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Cutting fluid aerosols
Carbon monoxide

Swedish Criteria Group for Occupational Standards
Ed. Johan Montelius
Swedish Work Environment Authority
S-112 79 Stockholm, Sweden

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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 comprehend-sive 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 scien-tific 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 35th in the series, and contains consensus reports approved by the Criteria Group from January, 2015 through June, 2016. The Criteria Group was closed down the 30th of June 2016. The two consensus reports in this number of Arbete och Hälsa will be the last published by the Criteria Group. The consensus reports in this and previous publications in the series are listed in the Appendix (page 53).

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Marianne Walding	observer	Swedish Work Environment Authority
Håkan Westberg		Dept. Environ. Occup. Medicine, University Hospital, Örebro

Contents

[1] Drafted by Anna Dahlman-Höglund and Jonas Brisman, Occupational and Environmental Medicine, Gothenburg, Sweden. The consensus report is translated from Swedish by John Kennedy, Space 360 and Johan Montelius, the Swedish Work Environment Authority. If there is any doubt as to the understanding or interpretation of the English version, the Swedish version shall prevail.

[2] Drafted by Ilona Silins, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Consensus Report for Cutting Fluid Aerosols

2016-06-16

This report on cutting fluid aerosols is based in part on a Criteria Document from DECOS 2011 (19). DECOS's last literature search was carried out in April 2010. Another report is a publication from the US agency NIOSH 1998 (49). The Criteria Group has previously published a consensus report on oil mist 1982 (62). The last literature search in PubMed was carried out on 26-05-2016. The abbreviations used are explained and particle fractions are defined in Appendix 1 at the end of the document.

Cutting fluid (also referred to as coolant, cooling fluid or MWF [metal working fluid]), is used in the engineering industry for metalworking such as grinding, turning, drilling and milling. Most cutting operations require a lubricant to reduce the friction between tool and metal, to cool and to remove the metallic debris that is formed. In the early stages of metalworking technology development, there were cutting fluids which contained only mineral oils with lubricating properties but no water content (10, 49). In 1945 the first synthetic cutting fluid was produced in the USA, and since the 1970s various types of non-mineral oil-based cutting fluids, including synthetic cutting fluids, have been used in Sweden.

Sweden has an exposure limit for the oil mist that forms when using cutting fluids containing mineral oil or vegetable/animal oils. Since the exposure limit was established in the 1980s, more and more cutting fluids with low or zero oil content have appeared, so an exposure limit based on oil mist is no longer relevant. This document describes the current state of knowledge for the various cutting fluids used in industry, above all in Sweden.

In addition, liquid nitrogen and liquid carbon dioxide are currently being tested as ”cutting fluids” in certain forms of processing. Liquid nitrogen and liquid carbon dioxide are vaporized directly at the cutting site (this type of cutting fluid is not covered in this report).

Mineral oil[1] is a mixture of various hydrocarbons, which are produced from fossil materials. They also contain traces of organic sulphur, oxygen, nitrogen, and various metal contaminants. Mineral oils are divided into different groups according to the type of refining involved in their production (31). After refining, each mineral oil has its own CAS number which serves as an ID number that can

[1] There are some slight differences in how mineral oil is defined. Sometimes the term is taken to mean roughly the same as crude oil, sometimes the liquid fraction of crude oil which is used in lubricating oils, etc.; for example, see https://en.wikipedia.org/wiki/Mineral_oil, http://g3.spraakdata.gu.se/saob/, https://sv.wikipedia.org/wiki/Petroleum. In this document the term means the fraction of crude oil which, after refining, is used in cutting fluids.

be used to search for information on physical and chemical properties. Mineral oils have historically contained PAH (polyaromatic hydrocarbons) at relatively high concentrations but in the 1950s work began on reducing the PAH content; by the mid-1980s it had been cut drastically (12). Since the start of the 1980s highly refined mineral oils that contain almost no polyaromatic hydrocarbons have been available in Sweden. This is described in a provision which is no longer in force (AFS 1986:13; http://www.jpinfonet.se/dokument/Foreskrifter/135214/AFS-1986_13-Oljor?pageid=17331, 2 June 2016).

In Europe and the USA mineral oil-based cutting fluids have mainly been replaced by cutting fluids containing emulsions, mixtures of mineral oil with water, and synthetic cutting fluids (3). The development of water-miscible cutting fluids has accelerated in recent years because of two factors: the demand for more effective processes and the greater attention paid to both indoor and outdoor environments. Water-miscible cutting fluids have much better cooling properties than oil which means they are particularly used in processes which generate a great deal of heat (10).

In the literature, cutting fluids are often divided into roughly four different types, and not always consistently so (10, 49):

- Mineral oil-based cutting fluids containing 60-100% mineral oil (sometimes the mineral oil has been replaced by vegetable oil). These cutting fluids contain no water and are non-water-miscible.
- Cutting fluids of the emulsion type containing 30-85% mineral oil or vegetable/animal oils and water in varying amounts as well as emulsifiers (fatty acids or esters).
- Semisynthetic cutting fluids containing 5-20% mineral oil or vegetable/animal oils and various chemicals, plus water.
- Synthetic cutting fluids containing no mineral oil or vegetable/animal oils but having a 70-95% water content and containing various synthetic chemicals.

Water-miscible cutting fluids comprise emulsions and semisynthetic or synthetic cutting fluids. Before use, these cutting fluids are diluted with water to a final concentration of 2-5% in the application system.

As mentioned above, cutting fluids contain various additives, such as antioxidants (e.g., zinc and magnesium salts), corrosion inhibitors (e.g., monoethanolamine, diethanolamine, triethanolamine), emulsifiers (e.g., aliphatic alcohols, ethanolamines, fatty acids) and antifoaming agents (e.g., polysiloxane). The water-miscible systems contain tensides (e.g., sodium sulphonate, C_{12}-C_{15} alcohols) as well as preservatives and biocides which are sometimes added at the beginning or during use to inhibit the growth of microorganisms.

The composition of cutting fluids changes with time during use. For example: metals (e.g., cobalt, chromium, nickel, iron) released from the material being worked may appear in the fluid, as well as microbial growth, hydraulic oils which leak into the cutting fluids, and newly formed substances, e.g., PAH.

The cutting fluids used nowadays therefore comprise a heterogeneous group of mixtures with various compositions (from pure mineral oils to entirely water-

based products) and various additives. The composition can be affected during use.

