatively young and the follow-up period was short. The same cohort of porcelain workers was investigated in a study from 2011 (95). The aim was to quantify the risk of silicosis and lung cancer in porcelain workers who had been exposed to respirable quartz. Exposure to >4 mg/m^3 x years (cumulative) or more than 0.15 mg/m^3 (mean) was strongly related to an increased risk of silicosis (ILO-classification ≥ 1/1), but no dose-response relationship was observed for increased risk of lung cancer.

An article from 2011 presents a study of occupational exposure and lung cancer amongst non-smoking Chinese individuals in Hong Kong. 132 cases of lung cancer were included in the study, along with 536 controls without cancer. A significantly increased risk of lung cancer was observed for jobs involving exposure to quartz dust. With quartz dust exposure the increase in lung cancer risk was associated with the duration of employment. Separate analyses were made for the risk of adenocarcinoma. A significantly increased odds ratio (2.9, 95% CI 1.1–7.7) was observed for workers exposed to quartz dust. The authors thought the study supported an independent effect of quartz on lung cancer risk in non-smokers (139).

A study from 2011 examined cause-specific mortality in an Italian cohort including silicosis patients. The study involved workers who had received compensation for silicosis between 1943 and 1986 (criteria for compensation were: radiologically confirmed silicosis, verified occupational exposure to silica dust, and a reduction in work capacity exceeding 10%, equivalent to a 35% reduction in pulmonary function). The cohort included 2034 men with silicosis. The follow-up period was from January 1987 to December 2006. The study revealed a significant increase in mortality from cancer of the trachea, bronchi, and lungs, tuberculosis, and cirrhosis of the liver. An increased risk of lung cancer, tuberculosis, and liver cirrhosis was observed for bricklayers/stone masons and an increased risk of non-malignant respiratory diseases, COPD, and throat cancer was observed for mine workers (117). The study did not have access to data on smoking habits.

A study from 2010 examined quartz exposure and mortality from lung cancer, renal cancer, other renal diseases, silicosis, and diseases of the respiratory organs in granite workers in Vermont, USA. A total of 7052 workers employed between 1947 and 1998 were included in the study. Mortality (SMR) from lung cancer was 1.4 (95% CI 1.2–1.5), from silicosis 59 (95% CI 45–77), from tuberculosis 22 (95% CI 18–26) and from other lung diseases 1.7 (95% CI 1.5–2.0). No increase in mortality was observed for renal cancer and other renal diseases. A significant relationship with cumulative quartz exposure was observed for silicosis as well as for other diseases of the respiratory organs. Exposure to quartz was higher before

1940 and the study found a strong relationship between quartz exposure and mortality from silicosis amongst men born before 1925. A dose-response analysis found no substantial evidence of an association between quartz exposure and lung cancer. The authors therefore thought that the increase in mortality from lung cancer was due instead to smoking or to some other exposure not related to work (142).

Dose-response studies for lung cancer which were mainly published after IARC's evaluation of 1997

Checkoway and co-workers reported a clear dose-response relationship between exposure to crystalline silica (primarily cristobalite) and mortality from lung diseases and lung cancer (33). The cohort comprised 2342 workers from a kieselguhr plant at Lompoc, California. Data from 5709 measurements made over the period 1962-1988 were obtained from the company. Measurement data prior to 1962 were based on particles whereas analyses carried out after 1962 used gravimetric measurements of total dust or respirable dust. An increase was found in mortality from non-malignant lung diseases (SMR 2.0, 95% CI 1.6–2.6) along with a smaller increase in the risk of mortality from lung cancer (SMR 1.3, 95% CI 1.0–1.6). The authors found a dose-response relationship between non-malignant lung diseases (principally silicosis and its disease sequelae) and both respirable dust and respirable quartz, after 15 years of exposure. For quartz concentrations lower than 0.5 mg/m^3 the relative risk was 1.0; for 0.5–<1.1 mg/m^3 2.04; for 1.1–<2.1 mg/m^3 1.96; for 2.1–<5.0 mg/m^3 3.2; concentrations above 5.0 mg/m^3 gave a relative risk of 5.4. A smaller but clear dose-response relationship was observed between lung cancer and respirable quartz (for ≤0.5 mg/m^3 1.0; for 0.5–<1.1 mg/m^3 0.96; for 1.1–<2.1 mg/m^3 0.77; for 2.1–<5.0 mg/m^3 1.3; for ≥5.0 mg/m^3 2.2) (33).

Steenland and Sanderson carried out a dose-response analysis with 4027 workers in the sand industry. Quantitative calculations of quartz exposure were made for each employee with respect to duration and occupation via a job-exposure matrix. Personal monitoring data for respirable quartz were available for the period 1974-1988. Exposure levels were calculated for four exposure categories and ten occupational categories. Earlier levels of exposure were extrapolated back in time from 1974. The follow up was carried out using a cause of death register. A more detailed dose-response analysis was undertaken in a case control study within the cohort. Although only a limited amount of data on smoking was found in the cohort, this was applied to the entire cohort. 99% of the cohort consisted of men, 24% of whom had died. The average follow-up period was 24 years. The average period of employment was 9 years (though 30% were employed for more than 10 years). SMR (standardized mortality ratio) for tuberculosis was 3.4 (95% CI 1.1–7.9), for lung cancer 1.6 (95% CI 1.3–1.9), for silicosis 66 (95% CI 33-120), and for heart disease 1.22 (95% CI 1.1–1.4). The dose-response analysis showed SMRs for lung cancer of 1.4 (>0-0.10 mg/m^3 x years), 1.3 (>0.1-0.51 mg/m^3 x years), 1.6 (>0.51–1.3 mg/m^3 x years), and 2.4 (>1.28 mg/m^3 x years) (lagged 5

years, the US population as reference) (130). Data on smoking showed that the cohort smoked slightly more than the US population (based on smoking data from 1987), especially amongst younger workers, but the authors estimated that this contributed to only 10-20% of the increase in lung cancer risk. Workers in the sand industry are probably not exposed to any other materials. The study showed an extra lung cancer risk of 60% compared with the US population (SMR=1.60, 95% CI 1.3–1.9).

A Swedish study from 2012 examined the relationship between quartz and lung cancer in a cohort study. It involved a total of 3045 workers from ten Swedish foundries who had worked for at least 1 year between 1913 and 2005. An analysis was made of the incidence of lung cancer between 1958 and 2004. A significant increase was observed in the risk of contracting lung cancer, SIR 1.6 (95% CI 1.2–2.1). No difference in risk was observed between the different exposure groups (short- and long-term exposure) but after a latency period of 20 years a significant increase in the risk of contracting lung cancer was seen in those groups exposed for 10-19 years and >20 years (SIR 2.4, 95% CI 1.1–4.3 and SIR 1.7, 95% CI 1.1–2.6, respectively). The authors saw no dose-response relationships with cumulative quartz exposure. The study lacked data on the smoking habits of the workers (148).

An epidemiological study showed an increase in mortality from lung cancer in American workers exposed to sand. The study involved eight sand producing companies and 2670 men who had worked for the companies for at least three years. A significant increase was found in mortality from tuberculosis, lung diseases, and lung cancer after more than 20 years exposure. Mortality from silicosis was high in the group of workers employed before 1940. The higher lung cancer mortality was due to mortality increases at four companies. For the remaining companies there was no increase in lung cancer mortality whereas mortality from silicosis was higher (90). Studying workers in the sand producing industry had the advantage of few confounders [no arsenic, nickel, radon, or polyaromatic hydrocarbons (PAH)] and a very high quartz content in the mineral (normally over 98%). According to the authors the estimates of exposure were relatively reliable and information on smoking habits was available. An updated study of the American sand companies from 2005 showed that the odds ratio increased with increases in cumulative exposure and average exposure to quartz. Mortality from silicosis was strongly related to exposure and the odds ratio (lagged 15 years) for cumulative exposure was (relative to the lowest exposure group, ≤ 0.7 mg/m^3 x years) 2.2 at 0.7-1.8 mg/m^3 x years, 4.3 at 1.8–5.1 mg/m^3 x years, and 5.5 at > 5.1 mg/m^3 x years. Data for lung cancer, see Table 9a. Adjustments were made for asbestos exposure and smoking. (91).

A study in Dutch workers found an increase in the relative risk of lung cancer in the group with the longest duration of exposure and the highest cumulative quartz exposure. The elevation in lung cancer risk was 1.7 (95% CI 1.1–2.4) for 26-51 years exposure, when compared with no exposure, and 1.5 (95% CI 0.93–2.3) for exposure levels ≥ 3 mg/m^3 x years, when compared with levels < 3 mg/m^3

x years. The authors concluded that, despite efforts to reduce levels of quartz in the workplace environment, levels can still be high (especially in the construction sector). The study included adjustments for smoking and the results did not appear to have been influenced by asbestos exposure. The authors were of the opinion that quartz should be regarded as a human carcinogen (109).

The relationship between lung cancer and quartz exposure was studied in 5115 ceramics workers in Stoke-on-Trent, England. The workers were born between 1916 and 1945 and 80% of them had started employment before 1970. A total of 88 workers (1.7%) had a diagnosis of lung cancer entered on their death certificates. Access to lung x-ray images was obtained for 83% of the cohort. An SMR of 1.9 (95% CI 1.5–2.4) was calculated for lung cancer, with the population of England as reference, and an SMR of 1.3 (1.0–1.6) with the population of Stoke-on-Trent as reference (37). Fifty two cases of lung cancer were examined in a case-control study and this revealed a dose-response relationship with intensity of exposure but not with duration of employment (37).

Studies containing pooled data/meta-analyses and review articles which could include data from several of the above mentioned original articles. See also Table 5

A study from 2000 investigated the dose-response relationships between quartz, silicosis, and lung cancer (53). The research was based on two studies published in 1997 and gave a quantitative meta-analysis for lung cancer in relation to quartz exposure. Cancer mortality was calculated as 1.4 (SMR) for a cumulative exposure of 3 mg/m^3 x years (12% increase in risk per mg/m^3 x years). The authors concluded that the risk of lung cancer could be increased 30% by a lifetime exposure of 0.1 mg/m^3 or more (53). Data for lung cancer, see Table 9b.

The relationship between quartz exposure and lung cancer was studied in a pooled cohort (including data from 10 previous studies) with a total of 44,160 mine workers and 21,820 controls. The median cumulative exposure in the 10 studies varied between 0.13 and 11 mg/m^3 x years (gold mine workers in the USA and gold mine workers in Australia, respectively). The median of average exposures for respirable quartz varied between 0.05 and 0.59 mg/m^3 (granite workers and gold mine workers in the USA and granite workers in Finland, respectively). An analysis of mortality from silicosis gave odds ratios of 1.0, 3.1 (2.5–4.0), 4.6 (3.6–5.9), 4.5 (3.5–5.8), and 4.8 (3.7–6.2) for the quintiles of cumulative exposure for the cases. No trend was observed for silicosis mortality and duration of exposure; odds ratios 1.0, 1.3 (1.0–1.6), 1.8 (1.4–2.3), 1.4 (1.1–1.7, and 1.2 (0.89–1.5). The authors concluded that the data was heterogeneous and that the highest value for South African gold mine workers could be influenced by confounding from radon. The authors found a positive monotonic dose-response trend for lung cancer with

Table 7. Epidemiological studies with SMR (standardized mortality ratio) for lung cancer which were used in the pooled cohort by Steenland *et al*. (129).

Study	SMR
Kieselguhr workers, USA	1.3 (1.0-1.6)
Granite workers, Finland	1.4 (1.0-2.0)
Granite workers, USA	1.2 (1.0-1.3)
Sand workers, USA	1.6 (1.2-1.9)
Ceramics workers, China	1.1 (0.84-1.4)
Tin workers, China	2.1 (1.7-2.6)
Tungsten workers, China	0.63 (0.53-0.75)
Gold mine workers, South Africa	-
Gold mine workers, USA	1.2 (1.0-1.4)
Gold mine workers, Australia	1.8 (1.5-2.1)
All (excluding gold mine workers, South Africa)	1.2 (1.1-1.3)

cumulative exposure: (categorical) odds ratio 1.0 at <0.4 mg/m^3 x years; 1.0 (0.85–1.3) at 0.4-2.0 mg/m^3 x years; 1.3 (1.1–1.7) at 2.0–5.4 mg/m^3 x years; 1.5 (1.2–1.9) at 5.4–13 mg/m^3 x years; 1.6 (1.3–2.1) at >13 mg/m^3 x years, (pooled results). There were no data for smoking (129). The SMRs for lung cancer in the different studies are shown in Table 7.

In a meta-analysis of the dose-response relationship, Lacasse (2009) and co-workers saw an increase in the relative risk of lung cancer with increased cumulative exposure to quartz. The studies were adjusted for smoking. The authors concluded that quartz is a lung carcinogen. A threshold value (exposure level above which the risk of lung cancer increases) was calculated as >1.8 mg/m^3 x years (84). The meta-analysis included studies published in 1997 or later. Data for lung cancer, see Table 9b.

Amongst the epidemiological studies that have been published, it has often been observed that the risk of lung cancer is higher in workers with silicosis. Some studies which show an increased risk of lung cancer with exposure to quartz, indicate that this mainly involved those groups with the highest cumulative exposure, interpreted by the authors as a threshold value (an exposure level below which lung cancer does not develop) (24). Most studies show an increase in the risk of lung cancer which in most cases is less than doubled for the group with the highest exposure (>3-5 mg/m^3 x years). According to many researchers this indicates that quartz is a weak carcinogen (109, 129).

At least two risk assessments (HSE 2003 and SCOEL 2003) were based on the assumption that exposure which does not lead to silicosis does not give rise to a significant risk of developing lung cancer (60, 120). Several cohort studies have reported a relative risk of lung cancer of 1.3–1.4 in workers exposed to quartz (84,

129, 145). If workers with confirmed silicosis are included the relative risk rises to 1.7–2.7 (84, 129, 145).

Erren *et al*. carried out a meta-analysis of 11 epidemiological studies. Adjustments to allow for smoking were made in only 3 of those studies which examined individuals who had been exposed to quartz but had not contracted silicosis. These three studies gave an overall relative risk of 1.0 (95% CI 0.8-1.3). The other eight studies, which were not adjusted for smoking, showed a small increase in the relative risk of lung cancer, 1.2 (95% CI 1.1–1.4). The authors considered that the study was unable to establish whether quartz exposure, in the absence of silicosis, could cause lung cancer (51). The analysis was to a large extent based on studies carried out before 1997.

The relationship between quartz exposure and lung cancer was studied in workers with silicosis. The overall relative risk assessed from seven cohorts and a case-control study was 1.7 (1.4–2.2). This research supported the relationship between silicosis and lung cancer. The relationship between quartz exposure and lung cancer in the absence of silicosis was also studied. The overall relative risk assessed from cohorts with workers in whom silicosis status was undefined was 1.3 (95% CI 1.2–1.3) (24 studies) and from case control studies was 1.4 (95% CI 1.2–1.7) (13 studies). The relative risk of lung cancer in two studies of workers without silicosis was 1.1 (95% CI 0.87–1.6) and 0.97 (95% CI 0.7–1.4), respectively (108). The lower relative risk for those exposed but without silicosis could be related to a lower level of exposure or unreliable data. To sum up, the authors concluded that there was a clear relationship between silicosis and lung cancer but that it was still unclear whether exposure to quartz could give rise to cancer in the absence of silicosis (no significant increase could be demonstrated, but the result was based on only two studies) (108).