Exposure to cutting fluid aerosols in the workplace environment

A review article by Park *et al*., which presents an assessment of the literature and measurement data, concludes that the factors affecting aerosol formation and exposure over decades are: type of industry, type of machine and cutting fluid. Type of industry and cutting fluid affected both the thoracic and respirable fractions (53).

Cutting fluids are normally stored in central tanks of various sizes, depending on the process, and are pumped to the machines and then back to the tank in a recycling system. In the machine the cutting fluid is applied via a high-pressure jet-, fine jet-, or spray-nozzle. While this takes place, aerosols are formed with various droplet sizes which depend on the speed at which the machine is operating, the composition of the fluid and the pressure of the jet (53). Higher machine speeds generate higher emissions than lower speeds and the amount of aerosol formed increases in proportion to the square of the machine's rotation speed (63). In a study of small businesses 1/3 of the employees (942 individuals) were working with machines that were more than 30 years old. New machines have twice the speed of 30-year-old machines and are therefore more powerful aerosol generators (53). Machine design has changed. Modern machines are enclosed, i.e., the doors are closed during operation to minimize exposure to aerosols. The operator cannot open the doors before the aerosols have been vented off. The use of older machines by smaller companies could explain why aerosol exposure is less than in the automotive and aviation industries (53). Studies in Germany have shown that the provision of protective equipment for personnel, local extraction, improved ventilation and protective encasement for machines is more common in medium-size companies with 50-249 employees than in small businesses with fewer than 50 employees (4). This study also showed that skin problems were more common amongst employees at smaller companies because protective gloves were not worn. In medium-size companies throat irritation and respiratory tract problems were more common amongst personnel who worked with more modern, automated machines.

Cutting fluid aerosols have been measured in workplace air as the concentration of inhalable, total or thoracic dust. In the years 1958 to 1987 the average concentration of cutting fluid aerosols measured as total dust fell significantly in the automotive industry from 5.42 mg/m^3 (AM) measured before 1970 to 1.82 mg/m^3 after 1980 (28), see Table 1. Levels of cutting fluid aerosols have subsequently fallen still further. Before 1980 37% of aerosol exposure measured as total dust was below 0.5 mg/m^3 and after 1990 this figure was 73%.

A study by Park *et al*. (54) which looked at many industries, particularly the automotive industry, observed a significant reduction in the concentration of cutting fluid aerosols measured as total dust from a mean value of 5.36 mg/m^3 before 1970 to 0.55 mg/m^3 in the 2000s, see Table 1. This study is based on

Table 1. Air concentrations of cutting fluid aerosols (all types of cutting fluids) measured as total dust, mg/m^3 air, in industry, particularly the automotive industry, from the 1950s up to and including the 2000s. na = not analysed

Period	Type of industry	Total aerosol, AM, mg/m^3 air	SD	Number of measurements	Ref.
1958-1987	Automotive industry	Down from 5.42 to 1.82			28
Before 1970	Many different industries	5.36	4.28	311	54
	Automotive industry	10.26	7.6	63	
1970s	Many different industries	2.52	1.76	874	54
	Automotive industry	2.12	1	627	
1980s	Many different industries	1.21	0.93	1085	54
	Automotive industry	1.15	0.93	988	
1990s	Many different industries	0.50	0.31	6002	54
	Automotive industry	0.98	1.6	127	
2000s	Many different industries	0.55	0.19	1107	54
	Automotive industry	0.70	na	33	

reports from the American automotive industry and it is unclear whether the same types of cutting fluids have been used in Europe and Sweden.

Since 1967 NIOSH has conducted more than 70 health studies of exposure to cutting fluid aerosols and oil mist in industry. Exposure data from 38 studies indicate that exposure to cutting fluids in the form of either oil mist or aerosols has decreased over time. Exposure (AM, measured as total dust) was measured, using personal monitors, as: 1.23 mg/m^3 (21 plants) during the 1970s; 0.57 mg/m^3 during the 1980s (15 plants) and 1.0 mg/m^3 during the 1990s (2 plants). The mean value for all measurements at the 38 plants was 0.96 mg/m^3. This figure is in good agreement with OSHA IMIS which calculated a mean value of 0.92 mg/m^3 (measured as total dust) over the same period (49). DECOS (19) arrived at approximately the same air concentration, i.e., during the 1990s the average occupational exposure to cutting fluid aerosols was about 1 mg/m^3 (measured as total dust).

In a Swedish study of three companies which worked with alloy steel, cast iron, and aluminium, Lillienberg *et al.* showed that, over many years, using compressed air, working with half-open machines, and grinding were important factors in exposure to inhalable aerosols and in governing exposure levels (42). Amongst Swedish companies AM varied between 0.19 and 0.25 mg/m^3. Analyses showed that cutting fluid aerosols made up 77% of the inhalable aerosol fraction, the rest coming from other sources, e.g., welding. The authors suggest that in work situations which involve cutting fluid aerosols and in which there are no other sources that could contribute particulate material, the amount of aerosol can be determined simply by weighing. The authors also measured triethanolamine which is an additive in cutting fluids; the mean concentration of triethanolamine in cutting fluid aerosols was 0.014 mg/m^3 (42).

A recently completed Swedish study of the engineering industry recorded 126 personal monitor measurements of cutting fluid aerosols and reported a mean value of 0.20 mg/m^3 (0.03-1.08) in the inhalable fraction. 70 stationary measurements of cutting fluid aerosols recorded alongside machines gave a mean value of 0.16 mg/m^3 (16).

Cutting fluid aerosols can be contaminated with metals from alloys in the worked materials. Some isolated studies show that machine operators have been exposed to cobalt and chromium from contaminated cutting fluids. The operators worked at machines in which working parts did not contain cobalt or chromium, but the machines were coupled to a central tank which was connected to many different machines. Urine tests revealed that the operators had been exposed to cobalt (65, 66).

Cutting fluids can contain many different microorganisms. Microorganisms that might be pathogenic are *Legionella sp., Klebsiella pneumonia, Pseudomonas aeruginosa,* and *Escherichia coli*. Bacterial contents of 10^4 to 10^{10} CFU/ml (colony-forming units per millilitre) have been measured in various cutting fluids (58). A study by Liu *et al.* (44) found that *Exiguobacterium, Micrococcus* and *Staphylococcus capitis* were the most dominant airborne bacteria (mean value 0-108 CFU/m^3) in some cutting fluid environments. One study showed that the microflora in cutting fluids from the automotive industry mostly comprised Gram-positive bacteria, whereas Gram-negative bacteria were more common in other industries (48). The same study also showed that Gram-negative bacteria grew in cutting fluids in the presence of the metals chromium, nickel and iron. Many other factors, such as type of production, environment, cutting fluid, pH, added biocides, temperature, ventilation and the presence of heavy metals, have an effect on which bacteria grow in the cutting fluid. Many different bacteria have been identified in various cutting fluids, but the dominant microorganisms that colonize cutting fluids belong to the genera *Pseudomonas* and *Mycobacterium* (*Mycobacterium immunogenum, Mycobacterium chelonae* and *Mycobacterium abscessus*) (35, 58).

Gram-negative bacteria such as, for example, *Pseudomonas*, *Escherichia coli* and *Legionella sp*., produce endotoxins in cutting fluids, which vary considerably in concentration, from a barely detectable 5.4 endotoxin units (EU)/ml to 105 EU/ml in the fluid and from non-detectable levels to 126 EU/m^3 in air (7). A Swedish study measured the amount of endotoxins using personal monitors worn by operators (121 samples). A mean value of 0.23 EU/m^3 was measured (16). No seasonal variations were observed (the measurements were made in autumn/winter and summer). Since 2010 the Netherlands has had a recommended occupational exposure limit for endotoxins of 90 EU/m^3 (18). The limit for endotoxins in the Netherlands are mostly based on measurements in many different sectors (textile industry, agriculture and animal husbandry), which do not use cutting fluids.

Large bacteria sediment onto surfaces whereas smaller bacteria can remain airborne for longer. Studies show that many bacteria are within the size range 4.7-7.0 μm and that endotoxins can be found on small particles (0.16-0.39 μm)

(44, 67). Swedish studies show that operators are exposed to endotoxins with various size fractions (0.25-10 μm) in air, the majority being in the 2.5-10 μm fraction (16, 17).

Fungi (yeasts and moulds) are also found as contaminants in cutting fluids. Various yeasts and the moulds *Penicillium, Aspergillus, Fusarium, Cladosporium* and *Cephalosporium* commonly occur in cutting fluids. Studies show that airborne microorganisms are present (mean concentration 20-233 CFU/m^3) in the size fraction 2.1-3.3 μm (44).

One problem with bacteria in water-miscible cutting fluids is that they can form aggregates, adhere to surfaces in industrial systems and form biofilms. A biofilm forms a protective surface that is more resistant to biocides and makes the bacteria more difficult to remove (45). Veillette *et al.* studied the growth of microorganisms after replacing cutting fluid and cleaning it in a tank system (68). After just 12 hours the bacterial concentration had reached 1.6 x 10^3 CFU/ml because the bacteria had not been completely removed in the cleaning. In cleaning it is important to know the composition of the microflora so that the correct cleaning agent is used, thus avoiding the creation of an imbalance in the system. One way of monitoring the bacterial concentration in cutting fluids is to take liquid samples at regular intervals. In England the HSE (30) has drawn up a recommended check list for industry to help monitor bacterial concentrations in cutting fluids. Cutting fluids are divided into 3 categories according to bacterial growth:

1. Bacterial concentration <10^3 CFU/ml. No measures are required.
2. Bacterial concentration between 10^3 and 10^6 CFU/ml. The system should be inspected and cleaned; alternatively, change the biocidal additives.
3. Bacterial concentration >10^6 CFU/ml. Replace the cutting fluid and clean the system.

In Swedish industry there is no such check list to help in monitoring bacterial concentrations in cutting fluids. A new report from IVL describes methods for reducing the dispersal of and exposure to cutting fluid aerosols by, for example, improvements in working methods, machines, encasements and ventilation (9).

Measurement of cutting fluid concentrations in the workplace environment

When measuring cutting fluid aerosols in air it is possible to sample the inhalable fraction or total dust fraction and then to use NIOSH method 5524 (though the method is described for the thoracic fraction) to analyse aerosols from various types of cutting fluid, both oil-based and water-based (50).

Analysis of cutting fluid aerosols

After taking samples, i.e., pumped sampling, the total amount of cutting fluid on the membrane filter is determined by weighing before and after extraction with two different solvent mixtures, i.e., polar and non-polar fractions. The difference between filter weighings gives the total amount of cutting fluid aerosol in the sample. A typical amount measured per sample might be 0.05 mg, with a measure-

ment uncertainty of ±25% with 0.05-0.10 mg per sample and ±10% with 0.50-2 mg. With air sample volumes of 240 and 480 litres, the quantitative analysis limits are 0.2 and 0.1 mg/m^3, respectively (50).

Some studies have calculated conversion factors between inhalable, total and thoracic fractions. A study by Woskie *et al.* (71) used measurement data from 6 other studies and came up with a conversion factor of 1.4 for converting the thoracic to the inhalable fraction. Another study by Verma (69) observed a relationship between cutting fluid in inhalable, thoracic and respirable fractions, measured using Respicon samplers which gravimetrically sampled all three fractions simultaneously. The content ratio between thoracic and inhalable fractions was 1.38 (69)**.** This is in good agreement with the conversion factor of 1.4 published by Woskie *et al.* (71).

Toxic effects

No information has been found in the literature about acute toxic effects of oral exposure.

Effects on respiratory tract and mucous membranes

Effect on pulmonary function

Kennedy *et al.* conducted a cross-sectional study of 89 machine operators and 42 non-exposed controls from the same workplaces (36). Both exposed and non-exposed workers were from two automotive plants. They were exposed to aerosols from mineral oil-based cutting fluids, emulsions or synthetic cutting fluids. Measurements were made throughout the full working day, on Monday and Friday in a selected week. Pulmonary ventilation was measured using spirometry before and after the work shift on Monday and Friday. The main results were expressed as the difference in FEV_1 before and after the work shift. A lower FEV_1 (≥5%) after the Monday and Friday shifts was more common amongst exposed workers than amongst controls. The OR for lower FEV_1 was 5.8 (95% CI 1.1-29) for mineral oil, 4.4 (95% CI 1.0-20) for emulsions, and 6.9 (95% 1.4-35) for synthetic cutting fluids. OR was adjusted for childhood asthma, smoking before testing and ethnicity. No significant differences in FEV_1 were observed between subjects before the Monday shift and subjects before the Friday shift. There was an association between lower FEV_1 after the work shift and exposure within the range 0.28-0.77 mg/m^3 (AM, inhalable cutting fluid aerosols, whole day measurements). The authors concluded that the study indicated that acute airway obstruction is associated with exposure to various types of cutting fluid aerosols. They also concluded that the results showed a dose-response relationship with the effect on health of inhalable exposure to more than 0.20 mg/m^3.