The exposure conditions that could modify the relationship between quartz and lung cancer include, amongst other things, the composition of the dust mixture, the interaction of other known or possible lung carcinogens, the total amount of inhaled dust, the concentration of quartz in the dust, the type of crystalline silica, and the surface characteristics of the quartz particles (40). The properties of the dust can also vary according to the geological source and can be altered during the industrial process. The difficulties generally encountered in epidemiological studies involving quartz dust exposure include limited access to historical exposure data, adjustments for possible confounding factors (for example, cigarette smoke where the risk of lung cancer is concerned) (39).

The epidemiological studies that were part of IARC's evaluation of carcinogenicity in 1997 included jobs in mining, quarrying, the granite and slate industries, ceramics, kieselguhr-processing industries, and foundry work. In many of these industries there is additional exposure to other carcinogenic agents; e.g., in most mines there are rock types that contain uranium, which means that radon gas is released. The greatest importance was attached to those studies that involved few or no confounders and that could establish a dose-response relationship (72). IARC's decision to classify quartz as a Group 1 carcinogen (carcinogenic to

humans) has in part been criticized. Some argue that the decision was based on studies which failed to demonstrate dose-response relationships and that the increased risk of lung cancer was so small that confounding or other lifestyle factors could be involved (55, 125). In his article from 2011 (55) Gamble only used material from IARC's review of 1997 and did not include studies carried out later. The article therefore did not shed any light on the current state of knowledge and is therefore of limited value. Several studies carried out after IARC's classification in 1997 have shown an increased risk of lung cancer and in 2009 IARC confirmed its classification of quartz (134).

Summary of the relationship between quartz, silicosis, and lung cancer

There are many studies which show an increased risk of lung cancer with exposure to quartz. The risk is still greater in workers with silicosis. It is still unclear whether workers without silicosis have a higher risk of lung cancer, as the few studies that have investigated this and that have made adjustments for smoking, have shown no increase or a non-significant increase. This could be because few studies with the relevant adjustment for smoking have examined this possibility or because there is no increase. IARC's conclusion does not mention silicosis as an important factor in the link with lung cancer but this is discussed in the main document and it is stated that a relationship between silicosis and lung cancer has been observed in several studies (72). Therefore there is no strong epidemiological evidence that lung cancer occurs without pre-existing silicosis but the data does not rule out a risk.

In an article from 2000 Checkoway and Franzblau discussed whether it is even possible, on the basis of epidemiological studies, to answer the question of whether silicosis is a necessary prerequisite for an increase in the risk of lung cancer in workers exposed to quartz (31). The authors believed there was a lot of uncertainty over diagnosis in which routine radiological examination could be relatively insensitive in detecting small changes in the lung at an early stage of the disease. They also thought that epidemiological studies aimed at investigating the risk of lung cancer with low levels of exposure to quartz should include large populations with a wide range of exposure groups (including low and high levels). The authors concluded that it was too early to draw the inference that silicosis was necessary for lung cancer to develop with exposure to quartz, and that silicosis and lung cancer should be regarded separately as these effects are not necessarily related (31). In a review article on quartz dust Steenland discussed whether, given that silicosis can be considered as a marker for high levels of quartz exposure, it was logical to think, if one assumes that quartz itself can cause lung cancer, that individuals with silicosis should have a higher risk of lung cancer than those without silicosis, even if lung cancer is independent of silicosis (127).

Cancers other than lung cancer

Studies have demonstrated an association between exposure to quartz and cancer of the oesophagus, stomach, skin, and skeletal system. The findings have been

inconsistent (few studies, both positive and negative results) and in most cases there has been a combination of exposure with other risk factors (24). Several studies show cancer of the stomach and oesophagus, see below.

A Swedish study from 2007 examined the risk of stomach cancer in Swedish workers. Moderate or high levels of exposure to quartz dust were seen to be associated with a significant increase in the risk of stomach cancer: incidence rate ratio (IRR) 1.2 (95% CI 1.0–1.4) and 1.3 (95% CI 1.0–1.7), respectively (122).

A Japanese study from 2001 observed a non-significant increase in stomach cancer and oesophageal cancer in individuals exposed to quartz and in silicosis patients. Adjustments had been made to allow for smoking (140).

Mortality in the German porcelain industry between 1985 and 2005 was investigated in a cohort study of 17,644 workers (20). Increased mortality from pancreatic cancer was observed amongst male workers, SMR 1.7 (95% CI 1.2–2.4). Increased mortality from liver cancer and silicosis was also observed, SMR 2.0 (95% CI 1.3–2.9) and 7.2 (95% CI 2.3–17), respectively. There was no increase in mortality from renal cancer. For women the only increase in mortality was from diabetes, SMR 1.7 (95% CI 1.1–2.7). The reference groups were the German population and the population of the German federal state of Bayern. A meta-analysis of occupational exposure and pancreatic cancer showed that exposure to quartz dust resulted in a non-significant increase in risk (meta-risk estimate) of 1.4 (95% CI 0.9-2.0) (102).

Autoimmune diseases

Occupational exposure to quartz dust was investigated as a possible risk factor for a number of systemic autoimmune diseases; e.g., rheumatoid arthritis, scleroderma, and SLE (systemic lupus erythematosus). Occupational groups in which these disease are found include mine workers, granite workers, and stonemasons (107). A Swedish study reported a strong link between quartz exposure and SLE (23).

Women diagnosed with SLE in Boston were studied in order to assess the risk of SLE and their history of exposure to quartz dust (52). Data was gathered at interviews to establish detailed work histories of all participants, including previous exposures. 95 patients were included in the study along with 191 controls matched for age and ethnic origin. A dose-response relationship was observed for duration of exposure. Exposure to quartz for more than one year was associated with SLE (odds ratio 4.3; 95% CI 1.7–11); with exposure for 1-5 years the odds ratio was 4.0 (95% CI 1.2–13); exposure for >5 years gave an odds ratio of 4.9 (95% CI 1.1–22). This effect was not influenced by smoking. In this study those occupations most commonly associated with quartz exposure were the manufacture of dental prosthetics (dental laboratory), sandblasting work, and the production of scouring powder.

A meta-analysis of 16 studies from 2010 examined the relationship between occupational exposure to quartz and scleroderma. The combined estimate for relative risk (CERR) was 1.0 (95% CI 0.74–1.4) for women and 3.0 (95% CI 1.2–7.4) for men. For case-control studies (nine) the CERR was 2.2 (95% CI 1.7–3.3)

and for cohort studies (three) it was 15 (95% CI 4.5–53). The authors concluded that exposure to quartz could be a significant risk factor for scleroderma, particularly in men (89).

Sluis-Cremer *et al*. investigated a possible association between silicosis and rheumatoid arthritis in a case-control study amongst South African gold mine workers. The authors calculated an odds ratio of 2.8 (95% CI 1.4–4.3) for rheumatoid arthritis amongst silicosis cases. No significant difference in cumulative dust exposure or duration of exposure was observed and the mean intensity of dust exposure was significantly lower for silicosis cases than for controls. The authors concluded that mine workers with rheumatoid arthritis had an increased risk of developing silicosis (124).

Two Swedish studies examined the relationship between quartz exposure and rheumatoid arthritis (132, 133). A case-control study with 577 cases and 659 controls showed that individuals exposed to quartz had a higher risk of rheumatoid arthritis (positive for ACPA, anti-citrullinated protein antibodies), odds ratio 1.7 (95% CI 1.1–2.5). Individuals who had worked in rock drilling had a further increase in risk (odds ratio 2.3, 95% CI 1.2–4.7). An even higher risk was found amongst smokers and the authors thought this indicated an interaction between smoking and quartz exposure.

A study from 1993 looked at 50 workers who had jobs in a scouring powder plant at Sevilla, Spain. The powder contained 90% crystalline silica. Thirty two (64%) of the workers had some form of autoimmune disease, which was a much higher percentage than for the general population (116).

Kidney diseases

Kidney diseases associated with exposure to quartz have also been reported. Ng and co-workers studied urine samples from granite workers. Workers with high-level, long-duration exposure (> 10 years) to quartz had higher levels of beta-2-microglobulin, alpha-1-microglobulin and beta-N-acetylglucosaminidase when compared with control individuals, which indicates renal toxicity. The authors also studied granite workers with silicosis (ILO-classification ≥ 1/0) and found that workers with silicosis had the highest levels of beta-2-microglobulin, alpha-1-microglobulin and beta-N-acetylglucosaminidase when compared with the group without silicosis (98).

A case-control study from 2011 reported that quartz exposure was associated with a 40% increase in the risk of chronic kidney disease (odds ratio = 1.40, 95% CI 1.04–1.89). The cases were patients with newly diagnosed chronic kidney disease and the controls were selected randomly and matched for age and gender. Both patients and controls were interviewed about any previous occupational exposure. As well as facing general questions on sand- or quartz-exposure and employment in industries where there is a potential for exposure, the workers were also asked whether, for each job they mentioned, they had been exposed to sand or quartz on at least 5 occasions. Quartz exposure was then individually assessed and a qualitative dose estimate was calculated for each job. The study contained no

quantitative data. The study included the following diagnoses of chronic kidney disease: diabetes with renal manifestations, hypertensive renal and heart disease, chronic glomerulonephritis, nephritis and nephropathy, chronic renal failure, renal sclerosis, chronic pyelonephritis. The average cumulative exposure to quartz was significantly higher in exposed cases than in exposed controls (33 compared with 25 years). Compared with non-exposed controls, the odds ratio was 1.20 (95% CI 0.77–1.9) for individuals whose exposure time was below the average value and 1.8 (95% CI 1.1–2.7) for those with an above-average exposure time (146).

A review article from 2005 examined available dose-response data for quartz and kidney disease. The increased risk of death from kidney disease or of contracting kidney disease by the age of 75 was studied for exposure to 0.1 mg/m^3 respirable crystalline silica for 45 years (lifetime exposure). The increased (absolute/excess) risk of kidney disease was 0.8–9.7%, based on data from three cohorts. Excess risk of kidney disease (end-stage) was estimated as 5.1% (2.2–7.3%, based on one cohort study) (127).

An epidemiological study of sand-exposed American workers, a total of 2670 men at eight sand-production companies, observed increased mortality from kidney disease amongst workers employed for more than 10 years (90).

Kidney disease and arthritis were studied in a cohort of 4626 quartz-exposed workers in the sand industry. The authors found an increase in mortality (SMR) of 2.6 (95% CI 1.5–4.2) for acute kidney disease, 1.6 (95% CI 1.1–2.2) for chronic kidney disease and 4.4 (95% CI 2.8–6.5) for arthritis. The authors found an increased incidence (standardized incidence ratio) of 2.0 (95% CI 1.3–3.0) for end-stage renal disease, with the incidence being highest for glomerulonephritis (renal inflammation), SIR 3.9 (95% CI 1.6–7.9). They also found a significant dose-response relationship between cumulative exposure and the development of kidney disease (131).

Heart disease

A study from 2007 showed an increase in mortality from ischaemic heart disease in Swedish mine workers and other workers exposed to quartz. However, the authors concluded that it was not clear whether the increase was due entirely to quartz exposure or whether other factors may have contributed (147). Lung inflammation was discussed as a possible cause; this was supported by the association between heart disease and inflammation caused by inhaled particles (101).

Steenland and Sanderson carried out a dose-response analysis with 4027 workers in the sand industry. The SMR (standardized mortality ratio) for heart disease was 1.2 (95% CI 1.1–1.4) (130). The study is referred to in more detail under the heading ”Dose-response studies for lung cancer which were mainly published after IARC's evaluation of 1997”. A total of 1130 men with silicosis were identified in the Swedish hospital discharge register and mortality was compared with that of the total population. An increase in mortality was observed for ischaemic heart disease (SMR 1.5, 95% CI 1.4–1.8) (23), which was probably not a secondary effect of silicosis as this disease usually (88%) occurs later.

Other respiratory system diseases

Studies have also shown a relationship between quartz exposure and emphysema, COPD and tuberculosis (34, 65, 110, 115).

Silicosis increases the likelihood of contracting tuberculosis, but even occupational exposure to quartz which has not resulted in silicosis increases the risk of tuberculosis (86). According to Smittskyddsinstitutet (the Swedish Institute for Infectious Disease Control) one third of the world's population carries the tuberculosis bacterium and every year 9 million people contract the disease and around 2 million people die from it. In Sweden an earlier decrease in the incidence of the disease has levelled off in subsequent years (http://www.smittskyddsinstitutet.se/sjukdomar/tuberkulos/, March 2012). An increase in the risk of pulmonary tuberculosis has been observed in patients with silicosis, even in regions where tuberculosis is uncommon. A study of gold mine workers in South Africa found that 15% of the cohort (178 out of 1153) developed tuberculosis between 1984 and 1991 (42). A total of 418 men had silicosis classified as main category 1 according to ILO classification, 355 as category 2 and 45 as category 3 (total 818). Tuberculosis was diagnosed bacteriologically, radiologically, with the tuberculin skin test and in some cases histologically. 23 of 335 workers without silicosis and 155 of 818 workers with silicosis developed tuberculosis, i.e., 7 and 19%, respectively. The relative risk of developing tuberculosis for men with silicosis was 2.8 (95% CI 1.9–4.1), compared with men without silicosis. Workers with silicosis classified in a higher category had an even higher risk of contracting tuberculosis (for category 3 silicosis the relative risk was 6.3 and for category 1 silicosis the risk was 2.2). The authors concluded that the study showed an unusually high incidence of tuberculosis, possibly because the research subjects included no women and were older on average than the general population. The most important factor was thought to be the regular monitoring and reporting of tuberculosis amongst workers compared with the general population (42).

A Swedish study from 1986 examined silicosis and the risk of lung cancer and tuberculosis in silicosis cases in the National Swedish Pneumoconiosis Register (1959-1977). The authors observed a higher risk of developing lung cancer in the category ”mine workers, tunnel workers, quarry workers” (mortality rate 1.3, incidence 2.1, compared with controls). An increased risk of tuberculosis was also observed in silicosis cases (29 cases of tuberculosis amongst silicosis cases, compared with 1 case amongst controls) (150).

An association between silicosis, HIV infection and tuberculosis has also been demonstrated. A retrospective cohort study of 1374 HIV-positive and 2648 HIV-negative quartz-exposed mine workers in South Africa showed tuberculosis incidences of 4.9 and 1.1 per 1000 person years for HIV-positive and HIV-negative workers, respectively. The authors concluded that the high prevalence of tuberculosis in HIV-positive mine workers could be attributed to a multiplicative effect of HIV infection and silicosis (41).

An association between chronic obstructive pulmonary disease (COPD) and quartz exposure has been reported. A review article from 2003 examined the

literature on COPD to determine whether exposure to low levels of quartz, which does not result in silicosis, can cause COPD (66). Pulmonary fibrosis and tuberculosis can contribute to peripheral airway obstruction in workers exposed to quartz. A number of epidemiological studies have reported a dose-response relationship between reduced FEV_1 and FEV_1/FVC and cumulative quartz exposure in both smokers and non-smokers as well as in workers without silicosis (average quartz levels were between 0.1 and 0.2 mg/m^3). Concomitant smoking was shown to increase the negative effect of quartz dust. The values were adjusted for age, height and smoking. The authors concluded that chronic exposure to low levels of quartz dust (which does not cause debilitating silicosis) can lead to emphysema, chronic bronchitis and airflow obstruction, even in the absence of radiological indications of silicosis (66). Studies of South African gold mine workers who began work between 1936 and 1943 showed that the combined effect of smoking and quartz exposure resulted in a higher rate of death from COPD than in non-smokers (all the deceased were smokers). This result indicated that the combined exposure to smoking and quartz dust acted synergistically in causing COPD (62). The authors concluded that workers who had been exposed to quartz dust and who also smoked had a higher risk of dying from COPD than smokers who had not been exposed to quartz dust.