A cross-sectional study by Kriebel *et al.* involved 216 machine operators from the automotive industry who were exposed to mineral oil-based cutting fluids or cutting fluids of the emulsion type and 170 controls from the same workplace (41). The controls were from other departments within the same company, such

as assembly. The same environmental measurements of exposure to aerosols were made with machine operators and controls. Some aerosol exposure was also found in the controls. It is not made clear to what extent this exposure involved cutting fluid aerosols or other aerosols. The aim of the study was to examine whether exposure to cutting fluid aerosols had a transient effect on pulmonary function over the working day. Exposure to cutting fluids of the emulsion type was on average 0.22 mg/m^3 and to mineral oil-based cutting fluids 0.24 mg/m^3 (AM, inhalable, whole day measurements). Pulmonary ventilation was measured using spirometry before and after the work shift. The main finding was that, in machine operators exposed to cutting fluid emulsions, pulmonary ventilation (expressed as FEV_1) before the shift was on average 115 ml less than in those who had not been exposed ($p=0.05$). FEV_1 was adjusted for age, duration of exposure, ethnicity, smoking and asthma. There was no significant disparity between exposed and non-exposed workers with regard to the difference in FEV_1 before and after a shift. On the other hand, a relationship (RR 3.2, 95% CI 1.2-8.7) was found between reduction in FEV_1 (≥5%) after a shift and before a shift amongst individuals exposed to aerosols ≥0.15 mg/m^3, mean value 0.31 mg/m^3 (including both machine operators exposed to either mineral oil-based or emulsion-type cutting fluids and "controls") compared with individuals exposed to aerosols ≤0.08 mg/m^3 (including both cutting fluid-exposed machine operators and "controls"). The model was adjusted for the variable "machine operator". The authors concluded that the study indicated that exposure to cutting fluid aerosols had both acute and chronic effects on the respiratory tract but that the effects were not particularly substantial. They also concluded that the results showed a dose-response relationship.

Robins *et al.* (56) carried out a cross-sectional study of 83 machine operators in the automotive industry who were exposed to cutting fluids of the emulsion-type and 46 non-exposed assembly workers from the same work place (56). The exposure for machine operators was 0.41 mg/m^3 (AM, thoracic, whole day measurements). Pulmonary ventilation was measured using spirometry before and after the shift on Mondays and Thursdays. The prevalence of respiratory tract problems was recorded via a questionnaire. The main finding was a significantly increased prevalence of a reduction of ≥10% in pulmonary ventilation over the working day (measured as either FEV_1 or FVC) in exposed workers who already had obstructive lung disease before the work shift ($FEV_1/FVC \leq 0.72$) at an average exposure of 0.34 mg/m^3. The authors' interpretation was that exposure to cutting fluids at levels normally occurring in the engineering industry, was in some individuals associated with clinically significant effects on pulmonary function.

There are several studies of pulmonary function which compared workers exposed to cutting fluid aerosols with non-exposed workers but did not examine the effect during the working day. Järvholm *et al.* (34) found no difference between exposed (mineral oil-based cutting fluids or emulsions) and non-exposed workers with an average exposure varying between 1 and 4.5 mg/m^3 (GM, particle size 2 μm). Ameille *et al.* (1) found a significantly lower FEV_1 in smokers expo-

sed to aerosols from mineral oil-based cutting fluids at an exposure level of 1.3-4.4 mg/m^3 (GM, total dust). No effect was found on pulmonary function in non-smokers or with exposure to water-miscible cutting fluids (the exposure was not measured). Massin *et al.* (46) reported no significant differences between exposed and non-exposed workers with regard to exposure to cutting fluids (emulsions or mineral oil-based) in different parts of a plant at various exposure levels (0.65, 1.49 and 2.2 mg/m^3, respectively, GM, total dust). Sprince *et al.* (61) found no difference between exposed machine operators and non-exposed assembly workers with regard to effect on pulmonary function, nor any difference during the working day, with exposure to cutting fluids of the emulsion type or semisynthetic cutting fluids at 0.33 mg/m^3 (GM, direct-reading short-term measurements). On the other hand a significant association was found between exposure to higher total numbers of culturable bacteria and reduced FEV_1.

Asthma and asthma-like symptoms

The occurrence of asthma in workers exposed to cutting fluids has been investigated in a number of studies. Besides diagnosed asthma, several studies have reported the occurrence of asthma-like symptoms such as wheezing or a feeling of tightness in the chest, breathlessness or irritation in the lower respiratory tract.

Eisen *et al.* (21) reanalysed data from the cross-sectional study by Greaves *et al.* (27) referred to below. The aim was to study the time of asthma onset in relation to the time of first exposure to cutting fluids, and to reduce the healthy-worker effect due to job transfer bias in cross-sectional studies. Twenty nine cases of asthma onset after time of hire were identified. Of these, 6 cases involved exposure to synthetic/semisynthetic cutting fluids which corresponded to an increased risk of asthma with OR 3.2 (95% CI 1.2-8.3). The exposure measured for these six cases was on average 0.60 mg/m^3 (thoracic fraction, range 0.36-0.91 mg/m^3). Exposure to mineral oil-based cutting fluids or cutting fluids of the emulsion type did not result in any significant change in the risk of developing asthma (OR 2.0, 95% CI 0.9-4.6, and OR 0.5, 95% CI 0.2-1.1, respectively).

Robins *et al.* (56) found no statistically significant relationship between exposure (0.41 mg/m^3 AM, thoracic, whole day measurements) and the prevalence of asthma.

Two studies are of particular interest because they were conducted relatively recently in Sweden and Finland, respectively.

Lillienberg *et al.* conducted a cross-sectional study using exposure measurements and a self-administered questionnaire to 1048 workers exposed to cutting fluids and 451 controls at five Swedish companies (43). No significant excess risk of asthma was found with mixed exposure to various types of cutting fluid (PR 1.20, 95% CI 0.71-2.03) in men, adjusted for age and smoking. The mean exposure was 0.21 mg/m^3 (AM, inhalable). No significant relationship was found between exposure to cutting fluids and wheezing (PR 1,19, 95% CI 0.88-1.62). However, significant relationships was found between wheezing and exposure to synthetic cutting fluids (PR 1.88, 95% CI 1.23-2.89) in cleaning with compressed

air for >30 minutes/day (PR 1.51, 95% CI 1.04-2.19) and when working with more open machines (PR 1.65, 95% CI 1.12-2.45). There are no exposure levels given for these types of work.

Jaakkola *et al.* conducted a cross-sectional study of 726 men exposed to cutting fluids and 84 controls from 64 Finnish metalworking companies (33). Direct-reading (DataRam) five-minute short-term measurements of cutting fluid aerosols, with particle size range 0.1-10 µm, were made at 57 workplaces, median 0.12 mg/m^3 (range 0.001-3.00). A non-significant association was observed between exposure similar to or above the median, ≥0.12 mg/m^3, and asthma (OR 4.1, 95% CI 0.8-20.5). There was a significantly increased prevalence of wheezing in workers who were exposed to ≥0.12 mg/m^3 (OR 4.8, 95% CI 1.6-4.8), and of breathlessness (OR 7.0, 95% CI 1.6-31.9). It is debatable whether it is possible to compare the study's short-term measurements using direct-reading instruments with measurements using conventionally pumped sampling during a full day. It is unclear whether the symptoms are provoked at average concentrations or high concentrations over short periods of exposure. Direct-reading instruments often have a relatively narrow measurement range and these measurement values cannot be compared with pumped sampling using a filter which can measure both respirable and inhalable fractions or total dust, over both longer and shorter periods.

Hannu *et al.* has conducted a clinical investigation of individuals with suspect ted work-related disorders (29) who were exposed to cutting fluids in the study by Jaakkola *et al.* (33). One case of occupational asthma caused by exposure to cutting fluids was observed. In this case inhalation provocation by cutting fluids from the individual's workplace was positive. A further five individuals were judged to have examination results compatible with occupational asthma, but with negative inhalation provocation.

In non-specific bronchial hyperresponsiveness the airways have an increased tendency to constrict when exposed to respiratory irritants. Bronchial hyperresponsiveness commonly occurs in asthma. In a follow-up study of trainees Kennedy *et al.* found that two years of exposure to soluble (not further defined) and synthetic cutting fluids at an average of 0.46 mg/m^3 (AM, total dust, GM 0.31 mg/m^3) was a predictor for non-specific bronchial hyperresponsiveness (37). Two other studies found some increase in bronchial hyperresponsiveness with exposure to high concentrations of mineral oil-based and water-soluble cutting fluids (1.3-4.4 and 5.2 mg/m^3, respectively, [GM, total dust]) (1, 46).

It has been reported that metal contaminants in cutting fluids can cause asthma, amongst other health problems. A case report describes four grinders with occupational asthma, caused by chromium in three cases and by cobalt in one case (65). The exposure is judged to have been mediated via the workplace's shared cutting fluid system as the individuals had not worked directly with either chromium or cobalt. A study of other employees at the workplace revealed a high incidence of rhinitis (27%) which it was suspected had been caused by exposure to chromium and/or cobalt in the cutting fluid. Individuals with respiratory tract

problems had on average higher concentrations of chromium and cobalt in urine samples than those without these problems.

Another case series describes 14 individuals from the same workplace with cobalt-provoked occupational asthma. The exposure to cobalt is thought to have been mediated by cutting fluid aerosols (66).

It has also been reported that asthma can be caused by ethanolamines which may be present in cutting fluids as corrosion inhibitors (55, 59).

Sprince *et al.* (61) conducted a cross-sectional study using a questionnaire at a large automobile transmission plant. Eighty percent of those questioned participated, i.e.,183 machine operators and 66 assembly workers who had not been exposed to cutting fluids. Both emulsions and semisynthetic cutting fluids were used. Exposure measurements were made as direct-reading five-minute short-term measurements, with a particle size range of 0.1-10 µm; the average concentration was 0.33 mg/m^3 (GM, total aerosol measured using MiniRam). The number of viable microorganisms was measured with an Anderson-sampler. A number of associations were observed between exposure and health problems following a shift, after adjustment for age, smoking, ethnicity and gender. The OR for throat irritation was 5.0 (95% CI 1.7-14.7) and for tightness in the chest 4.5 (95% CI 1.3-15.2). Dose-response analyses were also conducted, giving an OR of 3.7 for throat irritation (95% CI 1.04-12.9) with an average exposure of 0.20 mg/m^3 (GM, total aerosol); OR 3.7 (95% CI 1.03-12.9) with an average exposure of 0.31 mg/m^3 and OR 5.1 (95% CI 1.5-17.5) with an average exposure of 0.90 mg/m^3.

Greaves *et al.* (27) also conducted a cross-sectional questionnaire study at three companies in the automotive industry. 1811 individuals took part, 86% of those questioned. 769 were non-exposed controls, while the remainder were exposed to either emulsions of mineral oils in water or synthetic cutting fluids. Whole day measurements of cutting fluid aerosols were made in the thoracic fraction. The measurements were 0.43 mg/m^3 for mineral oil-based cutting fluids, 0.55 mg/m^3 for emulsions and 0.41 mg/m^3 for synthetic cutting fluids. For mineral oil-based cutting fluids there was a statistically significant relationship with wheezing (OR 2.2, adjusted for age, ethnicity, smoking, grinding and type of plant). For synthetic cutting fluids there was a statistically significant relationship with wheezing (OR 4.9) and with tightness in the chest (OR 3.9). There was no statistically significant relationship between exposure to cutting fluids of the emulsion type and asthma-like respiratory tract problems.

Oudyk *et al.* (52) also conducted a cross-sectional questionnaire study at a company in the automotive industry. 2368 individuals took part, 81% of those questioned. Exposure to cutting fluid aerosols (semisynthetic or emulsions) was determined for 63 different workplaces by direct-reading short-term measurements. Fifteen workplaces with 562 individuals served as low-exposure controls (mean value 0.06 mg/m^3, range 0.02-0.09 mg/m^3). Other workplaces were allocated to one of two exposure categories: medium (mean value 0.13 mg/m^3, range 0.10-0.16 mg/m^3) and high (0.32 mg/m^3, range 0.25-0.84 mg/m^3). A high, short-term exposure peak was also determined for each workplace. As shown in Table 2

a relationship was observed between various health problems and high exposure: wheezing OR 2.2 (95% CI 1.3-3.5), throat irritation OR 2.2 (95% CI 1.3-3.6), hoarse throat OR 1.7 (95% CI 1.03-2.9). The OR for medium exposure and wheezing was 1.4 (95% CI 1.04-1.9). An analysis in which peak exposure was included (four exposure groups: group 1, 0.02-0.09; group 2, 0.10-0.19; group 3, 0.20-0.47; and group 4, 0.59-2.85 mg/m^3) revealed a number of relationships: between peak exposure for group 3 and wheezing OR 1.8 (95% CI 1.2 – 2.8); between peak exposure for group 4 and wheezing OR 2.5 (95% CI 1.4-4.6); and between peak exposure for group 4 and tightness in the chest OR 2.2 (95% CI 1.4-3.6) and hoarse throat OR 2.3 (95% CI 1.3-4.3). The analyses were adjusted for period of employment and smoking.