Changes in lung function were studied in a group of Swedish granite workers. Forty-five workers who had been studied in 1976 were followed up in 1988 and were compared with control individuals who had not been exposed. A statistically significant reduction was observed in the concentration of total dust, respirable dust and respirable silica from the period before 1976 to the period 1976-1988 (the concentration of respirable silica was 0.21 mg/m^3 before 1976 and fell to 0.16 mg/m^3 in 1976-1988). Five of the workers had FEV_1-values less than 80% of the expected value (all were smokers or former smokers). One man had a severe reduction in lung function with a mixed restrictive and obstructive pattern and a reduced transfer factor consistent with silicosis. Another showed chest radiographic changes suggestive of silicosis as well as a reduction in static compliance. Five workers exhibited an obstructive decrease in lung function but had normal gas exchange. Compared with the control group, the granite workers had significantly lower FEV_1/VC (forced expiratory volume in the first second/vital capacity), FEF_{50} (forced expiratory flow at 50% FVC) and a steeper phase III slope with the nitrogen washout test. Over 12 years FEV_1 had fallen by 4.6%, FEV_1/VC by 5.4%, MEF (maximum expiratory flow, PEF) by 8% and FEF_{50} by 13.7%, compared with the control group. However, the change in lung function was not significantly correlated with inhaled respirable dust, nor with age and smoking. The authors concluded that peripheral airway obstruction can arise independently of and prior to silicosis (88).

Animal data

A large number of animal studies have been carried out to investigate the effects of quartz. Long term studies with animals have shown pulmonary toxicity, an effect on lung weight, pulmonary fibrosis, altered collagen content, cytotoxicity and biochemical changes in the lung, as well as reduced phagocytosis in alveolar macrophages (39). Long term exposure of rats to quartz resulted in significant increases in adenocarcinoma and squamous cell carcinoma in the lungs in most studies. Different animal species have been found to vary significantly in their sensitivity: quartz is clearly carcinogenic to rats whereas mice and hamsters are less sensitive (39, 45, 72).

Short term experiment summarized by CICAD: rats exposed to 12-50 mg quartz (Min-U-Sil with a particle diameter < 5 μm) by intratracheal instillation over 20-30 days. The exposure caused cell proliferation, increases in levels of water, protein, and phospholipase, and granuloma formation in the lung. An inhalation study with quartz particles (aerodynamic diameter 3.7 μm) in rats showed pulmonary inflammation and a deterioration in clearance function in alveolar macrophages. Progressive lung changes were observed within a month following 3 days of exposure to 100 mg/m^3 quartz in aerosol form. The changes developed into pneumonitis after 2 months. Apoptotic cells were observed in lavage from rats exposed to quartz 2.5–22.5 mg (intratracheal instillation), 1-56 days after exposure (39).

A two-year study in rats looked at the effect of inhaled silica of the type DQ-12 (87% alpha quartz). Fischer-344 rats (50 females and 50 males) inhaled 1 mg/m^3 crystalline silica 6 hours/day, 5 days/week for 24 months. The animals were killed six weeks after the end of exposure. The quartz-exposed animals had higher levels of material in the lymph nodes around the lung tissue than did rats exposed to TiO_2-particles. According to the authors this indicates a progressive and massive movement of the quartz particles from the lung to the lung-associated lymph nodes. Cytological changes were observed in bronchoalveolar lavage and lung clearance was inhibited. Inflammatory changes (leukocytes) and pulmonary fibrosis were also observed in 70 and 92% of the quartz exposed animals, respectively. Nearly all (95%) exposed rats had bronchoalveolar hyperplasia. Keratinizing squamous metaplasia were observed in 5 out of 50 males and 13 out of 50 females. An increase in lung tumours was observed, with a total of 20 primary lung tumours in 19 animals. 15 of the 20 tumours were of the adenoid type (94). CICAD has calculated the human equivalent concentration for LOAEL in the study (1 mg/m^3) as 0.18 mg/m^3 (39). According to CICAD there are not enough dose-response data for rats or other animals.

Lung toxicity and carcinogenicity caused by different dust particles were investigated in an animal study in which quartz was used as a positive control (80). Quartz in the form of DQ12 (90% < 2.3 μm, 50% < 1.1 μm, 10% < 0.6 μm) was dispersed in physiological saline solution and was administered to 59 animals via intratracheal instillation (0.3 ml suspension, 3 mg) once daily for 29 months. Nearly half (40%) the animals developed lung tumours, compared with 0% of

control animals. The most common tumour type was bronchioalveolar carcinoma (26%), followed by squamous cell carcinoma (13%) and bronchioalveolar adenoma (11%). 43% of the animals had bronchioalveolar hyperplasia and 43% had preneoplastic changes. Pulmonary inflammation and fibrosis were also observed. In the authors' opinion these findings confirmed data from previous studies and validated the use of DQ12 quartz as a positive control in instillation studies (80).

Mutagenicity, genotoxicity

Several studies have been carried out to investigate the genotoxic properties of quartz in standardized mutagenicity tests on bacteria, but few have yielded positive results. CICAD has concluded that direct genotoxic effects of quartz have neither been confirmed nor ruled out (39). A human study carried out in Turkey has shown a dose-dependent increase in the frequency of micronuclei in nasal epithelial cells and in lymphocytes from workers in the glass industry, and in sand blasting and stone polishing work which involve exposure to quartz-containing dust at levels that exceed the Turkish occupational exposure limit of 0.25 mg/m^3 (43). The workers had some level of protective equipment, with 86% using respirators and 74% using gloves. All workers were exposed to dust containing 70-100% quartz. For some carcinogens, micronuclei have been shown to be predictive for the later onset of cancer (21). This has not been studied for quartz.

CICAD has summarized a number of studies of the genotoxicity of quartz. DNA strand breaks and the occurrence of micronuclei have been demonstrated *in vitro*, sometimes at relatively high concentrations (up to 30,000 µg/ml). Positive results for cell transformation *in vitro* have also been observed. Studies have shown DNA damage (with comet assay) in lung fibroblasts at between 17 and 103 $µg/cm^2$ (39). HPRT mutations were detected *in vivo* in rats (alveolar epithelial cells) after intratracheal instillation (5 and 100 mg/kg body weight) (39). Rats exposed to quartz (2.5 mg/rat) had higher levels of 8-oxoguanine in the lungs 7, 21 and 90 days after exposure. Increased inflammation and cell proliferation were also observed (96). One study of coal workers showed higher levels of oxidative DNA damage (8-oxoguanine) in peripheral blood lymphocytes in coal miners than in non-exposed controls (119).

A review article from 2011 summarizes *in vitro* results from several genotoxicity studies with crystalline silica. The results showed that the estimated dose for a direct/primary genotoxic effect was 60-120 times higher than the dose that would produce an inflammatory effect. According to the authors these data show that inflammation is the driving force behind the genotoxicity observed *in vivo* which leads to cancer. The primary genotoxic effect of quartz should only play a role where the levels of quartz are very high (22). Genotoxicity caused by inflammation was regarded as secondary and the dose-response curve in secondary genotoxicity is considered to be non-linear and to have a threshold related to the thresholds for activation of inflammation and for the subsequent exhaustion of cellular defence mechanisms. Primary genotoxicity, on the other hand, is thought to follow a linear dose-response curve (22).

The criteria group concluded that oxidative DNA damage is likely. This is caused by reactive oxygen species (ROS) formed in inflammatory processes.

A study from 2000 investigated mutation spectra in lung tumours from workers with silicosis. The results showed high mutation frequency in the p53 gene, but the authors pointed out that the mutation pattern was different from those most commonly found in lung tumours (i.e., in tumours not caused by quartz) (87).

Reproductive effects

Data on the reproductive or developmental effects of quartz have not been found in the literature.

Dose-effect/dose-response relationship

Silicosis

A large number of occupational environmental studies have examined the risk of silicosis and dose-response relationships has been established, see Tables 8a and 8b. The studies were often based on radiological changes which probably gave some degree of under-diagnosis, particularly with mild illness. The present understanding is that the risk of silicosis can be estimated from the cumulative exposure. Acute silicosis develops when the concentration is very high (well over the current Swedish exposure limit of 0.1 mg/m^3). The dose-response relationship for acute silicosis is not known.

A number of studies conclude that an exposure level of 0.05 mg quartz/m^3 can cause silicosis and in some cases silicosis can arise at even lower levels if exposure has continued for many years. Thus Rosenman reports (114) that 0.8% of workers exposed to <0.05 mg/m^3 had silicotic changes in their lungs (ILO-classification ≥1/0). Park *et al.* (105) calculated a 1.6% increase in the risk of contracting silicosis (ILO-classification ≥ 1/0) with an average exposure level of 0.01 mg/m^3 over 45 years. The risk increased by 7.5% with an average exposure level of 0.05 mg/m^3 and by 14% with 0.1 mg/m^3. The workers were mainly exposed to cristobalite. Kreiss and Zhen (82) reported a 10% prevalence of silicosis (ILO-classification ≥1/0) amongst workers with an average exposure level of <0.05 mg/m^3 and a 20% prevalence with a cumulative exposure of 2 mg/m^3 x years (which would mean 0.05 mg/m^3 for 40 years of occupational exposure). A safe lower limit for quartz exposure cannot be specified but it should be possible to relate it to the level that can cause the inflammation which gives rise to silicosis.

A dose-response curve with breakpoints has been described where the increase in risk was greater with increased exposure above the breakpoint. Figure 1 shows the increase in the risk of radiological changes indicating silicosis (ILO-classification ≥1/0 or ≥1/1), based on data from four key studies (see Table 8a). The breakpoint lies at around 1-2 mg/m^3 x years (which should mean 0.025-0.05 mg/m^3 for 40 years of occupational exposure). Figure 2 shows the silicosis

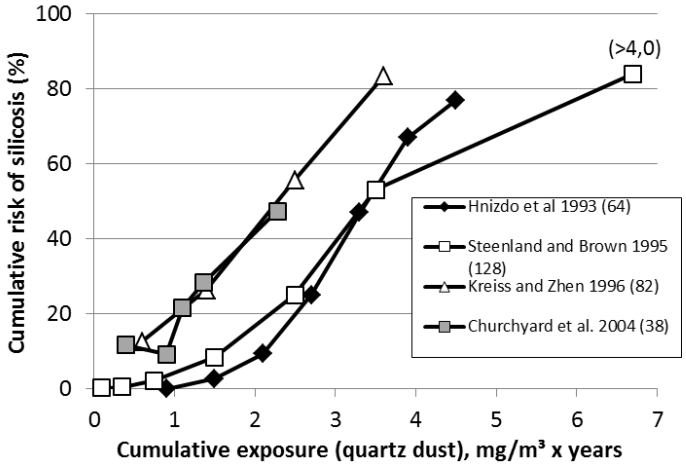

Figure 1. Examples of estimates of the risk of silicosis, using radiologically based diagnosis, with increased cumulative quartz exposure (lung radiological changes, see Table 8a). The study by Steenland and Brown 1995 also contains data for deaths from silicosis. Where the original studies presented only exposure intervals, the value at the mid-point has been used. The figure in parentheses (Steenland and Brown 1995) give the lower limit for an exposure interval without an upper limit and the value on the x-axis was obtained by multiplying the interval's lower limit by 5/3 (cf. US Environmental Protection Agency 2008 (143)).

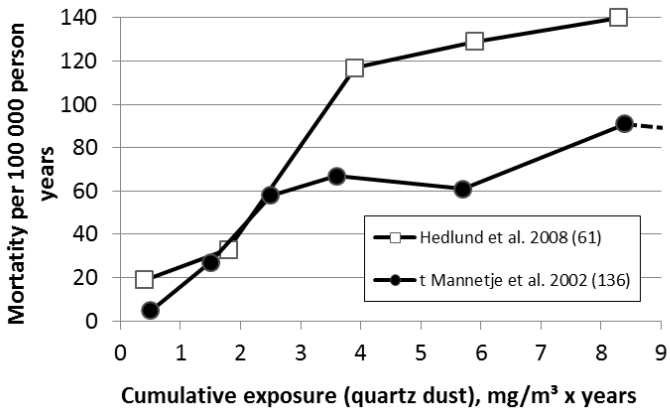

Figure 2. Examples of estimates of the risk of silicosis mortality with increased cumulative quartz exposure. In the study of 't Mannetje *et al*. 2002, the mid-point of the exposure intervals was plotted on the x-axis, and in the study by Hedlund *et al*. 2008 the average value of the exposure intervals was plotted on the x-axis (see Table 8b). Points not shown in 't Mannetje *et al*. 2002: 83/100,000 for 11.3 mg/m^3 x years; 145/100,000 for 14.5 mg/m^3 x years; 74/100,000 for 22 mg/m^3 x years; 234/100,000 for 28 mg/m^3 x years.

mortality rate per 100,000 person years of exposure, based on two key studies (see Table 8b). The breakpoint for this also lies at around 1-2 mg/m^3 x years. It is not clear whether the breakpoint has been statistically verified.

Cancer

Cancer risk assessment is complicated by the fact that a number of risk factors other than quartz have been present in many studies and by the fact that the increases in risk have been moderate. An increased risk of lung cancer has been observed with a cumulative dose of 1-2 mg/m^3 x years (equivalent to a concentration of 0.025-0.05 mg/m^3 for 40 years), an exposure level about the same as that which results in silicosis. Tables 9a and 9b summarize the dose-response relationship for lung cancer and Figure 3 shows examples of dose-response relationships for lung cancer mortality based on data from four key studies, see Table 9a.

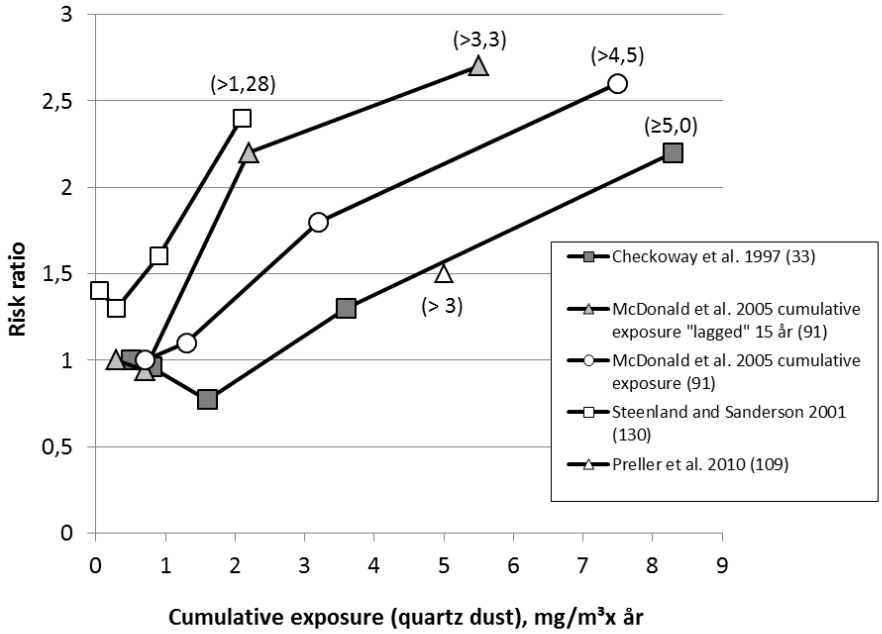

Figure 3. Examples of estimates of lung cancer risk. Where exposure intervals were presented in the original studies, the value at the mid-point has been used. For variability, see Table 9a. The figures in parentheses give the lower limit for an exposure interval with no upper limit and the value on the x-axis was obtained by multiplying the interval's lower limit by 5/3 (cf. US Environmental Protection Agency 2008 (143)).

The association between quartz, silicosis, and lung cancer

The question of whether silicosis always precedes lung cancer has been much examined but epidemiological studies have not provided a definite answer. It is an important question as it is generally accepted that below a certain, though as yet unknown, threshold level silicosis does not develop and because an association between silicosis and cancer could support an assumption that there is also a threshold level for cancer.

The shape of the dose-response curve for silicosis and lung cancer is discussed by Finkelstein (53) who concludes that most studies show a sigmoidal curve for silicosis, whereas the dose-response curve for lung cancer is unknown. According to the authors the dose-response curve can be linear for lung cancer but if silicosis is a prerequisite for the development of lung cancer then the curve is probably also sigmoidal for lung cancer.

In cell models quartz gives rise to inflammation at relatively low concentrations. The inflammation can lead to genotoxicity (secondary genotoxicity) and could explain the development of, e.g., micronuclei in exposed workers (43). It could also explain the genotoxicity that leads to cancer development. Direct genotoxicity (caused by direct contact with DNA) is first seen at higher quartz concentrations (22) and is considered to be a less plausible explanation of the genotoxicity which drives cancer development. This reasoning suggests that cancer does not develop at exposure levels that do not give rise to inflammation and therefore that quartz has a threshold in its dose-response curve for cancer, but this has not been demonstrated.

According to the British work environment authority HSE (60) several studies report that the increase in lung cancer mortality in workers exposed to quartz is limited to those who have silicosis and that exposure which does not lead to silicosis, does not lead to lung cancer. However, the opinion was later put forward that the existing occupational exposure limits were not always adequate for preventing silicosis and that increased risks of silicosis have been demonstrated even at exposure concentrations below 0.05 mg/m^3 (24). HSE has further concluded that it is difficult to identify a level of occupational exposure to quartz below which there is no risk of developing silicosis and also concluded that the risk of developing silicosis increases sharply when the average daily exposure to respirable quartz exceeds 0.1 mg/m^3 (60).

SCOEL (Scientific Committee on Occupational Exposure Limits) based its risk assessment for silicosis on a study by Buchanan *et al*. (26). The study showed a steep non-linear increase in silicosis at concentrations over 0.05 mg/m^3. The results showed that concentrations >2 mg/m^3 for just a few months were sufficient to increase the risk of silicosis. It was estimated that exposure to 0.02 mg/m^3 for 15 years would lead to a 0.25% increase in the risk of developing silicosis, with the curve increasing sharply at levels >0.05 mg/m^3 (26, 120). SCOEL states in its recommendations that the dose-response curve for silicosis appears to be sigmoidal and that keeping exposures below 0.05 mg/m^3 could prevent the effect seen

in the steeper section of the curve where relatively small increases in exposure can cause a significant increase in the risk of silicosis (120).

In a quantitative risk assessment by NIOSH (National Institute for Occupational Safety and Health) it was calculated that 1.9% of those workers exposed to the current US occupational exposure limit for respirable cristobalite dust (around 0.05 mg/m^3) for 45 years were at risk of dying from lung cancer. The death rate from lung diseases other than cancer was calculated at 5.4% and the death rate from radiologically diagnosed silicosis caused by exposure was calculated at 7.5% (100).

CICAD concluded that, on the basis of those studies of lung cancer and quartz exposure with the least confounding, the risk appears to increase with cumulative exposure (exposure time x exposure intensity), with the development of radiologically diagnosed silicosis, and with increased follow-up time after silicosis diagnosis (39).

Other effects

A review article by Hnizdo and Vallyathan in 2003 reported that rats developed emphysema with lower doses of quartz than those which resulted in fibrosis and silicotic nodules. It was also noted that several epidemiological studies which did not find any radiological indications of silicosis nevertheless showed a significant increase in airway resistance (reduced FEV_1/FVC) with low quartz exposure (66). However, the dose-response relationship is unclear as the contribution of quartz to a decline in lung function in dusty environments is uncertain and because the decline could be related to silicosis.

Kidney disease, autoimmune diseases and reduced resistance to tuberculosis infection have been shown to be consequences of quartz exposure but the dose-response relationship is unclear.

Conclusions

The critical effects of occupational exposure to quartz dust are silicosis and lung cancer. Increased risk of silicosis (radiological changes corresponding to ILO-classification ≥1/0 or ≥1/1), increased risk of death from silicosis, and increased risk of lung cancer have been observed with a cumulative dose of around 1-2 mg/m^3 x years (equivalent to a concentration of 0.025-0.05 mg/m^3 for 40 years). A non-effect level has not been identified.

It has not yet been determined whether silicosis is a prerequisite for the development of lung cancer resulting from quartz exposure. However, genotoxicological studies suggest that cancer development is driven by the inflammatory response to quartz.

Occupational exposure to quartz has been shown to give rise to chronic obstructive pulmonary disease (COPD), kidney disease and autoimmune diseases (scleroderma, rheumatoid arthritis, systemic lupus erythematosus). It has not been possible to establish effect levels but studies with rats and lung physiology data

indicate that COPD can occur without signs of silicosis. An increased risk of tuberculosis has also been associated with occupational exposure to quartz dust.

High exposure to quartz dust can cause acute silicosis (fulminant silicosis), often with rapid fatal outcome.

Table 8a. The dose-response relationship between cumulative quartz exposure and the contracting of silicosis (radiological changes in the lung).

Reference	Cumulative exposure (mg/m^3 x years)	Cumulative risk of silicosis (%)	ILO-classification
Hnizdo and Sluis-Cremer 1993[a,b] (64)	0.9	0	≤ 1/1
	1.5	2.7	
	2.1	9.3	
	2.7	25	
	3.3	47	
	3.9	67	
	4.5	77	
Steenland and Brown 1995[b,c] (128)	0-0.2	0.2	1/1 or 2/2
	0.2-0.5	0.5	
	0.5-1.0	2.2	
	1.0-2.0	8.4	
	2.0-3.0	25	
	3.0-4.0	53	
	>4.0	84	
Kreiss and Zhen 1996[b] (82)	>0-1 (0.6)[d]	12.5[e]	≤ 1/0
	>1-2 (1.4)	26.3	
	>2-3 (2.5)	55.6	
	>3 (3.6)	83.3	
Churchyard *et al*. 2004[f] (38)	0-0.8	11.6[e]	≤ 1/1
	0.8-0.99	9.2	
	0.99-1.24	21.6	
	1.24-1.48	28.3	
	1.48-3.08	47.3	

[a] Values read from a graph (cumulative dust dose), converted to quartz, assuming a 30% quartz content in the dust.
[b] Follow-up period >20 years.
[c] The study also includes silicosis mortality .
[d] Exposure interval's average value.
[e] Prevalence (%).
[f] Values read from a figure.

Table 8b. Dose-response relationship between cumulative quartz exposure and silicosis mortality. Pooled data or meta-analysis.

Reference	Cumulative exposure (mg/m^3 x years)	Silicosis mortality per 100,000 person years
't Mannetje *et al*. 2002 (136)	0-0.99	4.7
	0.99-2.0	27
	2.0-2.9	58
	2.9-4.3	67
	4.3-7.1	61
	7.1-9.6	91
	9.6-13	83
	13-16	145
	16-28	74
	>28	234
Hedlund *et al*. 2008 (61)	0-0.9 (0.4)*	19
	1-2.9 (1.8)	33
	3-4.9 (3.9)	117
	5-6.9 (5.9)	129
	>7 (8.3)	140

* Exposure interval's average value.

Table 9a. Dose-response relationship between cumulative quartz exposure and lung cancer.

Reference	Cumulative exposure (mg/m^3 x years)	Relative risk (95% CI)	Follow-up period
Checkoway *et al*. 1997[a,b] (33)	<0.5	1.0	7 years
	0.5 – <1.1	0.96 (0.47-2.0)	
	1.1 – <2.1	0.77 (0.35-1.7)	
	2.1 – <5.0	1.3 (0.62-2.6)	
	≤5.0	2.2 (1.1-4.3)	
Steenland and Sanderson 2001[a,b,c,d] (130)	>0 – 0.10	1.4 (0.67-2.6)	17 years
	>0.1 – 0.51	1.3 (0.79-2.0)	
	>0.51 – 1.3	1.6 (0.98-2.5)	
	>1.28	2.4 (1.4-3.9)	
McDonald *et al*. 2005[a,b,c,*] (91)	≥0.7	1.0	>20 years
	>0.7 – ≥1.8	1.1	
	>1.8 – ≥4.5	1.8	
	>4.5	2.6	
McDonald *et al*. 2005[a,b,c,e,*] (91)	≥0.3	1.0	>20 years
	>0.3 – ≥1.1	0.94	
	>1.1 – ≥3.3	2.2	
	>3.3	2.7	
Preller *et al*. 2010[b,f] (109)	<3	-	11 years
	>3	1.5 (0.93-2.3)	

*For the average concentration observed in this study (relative to the lowest exposure group, ≥0.07 mg/m^3) a relative risk of 1.0 (0.48–2.1) at >0.07– ≥0.16 mg/m^3, 1.6 (0.75–3.5) at >0.16–≥0.26 mg/m^3 and 2.4 (1.0–5.6) at >0.26 mg/m^3.

[a] Lung cancer mortality.

[b] Adjusted for smoking.

[c] Sand industries, low confounding.

[d] Excess lifetime risk.

[e] Lagged 15 years.

[f] Contracting lung cancer.

Table 9b. Dose-response relationship for lung cancer. Pooled data or meta-analysis.

Reference	Cumulative exposure (mg/m^3 x years)	Calculated risk
Finkelstein 2000[a] (53)	1	1.0
	2	1.2 (1.1-1.2)
	3	1.3 (1.3-1.4)
	4	1.5 (1.4-1.6)
	5	1.7 (1.7-1.8)
Lacasse *et al*. 2009[b] (84)	1.0	1.2 (1.0-1.5)
	6.0	1.8 (1.5-2.3)

[a] Mortality.

[b] Adjusted for smoking.

Potential conflicts of interest

Johan Högberg (member), Ulla Stenius (member) and Ilona Silins (author of draft), in a previous assignment from Swedish Work Environment Authority, have expressed opinions concerning questions posed in the consensus report on quartz.

Johan Högberg (member) and Ulla Stenius (member) have received research grants from AFA Insurance for a project on cancer risks from low-dose exposure to quartz.

Maria Albin (member), in a text book issued by Prevent and in the Bulletin from Arbets- och miljömedicin (Occupational and Environmental Medicine) in Lund, has argued that current knowledge indicates that the existing occupational exposure limit for quartz does not adequately protect those exposed from the risk of silicosis/lung cancer.

Gunnar Johanson (member) has declared that he was involved in SCOEL's evaluation of quartz and recommendations on health-based indicative occupational exposure limits for the EU.

Bengt Sjögren (member) and Gunnar Johanson (member), in a letter to Swedish Work Environment Authority dated 2006-05-05, have drawn this authority's attention to the view that the classification of quartz and cristobalite as carcinogens should be considered, on the basis of the published scientific evidence (Lundberg 1996, SCOEL 2002, IARC 1997).

Håkan Westberg (member) has declared that he has received research grants from AFA Insurance for a project ”Kvarts i svenska järngjuterier” (Quartz in Swedish iron foundries) in collaboration with SWEREA - Svenska Gjuteriföreningen (Swedish Foundry Association).

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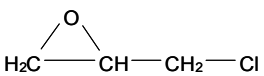
Consensus Report for Epichlorhydrin

October 2, 2013

This consensus report is largely based on a criteria document from the EU's scientific committee for establishing exposure limits, the Scientific Committee on Occupational Exposure Limits (SCOEL) (25). Complementary data searches were made on PubMed and Toxline over the period January 2009-August 2013.

Chemical-physical data

CAS no	106-89-8
Synonyms	1-chloro-2,3-epoxypropane, 1,2-epoxy-3-chloropropane, chloropropylene oxide, chloromethyloxirane, allyl chloride oxide
Structural formula	
Molecular weight	92.53
Melting point	-48 ºC
Boiling point	116 ºC
Vapour pressure	1.73 kPa (20 ºC)
Saturation concentration	17,000 ppm
Density	1.18 g/ml
Conversion factors	1 ppm = 3.84 mg/m^3; 1 mg/m^3 = 0.26 ppm
Other information	Phosgene is formed when epichlorhydrin is thermally decomposed

Epichlorhydrin is a colourless, reactive and flammable liquid with a sweet, chloroform-like smell. Amoore & Hautala (2) have reported an odour threshold of 0.93 ppm. The substance is soluble in water (6.59%) and miscible with ethers, alcohols, carbon tetrachloride and benzene (36).

Uses

Epichlorhydrin is used in the manufacture of epoxy- and phenoxy-resins. It is also used, e.g., in the manufacture of glycerine and the vulcanization of propylene-based rubber, and as a solvent for cellulose esters/ethers (25). In Sweden a total of 1566 tonnes were used in 197 different products in 2011. The main area of use is the manufacture of chemicals and chemical products. Smaller amounts are used in, for example, the manufacture of paper pulp/paper/paper products, in the rubber

and plastics industries, in construction work and in the paint industry (SPIN database 2013, www.kemi.se).

Uptake, biotransformation, excretion

Epichlorhydrin is absorbed and distributed rapidly and completely in laboratory animals, with both inhalation and peroral administration. More than 90% is taken up and distributed in rats within 2-4 hours. In studies in rats using radioactively labeled epichlorhydrin, the highest levels of radioactivity were found in the nasal mucosa after inhalation and in the stomach after peroral administration. The highest systemic concentrations were found in the kidneys, intestines, liver, lacrimal glands, pancreas and spleen (25). No quantitative data on dermal absorption has been found

Epichlorhydrin is a bifunctional alkylating substance which can bind covalently to macromolecules. Haemoglobin adducts and DNA adducts have been demonstrated *in vivo* (25). After an initial reaction with glutathione epichlorhydrin is metabolized to the mercapturic acid derivative which has been detected in urine, primarily N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine [and to a small extent also to S-(2,3-dihydroxypropyl)-L-cysteine and N-acetyl-S-(2,3-dihydroxypropyl)-L-cysteine)]. In addition the metabolite 3-chloro-1,2-propanediol is formed via hydrolysis (25). For a high peroral dose of epichlorhydrin (200 mg/kg; in water) the half life in the blood of mice was 5.5 minutes (24). Epichlorhydrin (metabolites) is mainly excreted in urine and via the lungs (25).