Meza *et al.* (47) conducted a cross-sectional questionnaire study with 183 workers exposed to cutting fluids and 224 controls from a company which manufactured aircraft engines and which had circa 275 metalworking machines. There were various types of metalworking involving a variety of metals, tool materials, operating speeds, age of machinery, and degrees of machine encasement and ventilation. Most of the machines were connected to one of three cutting fluid systems containing a semisynthetic cutting fluid. The incidence of upper and lower respiratory tract and skin problems was recorded using a validated questionnaire. The workers were also asked about the temporal relationship between their work and health problems. Personal monitor measurements of cutting fluid aerosols were made at the same time. There was a significant increase in prevalency ratios for asthma symptoms (PR 1.49, 95% CI 1.05-2.13) and work-related asthma symptoms (PR 1.92, 95% CI 1.19-3.09). The analyses were adjusted for smoking. Of 43 measurements, 18 were quantifiable with a mean value of 0.16 mg/m^3 (AM, thoracic fraction, range 0.11-0.29). Measurements were made of the occurrence of bacteria in cutting fluid tanks and of endotoxins in air samples but no relationship was observed between these biological samples and health problems.

A review article on the relationship between diseases and exposure to cutting fluid aerosols concluded that the number of reported cases of work-related asthma had fallen after the 1990s (57). This was based in part on data from monitoring systems for newly developed occupationally-related asthma in Michigan and in the English Midlands. It was explained by reduced exposure, with measured concentrations between 0.5 and 0.2 mg/m^3. In addition the authors believed that more attention was paid to problems with microbial growth in cutting fluids and that more measures were taken.

Cough, chronic bronchitis

A number of studies have examined the incidence of cough (sometimes expressed as chronic bronchitis) in workers exposed to cutting fluids compared with non-exposed controls. Chronic bronchitis is defined as a cough with phlegm lasting at least 3 months per year, over at least two consecutive years. Järvholm *et al.* (34) found a relative risk of 2.8 for cough (95% CI 1.3-2.6) at median exposures of

1-4.5 mg/m^3 (mineral oil-based cutting fluids or emulsions). The relative risk was adjusted for smoking and age.

Ameille *et al.* (1) found an OR of 2.2 (95% CI 1.01-4.9) for chronic cough (at least 3 months per year, for at least two consecutive years) with exposure to mineral oil-based cutting fluids in the range 1.3-4.4 mg/m^3 (GM, total dust). Exposure to water-miscible cutting fluids also occurred but the exposure was not measured. At another plant, Massin *et al.* (46) found an OR of 4.9 ($p<0.002$) for cough or phlegm when compared with non-exposed workers, adjusted for age and smoking. The exposures to cutting fluid aerosols (water-soluble and mineral oil-based) in three different parts of the plant were 0.65, 1.49 and 2.2 mg/m^3 (GM, total dust), respectively.

Kriebel *et al.* (41) reported a relationship between exposure to mineral oil-based cutting fluids and "chronic cough", with a PR of 2.2 (95% CI 1.1-4.6). Exposure to this cutting fluid was 0.24 mg/m^3 (AM, inhalable, whole day measurements).

Robins *et al.* (56) found a statistically significant relationship ($p<0.05$) between exposure (0.41 mg/m^3 AM, thoracic, whole day measurements), and a phlegmy cough (OR 3.1) and chronic bronchitis (OR 6.8).

Sprince *et al.* (61) found a number of relationships between exposed and non-exposed workers and cough with or without phlegm after adjustment for age, smoking, ethnicity and gender. The OR for cough was 3.1 (95% CI 1.4-6.9), for phlegmy cough 3.1 (95% CI 1.6-6.1) and for cough after a shift 4.0 (95% CI 1.2-14.1). An analysis of specific types of cutting fluid showed a relationship between semisynthetic cutting fluid aerosols and cough, OR 2.1 (95% CI 1.04-4.2). A dose-response analysis was also conducted, giving: an OR of 1.6 (95% CI 0.6-4.3) for cough with an average exposure of 0.20 mg/m^3 (GM, total aerosol, measured with MiniRam); an OR of 2.2 (95% CI 0.8-5.8) with an average exposure of 0.31 mg/m^3; and an OR of 3.0 (95% CI 1.2-8.0) with an average exposure of 0.90 mg/m^3. The corresponding analyses for phlegmy cough gave: an OR of 1.4 (95% CI 0.6-3.4) with an average exposure of 0.20 mg/m^3; an OR of 2.8 (95% CI 1.2-6.5) with an average exposure of 0.31 mg/m^3; and an OR of 3.8 (95% CI 1.7-8.8) with an average exposure of 0.90 mg/m^3.

Greaves *et al.* (27) found that for mineral oil-based cutting fluids there was a statistically significant relationship between exposure and cough without phlegm (OR 2.2, adjusted for age, ethnicity, smoking, grinding and type of plant). For synthetic cutting fluids a statistically significant relationship was found with cough, both with and without phlegm (OR 7.3 and OR 4.8. respectively), and for chronic bronchitis (OR 3.5). No statistically significant relationship was observed between exposure to cutting fluids of the emulsion type and cough.

Jaakkola *et al.* (33) reported a significant increase in the prevalence of cough in workers exposed to concentrations similar to or higher than the median of 0.12 mg/m^3 (OR 2.2, 95% CI 1.0-4.8) but this was not the case for chronic bronchitis (OR 1.6, 95% CI 0.5-4.5). On the other hand, a relationship was found between metalworking for ≥15 years and chronic bronchitis (OR 2.7, 95% CI

1.0-7.3) and a dose-response analysis revealed a significant relationship between exposure within the range 0.09-<0.17 mg/m^3 and cough.