Toxic effects

Human data

A cross-sectional study (20) reported increased incidence of symptoms of irritation in the respiratory tract (questionnaire) and poorer results in lung function tests in individuals exposed to epichlorhydrin. Average levels of epichlorhydrin in air were measured (sampling for 30 minutes to 3 hours) and the workers (n=167) were divided into three exposure groups (8-hour time-weighted average values): ”non-exposed” (<0.026 ppm) controls, low-level exposure group (0.026-<0.2 ppm; average value 0.064 ppm) and high-level exposure group (≤0.2 ppm, range 0.2-5.9 ppm; average value 1.7 ppm). There was also exposure to dimethylformamide (DMF) and toluene. The average values for the ”non-exposed”, low exposure and high exposure groups were 11.5 ppm, 13.9 ppm and 3 ppm, respectively, for DMF and 7.3 ppm, 1.1 ppm and 1.6 ppm, respectively, for toluene. Odds ratios (OR) (95% CI, adjusted for smoking, gender, duration of employment, DMF) for low- and high-epichlorhydrin exposure groups were 2.92 (1.07, 7.92) and 4.71 (1.36, 16.3), respectively, for cough (p trend=0.019), 2.36 (0.89, 6.3) and 3.74 (1.08, 12.9), respectively, for mucous (p trend=0.047), 2.41 (0.94, 6.2) and 3 (1.04, 8.67), respectively, for tightness in the chest (p trend=0.038) and 5.1 (1.01, 25.8) and 4.86 (0.85, 27.7), respectively, for breathlessness (p trend= 0.078). Signi-

ficantly ($p<0.05$) lower average values were observed in the lung function test, compared with controls (only 59 of 88 controls were tested) in both low exposure (MMEF, FEV_1) and high exposure (MMEF, FEV_1, FEV_1/FVC) groups. The prevalence of abnormal MMEF was 4/59 (6.8%) in controls, 11/38 (29%) in the low exposure group and 13/41 (31.7%) in the high exposure group, and OR (95% CI, adjusted for smoking, gender, duration of employment, DMF) were 6.82 (1.75, 26.6) and 7.46 (1.63, 34.1) (linear trend test $p=0.007$). The corresponding prevalences for FEV_1/FVC were 1/59 (1.7%), 2/38 (5.3%) and 4/41 (9.8%) and the odds ratios were 3.82 (0.28, 52.5) and 15.3 (0.66, 354) (linear trend test $p=0.16$). In multivariate logistic regression analysis both low and high epichlorhydrin exposure were significantly associated with abnormal MMEF values ($p=0.005$ and $p=0.0085$, respectively) after adjustment for other factors. High epichlorhydrin exposure also showed an association with abnormal FEV_1/FVC-values ($p=0.083$) that was of borderline significance. Neither gender, duration of employment, smoking status, nor DMF exposure was significantly associated with a decrease in lung function. The authors concluded that exposure to epichlorhydrin may be associated with respiratory tract irritation symptoms and small airway lung dysfunction and that such effects can occur at air levels <0.2 ppm. They also suggested that epichlorhydrin may cause obstructive lung abnormalities at higher concentrations (≤0.2 ppm). However, they emphasized that longitudinal studies are needed to determine a causal association (20). The study has a number of weaknesses, such as large confidence intervals and imprecise adjustments for concomitant exposure to DMF.

A subpopulation (total 68 workers) from the study by Luo *et al*. (20) was investigated in a subsequent study (21) with regard to the modifying effects of glutathione S-transferase polymorphism. The study showed that individuals lacking the GSTM1 gene were more sensitive to epichlorhydrin exposure (21). The results strengthens the causal association between epichlorhydrin exposure and the effects and present a reason for the variation in individual sensitivity. Circa 50% of the population lacks the GSTM1 gene (36).

Epichlorhydrin in liquid form is highly irritant to the skin and eyes (1). It has been reported that opacity and necrosis of the cornea occur with direct contact (25). Many cases of burn injuries to the skin have been reported amongst workers who have had skin contact with epichlorhydrin, though it is usually many minutes-hours before signs of skin damage appear (1). It has been reported that epichlorhydrin can penetrate leather shoes and rubber gloves, thereby causing chemical burn injuries (36). However, it has been reported that gloves made from butyl rubber, polyvinyl alcohol with an outer laminated polyethylene film, or polyvinyl alcohol, in themselves offer good protection against epichlorhydrin (Anders Boman, personal communication 2013-02-14).

Patch testing with epichlorhydrin (1% in vaseline) has shown positive results in individuals (around twenty) with allergic contact dermatitis who have been occupationally exposed to, amongst other things, epichlorhydrin, mainly in factories that manufacture epoxy resins (23, 34, 35).

Animal data

The LC_{50} for a 4-hour exposure of rats was 500 ppm (25). Laskin *et al*. (19) reported an LC_{50}-value of 360 ppm for a 6-hour exposure. The LD_{50} for peroral administration to rodents was circa 220 mg/kg body weight (25). The LD_{50} for dermal application in rabbits has been reported as 754 and 1038 mg/kg body weight (25). ACGIH reported that 7 out of 10 mice died when their tails were immersed in epichlorhydrin for 15-20 minutes (1).

A study in rats reported a clear reduction in respiratory rate within 15 minutes at an air level of 363 ppm and an RD_{50} (the air level that gives a reduction of 50% in respiratory rate) of 1342 ppm was reported (8, 25). Another study reported an RD_{50} of 687 ppm for mice. This concentration was reported to cause injuries in the nasal cavity and also in the lower respiratory tract (exposure 6 hours) (3). An old study (7) reported laboured breathing in rats after 3 hours exposure to 120 ppm. Increased urinary excretion of protein and histopathological changes in the lungs (including inflammation), kidneys (tubular atrophy) and liver were reported following repeated exposure to 120 ppm (Table 2).

An inhalation study in rats and rabbits exposed to 5, 25 or 50 ppm for 10 weeks showed dose-dependent irritation-related effects in the nose (mainly in the respiratory epithelium in the nasal turbinates), including inflammation, focal burn injury and metaplasia, at the two highest exposure levels. Such histopathological changes in the nose were not observed 10 weeks after the end of exposure. In addition, a significant reduction in body weight gain was reported for rats (both sexes) and rabbits at 50 ppm. Furthermore, a significant increase in absolute and relative kidney weights was observed in rats (both sexes), along with a small accentuation of spontaneous renal changes at 50 ppm. However, the authors reported that there were no indications of tubular degeneration or necrosis at any of the exposure levels and that the values for kidney function were normal (11), see Table 2. A cancer study in male rats with a lifetime exposure to 10 and 30 ppm revealed inflammatory changes in the lungs as well as squamous metaplasia in the nasal mucosa (2% and 4% vs. 0 in controls). In addition a dose-dependent increase was shown in the incidence and degree of renal changes, including degenerative changes in the tubules. Similar renal changes were seen in control animals. Renal changes (incidence and degree the same as at 30 ppm) were observed with exposure to 100 ppm for 30 days, along with severe inflammatory changes in the respiratory tract and squamous metaplasia in the nasal mucosa (19), see Table 2.

In one study epichlorhydrin was given perorally (gastric intubation) to rats for 10 days (3, 7, 19, 46 mg/kg body weight/day) or 90 days (1, 5, 25 mg/kg body weight/day) (Table 3). In the 10-day study a significant increase in relative kidney weight was observed and, in males, a significant increase in relative liver weight at doses ≤19 mg/kg/day. There was also a significant increase in relative liver weight in females and a significant increase in relative testicular weight at the highest dose. In the 90-day study a significant increase in relative liver weight was reported in males at 5 mg/kg/day as well as significant increases in absolute and

relative kidney and liver weights in both sexes at 25 mg/kg/day. In the high dose group haematological changes (reduction in red blood cell counts, haemoglobin, haematocrit) were also observed, as well as an increase in urine proteins (males) and other changes. An increased incidence of chronic inflammation in the kidneys was observed in males (90-day study) and the authors therefore did not rule out effects on the kidneys in males. (They also established that increased kidney weight occurred in both sexes; see above). However, histopathological changes that were clearly related to exposure were only seen in the stomach. Hyperplasia and hyperkeratosis in the gastric mucosa were observed at 5 and 25 mg/kg/day (significant increase in incidence and degree), but were not seen at 1 mg/kg/day. In the 10-day study an increased incidence of hyperplasia and hyperkeratosis in the stomach were seen at doses ≤3 mg/kg/day (females) and ≤7 mg/kg/day (males), respectively. For both exposure periods the changes were minimal-to-mild except at the highest doses (25 and 46 mg/kg/day) which caused more pronounced hyperplasia, especially in females. Low-grade gastric mucosal degeneration was observed at 46 mg/kg/day (both sexes). Dose-related gastric mucosal degeneration was also observed in the 90-day study (at all doses in males), but no details were reported. The authors established a LOAEL of 3 mg/kg body weight/day (10-day study) and a NOAEL of 1 mg/kg body weight/day (90-day study) (5). Gastric hyperplasia was observed in a cancer study in rats at doses of 2 and 10 mg/kg body weight (Table 3).

It was reported that a 5% solution of epichlorhydrin in cottonseed oil did not cause eye irritation in laboratory animals but undiluted or concentrated solutions caused pronounced eye irritation and damaged the cornea (36). Over a 24-hour period a 0.3% solution of epichlorhydrin in cottonseed oil (0.2 ml, occlusion) did not cause irritation to the skin of rabbits whereas the 5% solution caused pronounced skin irritation (36). Undiluted epichlorhydrin (0.5 ml, 24 hours) was reported to be intensely irritant and necrotic on the shaved skin of rabbits (36).

In a laboratory study aimed at investigating skin sensitizing properties in the Guinea pig maximization test (GPMT) a positive reaction was seen in 9/15 animals, with induction by 5% epichlorhydrin in ethanol and provocation by 1% epichlorhydrin in ethanol. No reaction was observed in control animals (0/15). Epichlorhydrin was classed as a moderate (Grade III) contact allergen (31).

Genotoxicity

Epichlorhydrin is a direct-acting mutagen which induces genotoxic effects in most test systems *in vitro* without metabolic activation. In bacterial tests, gene mutations and DNA damage were observed and in yeast also aneuploidy and recombinations. In mammalian cells epichlorhydrin caused mutations, DNA single- and double-strand breaks, and sister chromatid exchange (SCE). DNA adducts and DNA crosslinks have also been reported after reaction with epichlorhydrin *in vitro* (10, 15, 25). Induction of cell transformation has been demonstrated in mammalian cells *in vitro* but, at low-to-moderate concentrations of epichlorhydrin, only in the presence of tumour promoters (14).

Genotoxic effects have been reported in several studies involving the cytogenetic investigation of workers exposed to epichlorhydrin (Table 1). In a prospective study Czechoslovakian workers (31-35 individuals) were monitored at an epichlorhydrin production plant. Blood samples were taken before the start of production (controls) and after 1 and 2 years of exposure. A significant increase in structural chromosome-, chromatid-aberrations in lymphocytes was reported and the increase was greatest after 2 years. Exposures of 0.13-1.3 ppm (0.5-5.0 mg/m^3) were reported (17). Sram *et al.* (29) examined 23 of these workers (and 5 other workers exposed to epichlorhydrin) after a further 2 years. There was a significant increase in chromosomal aberrations when compared with 34 controls (matched by age, gender, smoking habits etc.) and 21 individuals from the general population. In the final 2 years air levels of epichlorhydrin were ca. 0.25 ppm (range 0.05-0.5 ppm; 0.94 mg/m^3, range 0.20-1.85 mg/m^3) (29, 30). A follow-up study involving exposure for a further 4 years reported some increase (non-significant) in chromosomal aberrations in lymphocytes in exposed workers (2.00% vs. 1.68%) compared with matched controls. In the final 6 months before sampling the average level of epichlorhydrin in the atmosphere was 0.1 ppm (range 0.01-0.3 ppm) (0.38 mg/m^3; range 0.05-1.11 mg/m^3) and it was stated that peak exposure rarely exceeded 0.26 ppm (1 mg/m^3) (30).

A significant increase in lymphocyte SCE was reported in a Taiwanese study in a group of 21 workers with "high" exposure to epichlorhydrin associated with the manufacture of epoxy resin (results were significant for smokers but not for non-smokers). The group with "high" exposure to epichlorhydrin was exposed to average air levels of 1.1-3.9 ppm (time-weighted average, median value). No increase in SCE frequency was observed in 35 workers exposed to low levels (0.1-0.2 ppm epichlorhydrin; time-weighted average, median value). No relationship between DMF exposure and SCE incidence was observed in the study (4). In another study a significant increase in SCE in lymphocytes was observed in 15 workers exposed to epichlorhydrin in a German factory, when compared with a German control group. An increase in micronucleus frequency was also seen, though this was of borderline significance, and no effect on gene mutations was observed. There was a significant increase in haemoglobin adducts for the exposed group, though only when compared with a Swedish control group. The level of haemoglobin adducts was higher in smokers than in non-smokers. Linear regression analysis revealed no significant correlation between individual data on haemoglobin adducts and genetic effects. Air levels of epichlorhydrin levels were 0.11-0.23 ppm for 45 hours/week and 0.2-2.6 ppm for 3 hours/week (18).

An increase in damaged cells (including cells with chromosome breakage) were observed in cytogenetic examination of peripheral lymphocytes from 93 workers who may have been exposed to high air levels of epichlorhydrin, when compared with 75 controls (matched for gender and to some extent for age). No exposure data was made available in the study but air levels of epichlorhydrin probably corresponded to current exposure limits (5 ppm, 8-hour time-weighted average) (22).

Results from laboratory animal studies are to some extent contradictory. An older study reported that epichlorhydrin increased the proportion of abnormal cells (e.g., with chromosome breakage) in the bone marrow of mice when injected into the abdominal cavity (1-50 mg/kg body weight; 5 x 5-20 mg/kg body weight) or administered perorally (5-100 mg/kg body weight; 5 x 20 mg/kg body weight) (28), see Table 3. However, in another study in mice a single peroral dose of epichlorhydrin (50 or 200 mg/kg body weight) did not cause any significant increase in the frequency of chromosomal aberrations in bone marrow cells (24). Covalent binding to DNA in various organs has been reported in research involving intra-abdominal injection in mice and rats (25). In a host-mediated assay in mice (with Salmonella bacteria as indicator organisms) an increase in mutations was observed after intramuscular (100 mg/kg body weight) and subcutaneous (50 and 100 mg/kg body weight) injections (28). Other host-mediated assay studies gave negative results (10). Further negative results have been reported in a number of studies involving dominant lethal tests and micronucleus tests in mice (25). Recessive lethal mutations in banana flies were reported in two studies, whereas a third study gave negative results. (25).

Carcinogenicity

No tumours were reported after exposure to 10 ppm in an inhalation study in rats subjected to whole body exposure to epichlorhydrin for up to 2 years (10 or 30 ppm) or for 30 days (100 ppm) with a lifetime follow-up. After exposure to 30 ppm tumours were found in the nasal cavity of 2/100 animals. At 100 ppm tumours were observed in the respiratory tract of 18/140 animals, with squamous cell carcinomas in the nasal cavity of 15/140 animals (not observed in control animals) (19), see Table 2. No tumours other than those found in the respiratory tract were regarded by the authors as exposure-related (there were, for example, 4 pituitary adenomas and 4 malignant lymphomas at 100 ppm).

Localized tumours in the gastrointestinal tract of rats have been observed in rats given epichlorhydrin perorally (Table 3). A dose-dependent increase in forestomach tumours was reported in a long term study with doses of 2 and 10 mg epichlorhydrin/kg body weight (gastric intubation 5 days/week, 2 years). No significant increase in tumours was found in other organs (37). A dose-dependent increase in forestomach tumours was seen in another study (375, 750, 1500 ppm in drinking water, 81 weeks) at total doses ≤8.9 g/rat (750 ppm). Tumours (squamous cell carcinomas) were also reported in the oral cavity in the high-dose group (total dose 15.1 g/rat; 2/12 animals) (16). Localized sarcomas have been observed in long term studies in mice subjected to repeated subcutaneous injections with epichlorhydrin (25).

In 1998 IARC concluded that there was sufficient evidence in experimental animals for the carcinogenicity of epichlorhydrin and that there was inadequate evidence in humans. However, the overall evaluation was that epichlorhydrin is probably carcinogenic to humans (Group 2A). In making the overall evaluation the known chemical reactivity of epichlorhydrin and its direct activity in a wide

range of genetic tests was considered (10). SCOEL (25) categorized epichlorhydrin as a genotoxic carcinogen for which there was no threshold (group A) because of the substance's clear, direct genotoxicity. A theoretical calculation using linear extrapolation, based on data in the study of Laskin *et al*. (19) and the incidence of localized tumours in the respiratory tract in rats at 30 ppm (2/100), gave an extra lifetime cancer risk of 4 per 100,000 for 40 years of occupational exposure to 0.19 mg epichlorhydrin/m^3 (0.05 ppm) and 4 per 1000 for 40 years of exposure to 19 mg/m^3 (4.9 ppm) (6).

Effects on reproduction

Effects on fertility were investigated in rats and rabbits while they were subjected to inhalation exposure to 5, 25 or 50 ppm epichlorhydrin for 10 weeks and during a recovery period of 10 weeks (11), see Table 2. Male rats were mated with non-exposed female rats (during and after the exposure period), females rats were mated with non-exposed male rats (after the exposure period) and male rabbits were mated with non-exposed female rabbits (during the exposure period). Sperm samples were taken from rabbits on repeated occasions before, during and after the exposure period. No effects on fertility were observed in male rats exposed to 5 ppm. Exposure to 25 and 50 ppm had dose-dependent negative effects with fewer fertile male rats (only significant at 50 ppm) and fewer implantations in non-exposed female rats. At both air levels the fertility of male rats returned to normal by 2 weeks after the end of exposure. The reproductive capacity of exposed female rats was unaffected at all exposure levels. Studies with male rabbits showed no effects on fertility or sperm (motility, viability, concentration, morphology) at any exposure level. Exposure to 50 ppm caused a significant reduction in body weight gain in both rats (both sexes) and rabbits.

Effects on embryos, foetuses and reproduction were examined for inhalation exposure to 2.5 or 25 ppm epichlorhydrin for a part of the pregnancy (12), see Table 2. Parameters investigated included the numbers of corpora lutea, implantations, resorptions and living foetuses, as well as foetus weight/length and malformations/variations. It was reported that epichlorhydrin was neither embryotoxic nor teratogenic at any exposure level in either rats or rabbits.

Sperm and reproductive organs were examined in male rats following peroral administration of epichlorhydrin for 10 weeks (0, 3.3, 10, 30 mg/kg/day). Sperm analysis revealed a dose-dependent reduction in the number of sperm (testicular and epididymal) and sperm motility and a dose-dependent increase in abnormal sperm. The high-dose group showed significant differences in these parameters when compared with the control group. Also reported was an essentially dose-dependent reduction in antioxidants/antioxidant enzymes (catalase, GST, SOD and GSH) and a dose-dependent increase in MDA (indicator of oxidative stress) in epididymides (at 3.3 mg/kg/day only the reduction in GSH was significant) (27).

In an older study epichlorhydrin was administered by gastric intubation to males rats (12.5, 25, 50 mg/kg body weight/day) for 21 days and to female rats (25, 50, 100 mg/kg/day) from 2 weeks before mating (non-exposed males) up until the end

of pregnancy. No significant effects on reproduction were observed in exposed females. Total infertility in males was observed at the highest dose (the only dose where this was studied). A significant dose-dependent deterioration of various parameters for epididymal sperm motility was observed at all doses. The number of sperm from the epididymides was somewhat (significantly) reduced at the highest dose but it was judged that this did not cause infertility (32). Various parameters for sperm motility (epididymal sperm) and fertility were examined further in a subsequent study in rats given 6.25, 12.5, or 25 mg/kg/day perorally for 23 days and mated with untreated females. A significant reduction was observed in the proportion of ova that were fertilized (84.1%, 28.1%, 1.8% vs. 97.4% for controls) at all doses, as well as a significant reduction in implantations (93,2%, 42,6%, 0% vs. 85.8% for controls) at the two highest doses. The only significant sperm analysis value for the low-dose group was the proportion of sperm that were motile (50.6% vs. 56.3%). In the mid-dose group there were also significant adverse effects on other sperm motility parameters and in the high-dose group these adverse effects were substantial (33). According to the authors (32, 33) the effects on sperm that were observed were consistent with reported metabolic changes in sperm exposed to the metabolite 3-chloro-1,2-propanediol. This metabolite has been reported to affect, amongst other things, ATP levels and sperm motility and to cause a deterioration in sperm function (25).

A substantial dose-dependent reduction in fertility (expressed as the frequency of implantations/corpus lutea of pregnancy; 8% and 2%, respectively, vs. 62% for controls) was observed in a study in rats in which male rats were injected intra-abdominally with 3 or 6.25 mg epichlohydrin/kg body weight/day for 4 days, before sperm from their epididymides were inserted into the uteri of female rats. No significant effects were observed on parameters relating to sperm morphology or sperm count but at the higher dose there was a significant reduction in the percentage of sperm that were motile or progressively motile (13).

Dose-effect/dose-response relationships

Genotoxic effects have been reported in several studies involving the cytogenetic investigation of workers exposed to epichlorhydrin (Table 1). Repeated studies involving workers at an epichlorhydrin production plant revealed a significant increase in the frequency of chromosomal aberrations in lymphocytes. Exposure was 0.13-1.3 ppm in the initial years but later increased to ca. 0.25 ppm (range 0.05-0.5 ppm) (17, 29). A significant increase in SCE in lymphocytes was reported in a group of workers (smokers) exposed to average air levels of 1.1-3.9 ppm epichlorhydrin but no increase in SCE was seen in workers exposed to 0.1-0.2 ppm (4). In another study with reported air levels of 0.11-0.23 ppm and 0.2-2.6 ppm for short periods, a significant increase was observed in SCE in lymphocytes as well as an increase in micronucleus frequency that was of borderline significance. A significant increase in haemoglobin adducts was also observed (particularly amongst smokers) but there was no correlation between individual data for haemoglobin adducts and genetic effects (18). An increase in peripheral lympho-

cytes with chromosome breakage was seen in workers who may have been exposed to high air levels of epichlorhydrin. There was a lack of exposure data but air levels were probably <5 ppm (22).

A cross sectional study reported that, when compared with non-exposed controls, epichlorhydrin at <0.2 ppm (8-hour time-weighted average) had a significant effect on lung function, with several individuals experiencing respiratory tract symptoms (20). There were a number of weaknesses in the study (large confidence intervals, concomitant DMF exposure, etc.). It was shown that individuals in a sub-population lacking the GSTM1 gene were more sensitive to epichlorhydrin exposure (21). These data strengthens the causal relationship and present a reason for the variation in individual sensitivity. However, the dose-response relationship is uncertain.

An inhalation study in rats showed squamous metaplasia in nasal mucosa (2/100 animals) and inflammatory changes in the lungs at 10 ppm. At 30 ppm tumours were observed in the nasal cavity in 2/100 animals (1 squamous cell carcinoma) and at 100 ppm squamous cell carcinomas were observed in the nasal cavity in 15/140 animals (19). Hyperplasia and a dose-dependent increase in gastric tumours were observed in a long term study in rats given 2 and 10 mg epichlorhydrin/kg body weight perorally (37). Ginsberg *et al.* reported that epichlorhydrin produced tumours when administered by the route that achieved the highest concentration (9). They compared the target organ concentrations in three studies using different methods of administration (16, 19, 37). The authors concluded that the local dose rate was the most important factor in determining cancer potency. A theoretical calculation with linear extrapolation, based on tumour incidence in the nasal cavity (2/100) in rats at 30 ppm in the study by Laskin *et al.* (19), gave an extra lifetime cancer risk of 4 per 100,000 for 40 years of occupational exposure to 0.19 mg epichlorhydrin/m^3 (0.05 ppm) and 4 per 1000 for 40 years of exposure to 19 mg/m^3 (4.9 ppm) (6).

A dose-dependent, reversible reduction in fertility was observed in male rats exposed via inhalation to 25 and 50 ppm epichlorhydrin (11). Some reductions were observed in the proportion of sperm that were motile and the proportion of ova that were fertilized when male rats were given 6.25 mg/kg body weight/day. At doses ≤12,5 mg/kg/day (male rats) a deterioration was observed in several parameters for sperm motility as well as dose-dependent reductions in fertilized ova and implantations (32, 33). Male rats injected intra-abdominally with 3 or 6.25 mg epichlohydrin/kg body weight/day for 4 days showed a substantial dose-dependent reduction in fertility compared with controls. A lower percentage of motile and progressively motile sperm was observed at the higher dose (13).

The study by Laskin *et al*. reported a dose-dependent increase in the incidence and degree of degenerative changes in the renal tubules (19) in long term exposure to 10 and 30 ppm. An increase in absolute and relative kidney weight was observed in rats (both sexes) at 50 ppm, but no effect on renal function was observed (11). Increased relative liver weight as well as an increased incidence of chronic kidney inflammation were reported for male rats given repeated peroral doses of

5 mg/kg body weight/day. Increased relative kidney weight was reported for both sexes at 19 mg/kg/day. Increases in absolute and relative kidney and liver weights were observed at 25 mg/kg/day (5), and in males also an increase in urine protein and in the incidence of chronic kidney inflammation.

The effects on laboratory animals exposed via inhalation and perorally are presented in Tables 2 and 3.

Conclusions

Epichlorhydrin is a direct-acting mutagenic substance which gives rise to tumours in laboratory animals and chromosomal aberrations in exposed workers and should be regarded as carcinogenic to humans despite a lack of conclusive epidemiological studies. An increased incidence of chromosomal aberrations in lymphocytes has been registered in workers exposed to 0.05-0.5 ppm. Symptoms of irritation and some deterioration in lung function have been reported in one human study with mid-level exposure, <0.2 ppm, but the dose-response relationship was uncertain and the critical effect could not be given.

A temporary decrease in fertility has been observed in male rats exposed to 25 ppm by inhalation.

Epichlorhydrin is a contact sensitizer and can cause allergic contact dermatitis. Exposure to epiclorhydrin as a liquid can cause severe skin and eye damage, depending on the substance's reactive properties. Epichlorhydrin is easily absorbed through the skin.

Table 1. Some studies involving genotoxic tests following occupational exposure to epichlorhydrin.

Target organ	End-point	Results	Exposure level	Comments	Ref.
peripheral lymphocytes	SCE	+[1]	high-level exposure: 1.1-3.9 ppm[2]	21 with high-level exposure to epichlorhydrin	4
		-	low-level exposure: 0.1-0.2 ppm[2]	21+14 with low-level exposure to epichlorhydrin 9+20 without exposure to epichlorhydrin	
peripheral lymphocytes	Hprt-mutations	-	0.11-0.23 ppm (45 h/wk) + 0.2-2.6 ppm (3 h/wk)	15 exposed 14 controls	18
	SCE	+			
	micronuclei	±			
red blood cells	haemoglobin adducts	+[3]	as above	15 exposed 11+10 controls	18
peripheral lymphocytes	chromosomal aberrations	+	0.13-1.3 ppm	35 individuals: before exposure (1.37% AC[4]) 33 exposed (ditto) 1 year exposure (1.91% AC) 31 exposed (ditto): 2 years exposure (2.69% AC)	17
peripheral lymphocytes	chromosomal aberrations	+	0.25 ppm (range: 0.05-0.5); earlier 0.13-1.3 ppm (same factory as above; ref. 17)	28 exposed (3.12% AC) 4 years exposure, 34 controls[5] (2.06% AC) 21 controls[6] (1.33% AC)	29, 30
peripheral lymphocytes	chromosomal aberrations	-	0.1 ppm (range: 0.01-0.3) and rarely peak-exposures >0.26 ppm for 6 months before taking samples; previously higher exposures (same factory as above; ref. 29)	33 exposed (2.00% AC) 8 years exposure, 25 controls (1.68% AC)	30
peripheral lymphocytes	chromosomal aberrations	+	not reported (assumed to be ≥5 ppm; 8-h time-weighted average)	93 exposed, 75 controls	22

+ = significant increase, ± = increase of borderline significance, - = no (significant) increase

[1] $p<0.02$ for smokers with high exposure to epichorhydrin (n=9) compared with smokers with low (n=19) or no (n=14) exposure to epiclorhydrin; $p<0.05$ for smokers and non-smokers with high exposure compared with low or no exposure to epichlorhydrin.

[2] time-weighted average values (median values)

[3] significant when compared with Swedish control group (n=10)

[4] AC=aberrant cells

[5] matched controls

[6] controls from the general population

Table 2. Effects of inhalation exposure in some laboratory animal studies.

Exposure		Species (sex)	Effects	Ref.
ppm	time			
2.5	7 hours/day, days 6-15 (rats) and days 6-18 (rabbits) of pregnancy	rats (♀) rabbits (♀)	Rats, rabbits: no effects on reproduction/embryo/foetus.	12
5	6 hours/day, 5 days/week, 10 weeks	rats (♂♀)[3] rabbits (♂)	Rats, rabbits: no irritation-related effects; no reduction in fertility.	11
10[1]	6 hours/day, 5 days/week, lifetime exposure	rats (♂)	Squamous cell metaplasia in nasal mucosa (2/100), histopathological changes in the lungs (including inflammation), some increase in the incidence and degree of degenerative changes in renal tubules.	19
25	6 hours/day, 5 days/week, 10 weeks	rats (♂♀)[3] rabbits (♂)	Rats: reversible minimal-to-moderate irritation-related effects in the nose (inflammation, focal burn injuries, metaplasia, hyperplasia); reduced fertility in males (reversible), no reduction in female fertility. Rabbits: reversible irritation-related effects in the nose (inflammation, focal burn injuries, metaplasia); no effects on fertility/sperm.	11
25	7 hours/day, days 6-15 (rats) and days 6-18 (rabbits) of pregnancy	rats (♀) rabbits (♀)	Rats: reduced body weight gain and feed consumption in mothers; no effects on reproduction/embryo/foetus. Rabbits: no effects on reproduction/embryo/foetus.	12
30[1]	6 hours/day, 5 days/week, lifetime exposure	rats (♂)	Squamous metaplasia in nasal mucosa (4/100), tumours in the nasal cavity (2/100, 1 squamous cell carcinoma, 1 papilloma), histopathological changes in the lungs (including inflammation), increased incidence and degree of degenerative changes in renal tubules, reduced weight development, etc.	19
50[2]	6 hours/day, 5 days/week, 10 weeks	rats (♂♀)[3] rabbits (♂)	Rats: reversible moderate-to-severe irritation-related effects in the nose (see 25 ppm), some reduction in weight gain, increased absolute and relative kidney weights (no effect on renal function); substantial reduction in fertility in males (reversible), no fertility reduction in females. Rabbits: reduced weight gain, reversible irritation-related effects in the nose (see 25 ppm); no effect on fertility/sperm.	11
100[1]	6 hours/day, 30 days	rats (♂)	Squamous metaplasia in nasal mucosa (14/140), tumours in the nasal cavity (17/140, 15 squamous cell carcinomas, 2 papillomas), bronchial tumours (1/140, papilloma) severe inflammatory changes in the respiratory tract, increased incidence and degree of, for example, degenerative changes in renal tubules.	19

Table 2. Continued.

Exposure		Species (sex)	Effects	Ref.
ppm	time			
120	6 hours/day, 5 days/week, 11 exposures	rats (♂♀)	Laboured breathing (after 3 hours), weight loss, increased protein excretion in the urine, histopathological changes in the lungs (including inflammation, oedema), kidneys (including atrophy in tubules) and liver.	7
360	6 hours	rats (♂)	LC_{50}, bleeding and oedema in the lungs.	19
363	15 minutes	rats (♂)	33% reduction in respiration rate.	8

[1] 10, 30 and 100 ppm corresponds to 11, 33 and 110 mg/kg body weight/day (9).
[2] The authors state that the (daily) dose corresponds to 58 mg/kg (rats) and 36 mg/kg (rabbits), respectively, if one assumes 100% absorption.
[3] Female rats were mated with non-exposed males after the period of exposure.

Table 3. Effects of peroral administration in some laboratory animal studies.