Lillienberg *et al.* (43) found no significant relationship between exposure to cutting fluids and chronic bronchitis (PR 2.00, 95% CI 0.97-4.10). Separate analyses showed a significant relationship for cleaning with compressed air for >30 minutes/day (PR 3.01, 95% CI 1.33-6.79) and for working with open machines (PR 2.45, 95% CI 1.01-5.95). The relationship was significant for cutting fluids of the emulsion type (PR 2.20, 95% CI 1.01-4.78) and for synthetic cutting fluids (PR 3.05, 95% CI 1.16-8.01) but not for mineral oil-based cutting fluids (PR 0.72, 95% CI 0.16-3.34).

Eye-, nose- and throat irritation

In the study by Oudyk *et al.* (52), see also above, 42% of all respondents reported nasal problems (runny or blocked nose, daily or weekly) but no statistically significant relationship was found between exposure to cutting fluid aerosols and nasal problems.

Jaakkola *et al.* (33), see also above, observed a significant increase in the prevalence of nasal problems amongst those exposed to ≥0.12 mg/m^3 (OR 1.8, 95% CI 1.0-3.3).

Lillienberg *et al.* (43) found a significant relationship between exposure to cutting fluids (average exposure 0.21 mg/m^3, AM, inhalable) and chronic nasal symptoms (PR 1.30, 95% CI 1.02-1.66). The relationship was significant for cutting fluids of the emulsion type (PR 1.33, 95% CI 1.02-1.74) but not for mineral oil-based cutting fluids or synthetic cutting fluids, for which the risk estimates were low. A significant relationship was also found between simultaneous exposure to various types of cutting fluid aerosols and eye irritation (PR 1.32, 95% CI 1.09-1.61). The relationship was significant for synthetic cutting fluids (PR 1.42, 95% CI 1.05-1.93).

Fornander *et al.* (23) published a cross-sectional study of 271 individuals exposed to "water-based" cutting fluids and 24 non-exposed controls at a Swedish company with a high prevalence of respiratory tract disorders amongst employees. A significant increase was observed in the prevalence of nasal symptoms (37%) and cough (17%) compared with various control groups. The exposure to cutting fluid aerosols and oil mist was 0.46 mg/m^3 (AM, total dust). Exposure to formaldehyde was also measured as 0.1 mg/m^3.

Meza *et al.* (47) (see also above) reported a significant increase in the prevalence of work-related nasal symptoms (PR 1.36, 95% CI 1.003-1.86) in workers exposed to semisynthetic cutting fluids, compared with controls (0.16 mg/m^3 AM, thoracic fraction).

Allergic alveolitis

Allergic alveolitis is a lung disease caused by repeated inhalation of organic material. Exposure leads to an immune-mediated inflammatory hypersensitivity reaction in the lungs. The symptoms include episodes of fever and feeling gene-

rally unwell, often referred to as "influenza-like symptoms". The term hypersensitivity pneumonitis is often used in international literature . This illness is usually occupationally related and is more common in non-smokers. There are many different forms of exposure that can cause allergic alveolitis, including exposure to bacteria and moulds.

Many cases of allergic alveolitis have been described which involve an association with exposure to cutting fluids. Several accumulations of allergic alveolitis cases in individual workplaces have also been described. A workshop (40) concluded that there was a risk of allergic alveolitis with exposure to water-based cutting fluids and that it is the microorganisms in cutting fluids which cause the allergic alveolitis. Bukowski arrived at the same conclusion in a systematic literature review (6). Bacteria of the genera *Mycobacterium* and *Pseudomonas* are often but not always found in cutting fluids in association with the outbreaks of allergic alveolitis.

A systematic overview has examined the literature on allergic alveolitis and asthma published between 1990 and October 2011 (7). 27 "outbreaks" of allergic alveolitis have been reported; these were often described as case series or cross-sectional studies. Measurements were normally made. The majority of reported outbreaks were from car- or aeronautical-manufacturing plants in the USA and at companies with at least 100 individuals exposed to cutting fluids. Environmental investigations were unable to show that any particular form of exposure consistently resulted in outbreaks. The variables were the type of synthetic cutting fluid or emulsion, the incidence of microbial growth and the intensity of exposure. The authors concluded that, despite several detailed studies, there is still only a limited understanding of what causes outbreaks of allergic alveolitis and asthma in individuals exposed to cutting fluids.

Lillienberg *et al.* (43) conducted an epidemiological investigation of the occurrence of suspected allergic alveolitis by enquiring about influenza-like symptoms but found no significant relationship with exposure to cutting fluids (PR 1.53, 95% CI 0.92-2.55). However, the relationship was significant for synthetic cutting fluids (PR 2.07, 95% CI 1.00-4.27) in work with open machines (PR 2.71, 95% CI 1.50-4.88) and with grinding work (PR 1.95, 95% CI 1.11-3.44).

In the previously mentioned review article on diseases associated with exposure to cutting fluid aerosols (57) it states that the incidence of reported cases of allergic alveolitis had fallen after the 1990s.

Cardiovascular disease

A cohort comprising a total of 39,412 automobile workers from three automotive plants in Michigan who had worked for at least 3 years during the period 1938-1985, was followed up, up to and including 1994. 88% were men. The risk of ischaemic heart disease showed a U-shaped relationship with cumulative exposure to mineral oil-based cutting fluids (straight metalworking fluid) and the highest risk of ischaemic heart disease was observed in the highest exposure category,

>2.77 mg/m^3 x years (Hazard ratio 1.53, 95% CI 1.15-2.05). Exposure over the years 1941-1970 did not result in any significant excess risks, even though it was assumed that the highest exposure to PAH occurred in the period before 1971. Exposure over the period 1971-1994 showed a U-shaped relationship with ischaemic heart disease (14).

This cohort was also used to study the so-called ”healthy worker survivor effect”. Workers with long-term exposure might possibly comprise an innately healthier-than-average selection of workers and this could introduce a systematic error when comparing workers with long-term and short-term exposure with regard to morbidity and mortality. The total cohort consisted of 38,747 auto workers who had worked for at least 3 years over the period 1941-1982 and who were followed up, up to and including 1994. The average duration of employment was 18.1 years and the average exposure time for mineral oil-based cutting fluids 4.1 years. G-estimation is an alternative way of avoiding the error that arises as a result of the ”healthy worker survivor effect”. The risk of ischaemic heart disease after 5 years of exposure increases after this adjustment is made (Hazard Ratio 1.15, 95% CI 1.11-1.19). The corresponding calculation gives a lower figure for risk of lung cancer (HR 1.07, 95% CI 1.04-1.14) (8). A lower risk for lung cancer than for ischaemic heart disease indicates that smoking cannot explain the higher risk for heart disease.