Exposure		Species (sex)	Effects	Ref.
dose, mg/kg bw/day	time			
1 (gast. intub.)	90 d	rats (♂♀)	NOAEL in the study.	5
2 (gast. intub.)	5 h/wk, 2 years	rats (♂♀)	Stomach: hyperplasia 24/49 (♂) 12/44 (♀), papillomas 6/49 (♂) 3/44 (♀), squamous cell carcinomas 6/49 (♂) 2/44 (♀).	37
3 (gast. intub.)	10 d	rats (♂♀)	Minimal hyperplasia/hyperkeratosis in gastric mucosa (♀).	5
3.3	10 wk	rats (♂)	Significant reduction in GSH in epididymides.	27
5	one dose	mice (♀)	Increased proportion of abnormal cells in bone marrow (6.0%; 4.0% in DMSO-controls).	28
5 (gast. intub.)	90 d	rats (♂♀)	Minimal hyperplasia/hyperkeratosis in gastric mucosa, some degeneration in gastric mucosa (♂), significantly increased relative liver weight (♂), increased incidence of chronic inflammation in the kidneys (♂).	5
6.25 (gast. intub.)	23 d	rats (♂)	Significant reduction in the proportion of sperm that were motile and in the proportion of ova that were fertilized.	33
7 (gast. intub.)	10 d	rats (♂♀)	Minimal hyperplasia/hyperkeratosis in gastric mucosa.	5
10	10 wk	rats (♂)	Significant reduction in antioxidants/antioxidant enzymes (catalase, GST, SOD and GSH) and significant increase in MDA in epididymides.	27

Table 3. Continued.

Exposure		Species (sex)	Effects	Ref.
dose, mg/kg bw/day	time			
10 (gast. intub.)	5 d/wk, 2 years	rats (♂♀)	Stomach: hyperplasia 6/49 (♂) 7/39 (♀), papillomas 4/49 (♂), squamous cell carcinomas 35/49 (♂) 24/39 (♀).	37
12.5 (gast. intub.)	21 d	rats (♂)	Significant deterioration in various parameters for sperm motility.	32
12.5 (gast. intub.)	23 d	rats (♂)	Significant reduction in the proportion of sperm that were motile, significant deterioration in sperm motility parameters, significant reduction in the proportion of ova that were fertilized, significant reduction in the proportion of fertilized ova that had implanted.	33
19 (gast. intub.)	10 d	rats (♂♀)	Minimal-to-mild hyperplasia/hyperkeratosis in gastric mucosa, significant increase in relative kidney weight; significant increase in relative liver weight and some reduction in weight development (♂).	5
20	one dose	mice (♀)	Increased proportion of abnormal cells in bone marrow (24.0%, 4.0% in DMSO controls).	28
25 (gast. intub.)	21 d	rats (♂)	Significant deterioration in various sperm motility parameters.	32
25 (gast. intub.)	23 d	rats (♂)	Significant reduction in the proportion of sperm that were motile, significant deterioration in sperm motility parameters, significant reduction in the proportion of ova that were fertilized, significant reduction in the proportion of fertilized ova that had implanted.	33
25 (gast. intub.)	2 wk before mating, up until the end of pregnancy	rats (♀)	No significant effects on reproduction.	32
25 (gast. intub.)	90 d	rats (♂♀)	Mild-moderate hyperplasia/hyperkeratosis of gastric mucosa, some degeneration in gastric mucosa (♂), significant reduction in haemoglobin (♂), haematocrit (♂) and red blood cell count, significant increase in absolute and relative kidney and liver weights, significant reduction in serum creatinine levels (♀), increase in urine protein and increased incidence of chronic inflammation of the kidneys (♂).	5
30	10 wk	rats (♂)	Significant reduction in antioxidants/antioxidant enzymes (catalase, GST, SOD and GSH) and significant increase in MDA in epididymides, significant reduction in sperm counts (testes, epididymides) and sperm motility, significant increase in abnormal sperm.	27

Table 3. Continued.

Exposure		Species (sex)	Effects	Ref.
dose, mg/kg bw/day	time			
375 ppm*	81 wk	rats (♂)	Stomach (squamous epithelia): hyperplasia 7/9, papillomas 0/9, carcinomas 0/9.	16
40	one dose	mice (♀)	Increased proportion of abnormal cells in bone marrow (22.4%; 4.0% in DMSO-controls).	28
46 (gast. intub.)	10 d	rats (♂♀)	Mild-moderate hyperplasia/hyperkeratosis and low-grade degeneration in gastric mucosa, significant increase in relative liver, kidney and testicular weights, significant reduction in weight development (and feed intake), effects on blood count.	5
50	one dose	mice (♂)	Increase (not significant) in frequency of chromosomal aberrations in bone marrow cells.	24
50 (gast. intub.)	21 d before mating	rats (♂)	Infertility, significant deterioration in various sperm motility parameters, small (significant) reduction in sperm count (epididymides).	32
50 (gast. intub.)	2 wk before mating, up until the end of pregnancy	rats (♀)	No significant effects on reproduction.	32
750 ppm*	81 weeks	rats (♂)	Stomach (squamous epithelia): hyperplasia 9/10, papillomas 1/10, carcinomas 1/10.	16
100 (gast. intub.)	2 wk before mating, up until the end of pregnancy	rats (♀)	No significant effects on reproduction.	32
1500 ppm*	81 wk	rats (♂)	Stomach (squamous epithelia): hyperplasia 12/12, papillomas 7/12, carcinomas 2/12; oral cavity (squamous epithelia): carcinomas 2/12.	16

(gast. intub.) = gastric intubation; d = days; wk = weeks; bw = body weight
*In drinking water; 375 ppm (total dose 5 g/rat), 750 ppm (total dose 8.9 g/rat), 1500 ppm (total dose 15.1 g/rat) = 34, 70 and 175 mg/kg body weight/day (9).

Potential conflicts of interest

Gunnar Johanson (member) has declared that he was involved in SCOEL's evaluation of epichlorhydrin in 2011.

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Summary

Montelius J (ed). Swedish Criteria Group for Occupational Standards. *Scientific Basis for Swedish Occupational Standards.* XXXIII. Arbete och Hälsa 2014;48(3):1-103. University of Gothenburg, Sweden.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish Work Environmental Authority from June, 2012 through October, 2013.

Key Words: Crystalline Silica, Consensus report, Epichlorohydrin, N-Methyl-2-pyrrolidone, Occupational exposure limit (OEL), Quartz, Risk assessment, Scientific basis, Toxicology.

Sammanfattning

Montelius J (ed). Kriteriegruppen för hygieniska gränsvärden. *Vetenskapligt underlag för hygieniska gränsvärden.* XXXIII. Arbete och Hälsa 2014;48(3):1-103. Göteborgs Universitet.

Sammanställningar baserade på kritisk genomgång och värdering av de vetenskapliga fakta, vilka är relevanta som underlag för fastställande av hygieniskt gränsvärde. Volymen omfattar de underlag som avgivits från Kriteriegruppen för hygieniska gränsvärden under perioden juni 2012 – oktober 2013.

Nyckelord: Epiklorhydrin, Hygieniskt gränsvärde, Kristallin kiseldioxid, Kvarts, N-Metyl-2-pyrrolidon, Riskvärdering, Toxikologi, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2013;47(8):1-101.

APPENDIX

Consensus reports in this and previous volumes

Substance	Consensus date	Published in Arbete och Hälsa year;volume(No)	No. in series of Consensus Reports
Acetaldehyde	February 17, 1987	1987;39	VIII
Acetamide	December 11, 1991	1992;47	XIII
Acetic acid	June15, 1988	1988;32	IX
Acetone	October 20, 1987	1988;32	IX
Acetonitrile	September 12, 1989	1991;8	XI
Acrylamide	April 17, 1991	1992;6	XII
Acrylates	December 9, 1984	1985;32	VI
Acrylonitrile	April 28, 1987	1987;39	VIII
Aliphatic amines	August 25, 1982	1983;36	IV
Aliphatic hydrocarbons, C10-C15	June 1, 1983	1983;36	IV
Aliphatic monoketons	September 5, 1990	1992;6	XII
Allyl alcohol	September 9, 1986	1987;39	VIII
Allylamine	August 25, 1982	1983;36	IV
Allyl chloride	June 6, 1989	1989;32	X
Aluminum	April 21, 1982	1982;24	III
revised	September 14, 1994	1995;19	XVI
Aluminum trifluoride	September 15, 2004	2005;17	XXVI
p-Aminoazobenzene	February 29, 1980	1981;21	I
Ammonia	April 28, 1987	1987;39	VIII
revised	October 24, 2005	2006;11	XXVII
Ammonium fluoride	September 15, 2004	2005;17	XXVI
Amylacetate	March 23, 1983	1983;36	IV
revised	June 14, 2000	2000;22	XXI
Aniline	October 26, 1988	1989;32	X
Anthraquinone	November 26, 1987	1988;32	IX
Antimony + compounds	December 8, 1999	2000;22	XXI
Arsenic, inorganic	December 9, 1980	1982;9	II
revised	February 15, 1984	1984;44	V
Arsine	October 20, 1987	1988;32	IX
Asbestos	October 21, 1981	1982;24	III
Asphalt fumes	April 14, 2010	2011;45(6)	XXXI
Barium	June 16, 1987	1987;39	VIII
revised	January 26, 1994	1994;30	XV
Benzene	March 4, 1981	1982;9	II
revised	February 24, 1988	1988;32	IX
Benzoyl peroxide	February 13, 1985	1985;32	VI
Beryllium	April 25, 1984	1984;44	V
Bitumen fumes	April 14, 2010	2011;45(6)	XXXI
Borax	October 6, 1982	1983;36	IV
Boric acid	October 6, 1982	1983;36	IV
Boron Nitride	January 27, 1993	1993;37	XIV
Butadiene	October 23, 1985	1986;35	VII

1-Butanol	June 17, 1981	1982;24	III
Butanols	June 6, 1984	1984;44	V
Butyl acetate	June 6, 1984	1984;44	V
Butyl acetates	February 11, 1998	1998;25	XIX
n-Butyl acrylate	September 28, 2011	2013;47(6)	XXXII
Butylamine	August 25, 1982	1983;36	IV
Butyl glycol	October 6, 1982	1983;36	IV
γ-Butyrolactone	June 2, 2004	2005;7	XXV
Cadmium	January 18, 1980	1981;21	I
revised	February 15, 1984	1984;44	V
revised	May 13, 1992	1992;47	XIII
revised	February 5, 2003	2003;16	XXIV
Calcium fluorid	September 15, 2004	2005;17	XXVI
Calcium hydroxide	February 24, 1999	1999;26	XX
Calcium nitride	January 27, 1993	1993;37	XIV
Calcium oxide	February 24, 1999	1999;26	XX
Caprolactam	October 31, 1989	1991;8	XI
Carbon dioxide	June 15, 2011	2013;47(6)	XXXII
Carbon monoxide	December 9, 1981	1982;24	III
Cathecol	September 4, 1991	1992;47	XIII
Chlorine	December 9, 1980	1982;9	II
Chlorine dioxide	December 9, 1980	1982;9	II
Chlorobenzene	September 16, 1992	1993;37	XIV
revised	April 2, 2003	2003;16	XXIV
o-Chlorobenzylidene malononitrile	June 1, 1994	1994;30	XV
Chlorocresol	December 12, 1990	1992;6	XII
Chlorodifluoromethane	June 2, 1982	1982; 24	III
Chlorophenols	September 4, 1985	1986;35	VII
Chloroprene	April 16, 1986	1986;35	VII
Chromium	December 14, 1979	1981;21	I
revised	May 26, 1993	1993;37	XIV
revised	May 24, 2000	2000;22	XXI
Chromium trioxide	May 24, 2000	2000;22	XXI
Coal dust	September 9, 1986	1987;39	VIII
Cobalt	October 27, 1982	1983;36	IV
Cobalt and cobalt compounds	October 22, 2003	2005;7	XXV
Copper	October 21, 1981	1982;24	III
Cotton dust	February14, 1986	1986;35	VII
Creosote	October 26, 1988	1989;32	X
revised	December 5, 2007	2009;43(4)	XXIX
Cresols	February 11, 1998	1998;25	XIX
Crystalline Silica	December 31, 2012	2014;48(3)	XXXIII
Cumene	June 2, 1982	1982;24	III
Cyanamid	September 30, 1998	1999;26	XX
Cyanoacrylates	March 5, 1997	1997;25	XVIII
Cycloalkanes, C5-C15	April 25, 1984	1984;44	V
Cyclohexanone	March 10, 1982	1982;24	III
revised	February 24, 1999	1999;26	XX
Cyclohexanone peroxide	February 13, 1985	1985;32	VI
Cyclohexylamine	February 7, 1990	1991;8	XI
Desflurane	May 27, 1998	1998;25	XIX

Diacetone alcohol	December 14, 1988	1989;32	X
Dichlorobenzenes	February 11, 1998	1998;25	XIX
1,2-Dibromo-3-chloropropane	May 30, 1979	1981;21	I
Dichlorodifluoromethane	June 2, 1982	1982;24	III
1,2-Dichloroethane	February 29, 1980	1981;21	I
Dichloromethane	February 29, 1980	1981;21	I
Dicumyl peroxide	February 13, 1985	1985;32	VI
Dicyclopentadiene	March 23, 1994	1994;30	XV
Diesel exhaust	December 4, 2002	2003;16	XXIV
Diethanolamine	September 4, 1991	1992;47	XIII
Diethylamine	August 25, 1982	1983;36	IV
revised	February 16, 2011	2013;47(6)	XXXII
2-Diethylaminoethanol	January 25, 1995	1995;19	XVI
Diethylene glycol	September 16, 1992	1993;37	XIV
Diethyleneglycol ethylether + acetate	December 11, 1996	1997;25	XVIII
Diethyleneglycol methylether + acetate	March 13, 1996	1996;25	XVII
Diethyleneglycol monobutylether	January 25, 1995	1995;19	XVI
Diethylenetriamine	August 25, 1982	1983;36	IV
revised	January 25, 1995	1995;19	XVI
Diisocyanates	April 8, 1981	1982;9	II
revised	April 27, 1988	1988;32	IX
revised	May 30, 2001	2001;20	XXII
Diisopropylamine	February 7, 1990	1991;8	XI
N,N-Dimethylacetamide	March 23, 1994	1994;30	XV
Dimethyl adipate	December 9, 1998	1999;26	XX
Dimethylamine	December 10, 1997	1998;25	XIX
N,N-Dimethylaniline	December 12, 1989	1991;8	XI
Dimethyldisulfide	September 9, 1986	1987;39	VIII
Dimethylether	September 14, 1994	1995;19	XVI
Dimethylethylamine	June 12, 1991	1992;6	XII
Dimethylformamide	March 23, 1983	1983;36	IV
Dimethyl glutarate	December 9, 1998	1999;26	XX
Dimethylhydrazine	January 27, 1993	1993;37	XIV
Dimethyl succinate	December 9, 1998	1999;26	XX
Dimethylsulfide	September 9, 1986	1987;39	VIII
Dimethylsulfoxide, DMSO	December 11, 1991	1992;47	XIII
Dioxane	August 25, 1982	1983;36	IV
revised	March 4, 1992	1992;47	XIII
Diphenylamine	January 25, 1995	1995;19	XVI
4,4'-Diphenylmethanediisocyanate (MDI)	April 8, 1981	1982;9	II
revised	May 30, 2001	2001;20	XXII
Dipropylene glycol	May 26, 1993	1993;37	XIV
Dipropyleneglycol monomethylether	December 12, 1990	1992;6	XII
Disulfiram	October 31, 1989	1991;8	XI
Epichlorohydrin	October 2, 2013	2014;48(3)	XXXIII
Enzymes, industrial	June 5, 1996	1996;25	XVII
Ethanol	May 30, 1990	1991;8	XI
Ethanolamine	September 4, 1991	1992;47	XIII
revised	May 30, 2012	2013;47(6)	XXXII
Ethylacetate	March 28, 1990	1991;8	XI
Ethylamine	August 25, 1982	1983;36	IV
revised	February 16, 2011	2013;47(6)	XXXII

Ethylamylketone	September 5, 1990	1992;6	XII
Ethylbenzene	December 16, 1986	1987;39	VIII
Ethylchloride	December 11, 1991	1992;47	XIII
Ethylene	December 11, 1996	1997;25	XVIII
Ethylene chloride	February 29, 1980	1981;21	I
Ethylene diamine	August 25, 1982	1983;36	IV
Ethylene glycol	October 21, 1981	1982;24	III
Ethylene glycol ethylether + acetate	February 6	2009;43(4)	XXIX
Ethylene glycol methylether + acetate	June 2, 1999	1999;26	XX
Ethyleneglycol monoisopropylether	November 16, 1994	1995;19	XVI
Ethyleneglycol monopropylether + acetate	September 15, 1993	1994;30	XV
Ethylene oxide	December 9, 1981	1982;24	III
Ethylenethiourea	September 27, 2000	2001;20	XXII
Ethylether	January 27, 1993	1993;37	XIV
Ethylglycol	October 6, 1982	1983;36	IV
Ferbam	September 12, 1989	1991;8	XI
Ferric dimethyldithiocarbamate	September 12, 1989	1991;8	XI
Flour dust	December 10, 1997	1998;25	XIX
Fluorides	September 15, 2004	2005;17	XXVI
Formaldehyde	June 30, 1979	1981;21	I
revised	August 25, 1982	1983;36	IV
revised	June 9, 2010	2011;45(6)	XXXI
Formamide	December 12, 1989	1991;8	XI
Formic acid	June 15, 1988	1988;32	IX
Furfural	April 25, 1984	1984;44	V
Furfuryl alcohol	February 13, 1985	1985;32	VI
Gallium + Gallium compounds	January 25, 1995	1995;19	XVI
Glutaraldehyde	September 30, 1998	1999;26	XX
Glycol ethers	October 6, 1982	1983;36	IV
Glyoxal	September 13, 1996	1996;25	XVII
Grain dust	December 14, 1988	1989;32	X
revised	February 4, 2009	2010;44(5)	XXX
Graphite	December 10, 1997	1998;25	XIX
Halothane	April 25, 1985	1985;32	VI
2-Heptanone	September 5, 1990	1992;6	XII
3-Heptanone	September 5, 1990	1992;6	XII
Hexachloroethane	September 15, 1993	1994;30	XV
Hexamethylenediisocyanate (HDI)	April 8, 1981	1982;9	II
revised	May 30, 2001	2001;20	XXII
Hexamethylenetetramine	August 25, 1982	1983;36	IV
n-Hexanal	March 29, 2006	2006;11	XXVII
n-Hexane	January 27, 1982	1982;24	III
2-Hexanone	September 5, 1990	1992;6	XII
Hexyleneglycol	November 17, 1993	1994;30	XV
Hydrazine	May 13, 1992	1992;47	XIII
Hydrochloric acid	June 3, 2009	2010;44(5)	XXX
Hydrogen bromide	February 11, 1998	1998;25	XIX
Hydrogen cyanide	February 7, 2001	2001;20	XXII
Hydrogen fluoride	April 25, 1984	1984;44	V
revised	September 15, 2004	2005;17	XXVI

Hydrogen peroxide	April 4, 1989	1989;32	X
Hydrogen sulfide	May 4, 1983	1983;36	IV
Hydroquinone	October 21, 1989	1991;8	XI
Indium	March 23, 1994	1994;30	XV
Industrial enzymes	June 5, 1996	1996;25	XVII
Isocyanic Acid (ICA)	December 5, 2001	2002;19	XXIII
Isophorone	February 20, 1991	1992;6	XII
Isopropanol	December 9, 1981	1982;24	III
Isopropylamine	February 7, 1990	1991;8	XI
Isopropylbenzene	June 2, 1982	1982;24	III
Lactates	March 29, 1995	1995;19	XVI
Lactate esters	June 2, 1999	1999;26	XX
Laughing gas	June 7, 2006	2006;11	XXVII
Lead, inorganic	February 29, 1980	1981;21	I
revised	September 5, 1990	1992;6	XII
revised	December 8, 2004	2005;17	XXVI
Lithium and lithium compounds	June 4, 2003	2003;16	XXIV
Lithium boron nitride	January 27, 1993	1993;37	XIV
Lithium nitride	January 27, 1993	1993;37	XIV
Maleic anhydride	September 12, 1989	1991;8	XI
Manganese	February 15, 1983	1983;36	IV
revised	April 17, 1991	1992;6	XII
revised	June 4, 1997	1997;25	XVIII
Man made mineral fibers	March 4, 1981	1982;9	II
revised	December 1, 1987	1988;32	IX
Mercury, inorganic	April 25, 1984	1984;44	V
Mesityl oxide	May 4, 1983	1983;36	IV
Metal stearates, some	September 15, 1993	1994;30	XV
Methacrylates	September 12, 1984	1985;32	VI
Methanol	April 25, 1985	1985;32	VI
Methyl acetate	March 28, 1990	1991;8	XI
Methylamine	August 25, 1982	1983;36	IV
Methylamyl alcohol	March 17, 1993	1993;37	XIV
Methyl bromide	April 27, 1988	1988;32	IX
Methyl chloride	March 4, 1992	1992;47	XIII
Methyl chloroform	March 4, 1981	1982;9	II
4,4´-methylene-bis-(2-chloroaniline)	February 4, 2004	2005;7	XXV
Methylene chloride	February 29, 1980	1981;21	I
4,4'-Methylene dianiline	June 16, 1987	1987;39	VIII
revised	October 3, 2001	2002;19	XXIII
Methyl ethyl ketone	February 13, 1985	1985;32	VI
Methyl ethyl ketone peroxide	February 13, 1985	1985;32	VI
Methyl formate	December 12, 1989	1991;8	XI
Methyl glycol	October 6, 1982	1983;36	IV
Methyl iodide	June 30, 1979	1981;21	I
Methylisoamylamine	September 5, 1990	1992;6	XII
Methylisoamylketone	February 6, 2002	2002;19	XXIII
Methylisocyanate (MIC)	December 5, 2001	2002;19	XXIII
Methyl mercaptane	September 9, 1986	1987;39	VIII
Methyl methacrylate	March 17, 1993	1993;37	XIV

Methyl pyrrolidone	June 16, 1987	1987;39	VIII
revised	December 5, 2012	2014;48(3)	XXXIII
α-Methylstyrene	November 1, 2000	2001;20	XXII
Methyl-t-butyl ether	November 26, 1987	1988;32	IX
revised	September 30, 1998	1999;26	XX
Mixed solvents, neurotoxicity	April 25, 1985	1985;32	VI
MOCA	February 4, 2004	2005;7	XXV
Molybdenum	October 27, 1982	1983;36	IV
revised	Februari 4, 2009	2010;44(5)	XXX
Monochloroacetic acid	February 20, 1991	1992;6	XII
Monochlorobenzene	September 16, 1993	1993;37	XIV
Monomethylhydrazine	March 4, 1992	1992;47	XIII
Mononitrotoluene	February 20, 1991	1992;6	XII
Monoterpenes	February 17, 1987	1987;39	VIII
Morpholine	December 8, 1982	1983;36	IV
revised	June 5, 1996	1996;25	XVII
Naphthalene	May 27, 1998	1998;25	XIX
Natural crystallinic fibers, except asbestos	June 12, 1991	1992;6	XII
Nickel	April 21, 1982	1982;24	III
Nicotine	June 2, 2004	2005;7	XXV
Nitric acid	June 3, 2009	2010;44(5)	XXX
Nitric oxide	December 11, 1985	1986;35	VII
revised	June 13, 2007	2008;42(6)	XXVIII
Nitroethane	April 4, 1989	1989;32	X
Nitrogen dioxide	December 11, 1985	1986;35	VII
revised	September 12, 2007	2008;42(6)	XXVIII
Nitrogen oxides	December 11, 1985	1986;35	VII
Nitroglycerin	February 13, 1985	1985;32	VI
Nitroglycol	February 13, 1985	1985;32	VI
Nitromethane	January 6, 1989	1989;32	X
Nitropropane	October 28, 1986	1987;39	VIII
2-Nitropropane	March 29, 1995	1995;19	XVI
Nitroso compounds	December 12, 1990	1992;6	XII
Nitrosomorpholine	December 8, 1982	1983;36	IV
Nitrotoluene	February 20, 1991	1992;6	XII
Nitrous oxide	December 9, 1981	1982;24	III
revised	June 7, 2006	2006;11	XXVII
Oil mist	April 8, 1981	1982;9	II
Organic acid anhydrides, some	September 12, 1989	1991;8	XI
revised	June 4, 2008	2009;43(4)	XXIX
revised	September 29, 2010	2011;45(6)	XXXI
Oxalic acid	February 24, 1988	1988;32	IX
Ozone	April 28, 1987	1987;39	VIII
revised	February 7, 2007	2008;42(6)	XXVIII
Paper dust	February 7, 1990	1991;8	XI
Penicillins	November 23, 2005	2006;11	XXVII
Pentaerythritol	November 16, 1994	1995;19	XVI
1,1,1,2,2-Pentafluoroethane	February 24, 1999	1999;26	XX
Pentyl acetate	June 14, 2000	2000;22	XXI
Peroxides, organic	February 13, 1985	1985;32	VI

Phenol	February 13, 1985	1985;32	VI
Phosphoric acid	June 3, 2009	2010;44(5)	XXX
Phosphorous chlorides	September 30, 1998	1999;26	XX
Phosphorous oxides	February 11, 1998	1998;25	XIX
Phthalates	December 8, 1982	1983;36	IV
Phthalic anhydride	September 12, 1989	1991;8	XI
Piperazine	September 12, 1984	1985;32	VI
Plastic dusts	December 16, 1986	1987;39	VIII
Platinum	June 4, 1997	1997;25	XVIII
Polyaromatic hydrocarbons	February 15, 1984	1984;44	V
Polyisocyanates	April 27, 1988	1988;32	IX
Potassium aluminium fluoride	June 4, 1997	1997;25	XVIII
Potassium cyanide	February 7, 2001	2001;20	XXII
Potassium dichromate	May 24, 2000	2000;22	XXI
Potassium Fluoride	September 15, 2004	2005;17	XXVI
Potassium hydroxide	Marsh 15, 2000	2000;22	XXI
2-Propanol	December 9, 1981	1982;24	III
Propene	September 13, 1996	1996;25	XVII
Propionic acid	November 26, 1987	1988;32	IX
Propylacetate	September 14, 1994	1995;19	XVI
Propylene glycol	June 6, 1984	1984;44	V
Propylene glycol-1,2-dinitrate	May 4, 1983	1983;36	IV
Propylene glycol monomethylether	October 28, 1986	1987;39	VIII
Propylene oxide	June 11, 1986	1986;35	VII
Pyridine	May 13, 1992	1992;47	XIII
Quartz	March 13, 1996	1996;25	XVII
revised	December 31, 2012	2014;48(3)	XXXIII
Resorcinol	September 4, 1991	1992;47	XIII
Selenium	December 11, 1985	1986;35	VII
revised	February 22, 1993	1993;37	XIV
Sevoflurane	May 27, 1998	1998;25	XIX
Silica	March 13, 1996	1996;25	XVII
Silver	October 28, 1986	1987;39	VIII
Sodium cyanide	February 7, 2001	2001;20	XXII
Sodium Fluoride	September 15, 2004	2005;17	XXVI
Sodium hydroxide	August 24, 2000	2000;22	XXI
Stearates, metallic, some	September 15, 1993	1994;30	XV
Stearates, non-metallic, some	November 17, 1993	1994;30	XV
Strontium	January 26, 1994	1994;30	XV
Styrene	February 29, 1980	1981;21	I
revised	October 31, 1989	1991;8	XI
revised	April 1, 2009	2010;44(5)	XXX
Sulfur dioxide	April 25, 1985	1985;32	VI
Sulfur fluorides	March 28, 1990	1991;8	XI
Sulfuric acid	June 3, 2009	2010;44(5)	XXX
Synthetic inorganic fibers	March 4, 1981	1982;9	II
revised	December 1, 1987	1988;32	IX
revised	December 3, 2003	2005;7	XXV
Synthetic organic and inorganic fibers	May 30, 1990	1991;8	XI
Talc dust	June 12, 1991	1992;6	XII

Terpenes, mono-	February 17, 1987	1987;39	VIII
Tetrabromoethane	May 30, 1990	1991;8	XI
Tetrachloroethane	June 4, 1997	1997;25	XVIII
Tetrachloroethylene	February 29, 1980	1981;21	I
1,1,1,2-Tetrafluoroethane	March 29, 1995	1995;19	XVI
Tetrahydrofuran	October 31, 1989	1991;8	XI
Tetranitromethane	April 4, 1989	1989;32	X
Thioglycolic acid	June 1, 1994	1994;30	XV
Thiourea	December 1, 1987	1988;32	IX
revised	June 2, 1999	1999;26	XX
Thiram	October 31, 1989	1991;8	XI
Thiurams, some	October 31, 1989	1991;8	XI
Tin and inorganic tin compounds	October 22, 2003	2005;7	XXV
Titanium dioxide	February 21, 1989	1989;32	X
Toluene	February 29, 1980	1981;21	I
revised	February 6, 2002	2002;19	XXIII
Toluene-2,4-diamine	November 1, 2000	2001;20	XXII
Toluene-2,6-diamine	November 1, 2000	2001;20	XXII
Toluene-2,4-diisocyanate	April 8, 1981	1982;9	II
revised	May 30, 2001	2001;20	XXII
Toluene-2,6-diisocyanate	April 8, 1981	1982;9	II
revised	May 30, 2001	2001;20	XXII
1,1,1-Trifluoroethane	February 24, 1999	1999;26	XX
Trichlorobenzene	September 16, 1993	1993;37	XIV
1,1,1-Trichloroethane	March 4, 1981	1982;9	II
Trichloroethylene	December 14, 1979	1981;21	I
Trichlorofluoromethane	June 2, 1982	1982;24	III
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2, 1982	1982;24	III
Triethanolamine	August 25, 1982	1983;36	IV
revised	October 23, 2002	2003;16	XXIV
Triethylamine	December 5, 1984	1985;32	VI
Trimellitic anhydride	September 12, 1989	1991;8	XI
Trimethylolpropane	November 16, 1994	1995;19	XVI
Trinitrotoluene	April 17, 1991	1992;6	XII
Vanadium	March 15, 1983	1983;36	IV
Vinyl acetate	June 6, 1989	1989;32	X
Vinyl toluene	December 12, 1990	1992;6	XII
White spirit	December 16, 1986	1987;39	VIII
revised	November 13, 2006	2008;42(6)	XXVIII
Wood dust	June 17, 1981	1982;9	II
revised	June 25, 2000	2000;22	XXI
Xylene	February 29, 1980	1981;21	I
revised	September 14, 2005	2005;17	XXVI
Zinc	April 21, 1982	1982;24	III
Zinc chromate	May 24, 2000	2000;22	XXI
Zinc dimethyl dithiocarbamate	September 12, 1989	1991;8	XI
Ziram	September 12, 1989	1991;8	XI

Sent for publication November 2014

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