A later study (15) of the same cohort, comprising 39,412 auto workers, analyzed the relationship between emulsions (soluble) or synthetic cutting fluids and mortality from ischaemic heart disease. African American men with a cumulative exposure (the highest exposures level was >0.65 mg/m^3 x years) to synthetic cutting fluids showed an excess risk of ischaemic heart disease (HR 3.29, 95% CI 1.49-7.31). A higher mortality (HR 2.44, 95% CI 0.96-6.22) was also observed in white women in the next highest exposure category (1.81-3.44 mg/m^3 x years) who were exposed to soluble cutting fluids. On the other hand, no association was found between exposure to soluble or synthetic cutting fluids and mortality from ischaemic heart disease in white men.

The Criteria Group's conclusion, based on the American auto worker cohorts, is that there is limited support for an association between exposure to various types of cutting fluids and ischaemic heart disease.

Skin

It is well known that dermal exposure to mineral oil-based cutting fluids can cause various skin problems, such as contact dermatitis, folliculitis, oil acne, lipid granuloma, or melanosis (19). Emulsions can cause both irritant and allergic contact dermatitis whereas mineral oil-based cutting fluids usually cause only irritant contact dermatitis. Work with synthetic cutting fluids poses the greatest risk of contact eczema (51). According to Simpson *et al.* (60) water-miscible cutting fluids cause dermatitis more often than do pure mineral oils.

Many of the additives in cutting fluids are clinically established contact allergens and can sensitize and provoke allergic contact dermatitis on exposure. In

Sweden a patch test series involving 35 substances is currently used when there is suspicion of contact allergy to any cutting fluid additives (http://www.chemotechnique.se/products/series/oil-amp-cooling-fluid-series/, Feb 2016). It has been reported that chemical additives in synthetic cutting fluids penetrate the skin to a lesser extent than those in emulsions, which can increase the risk of contact allergy (70).

In recent years two studies have been published on dermatological diseases caused by occupational exposure to cutting fluids. Hannu *et al*. conducted a clinical cross-sectional study in Finland and found a 12% prevalence of work-related skin disorders. Fifteen individuals were patch-tested; five showed allergic contact dermatitis reactions to various substances in cutting fluids and three had irrititant contact dermatitis (29).

In a cross-sectional study of workers exposed to semisynthetic cutting fluids Meza *et al.* (47) (see also above) found a PR of 1.86 (95% CI 1.20-2.90) with regard to a one-year prevalence of work-related skin disorders, compared with controls. No clinical study was conducted.

Mutagenicity

Apostoli *et al.* (2) reported that the PAH content and mutagenicity of a mineral oil-based cutting fluid in the Ames test increased with time of use. The cutting fluid tested contained 23% semisynthetic mineral oil. A clear increase in mutagenic hydrocarbons, including benzo(a)anthracene and benzo(a)pyrene, was measured in the used cutting fluids. Cutting fluids that had been used for 6 or 9 months, but not those that had been used for 3 months, showed a sharp increase in the number of mutations in Salmonella typhimurium TA98, with metabolic activation (S9 mix) but not without metabolic activation. The results are in line with what would be expected if the mutagenicity had been caused by PAH. Toxicity and mutagenicity in the Ames test has also been demonstrated in water-soluble cutting fluids with undefined contents which were tested after use (38) as well as in unused water-soluble cutting fluids containing formaldehyde-generating substances (39).

Carcinogenicity

Mineral oils that have previously been used in cutting fluids and have not had PAH removed have been classified by the IARC as carcinogenic to humans (”Untreated and mildly treated mineral oils are carcinogenic to humans [Group 1]”) (31, 32). The most well-documented outcome in individuals who had worked with this type of PAH-containing cutting fluid was squamous cell carcinoma of the skin.

There are many studies of the relationship between working with cutting fluids and the incidence of cancer. These do not always state what type of cutting fluid was used or give information about the extent of exposure (19). Many studies proceed from the large-scale American study of 46,000 exposed workers at three different companies in the automotive industry (the UAW/GM cohort). They had

been employed between 1917 and 1981 and had worked for at least three years prior to 1985. For this cohort there was data on what type of cutting fluid had been used at the various plants and for what period of time. There are many publications which have used this study base as their starting point. These include various types of study, many different forms of cancer and different time periods.

Eisen *et al.* (20) and Tolbert *et al.* (64) reported an increased risk of leukaemia (Standardized mortality ratio, SMR 1.57, 95% CI 1.21-2.00) and pancreatic cancer (1.70, 95% CI 1.05-2.61).

DECOS (19) reported on three follow-ups of the UAW/GM cohort. In a follow-up, up to and including 1994 (22), a "weak relationship" was found between exposure to mineral oil-based cutting fluids and cancer of the oesophagus, larynx and rectum (relative risks 1.1-2.0). A relationship was found between exposure to "water-soluble" cutting fluids and cancer of the oesophagus, larynx, skin and brain. In addition, a relationship was found between exposure to synthetic cutting fluids and cancer of the oesophagus, liver, and prostate. DECOS concluded that exposure to cutting fluid aerosols can cause cancer in auto workers but this risk appears to decrease with more-refined mineral oils and that there may be an increased risk with current exposure to water-soluble cutting fluids.

A follow-up study examined new cases between 1985 and 2000 (72). The main finding was a relationship between cumulative exposure to mineral oil-based cutting fluids and laryngeal cancer. No association was found with other types of cutting fluids or other forms of cancer. A re-analysis using other epidemiological techniques examined the association between rectal cancer and cumulative exposure to mineral oil-based cutting fluid and found a dose-response relationship.

A third follow-up study was conducted with a sub-group of 21,999 men, looking at lung and bladder cancer, up to and including 2004 (24). A relationship was observed between cumulative exposure to mineral oil-based cutting fluids and bladder cancer, with a 20-year latency period. There was no association between exposure to any type of cutting fluid and lung cancer. The authors interpreted the results as support for the importance of PAH in the development of bladder cancer.

According to DECOS (19) several case-control studies were also conducted in the UAW/GM cohort. A relationship was found between exposure to mineral oil-based cutting fluids and laryngeal cancer (an association with elementary sulphur additives was also discussed). A case-control study of oesophageal cancer found a significant relationship with emulsions and synthetic cutting fluids in grinding. There was also an association with exposure to nitrosamines and biocides but it was not possible to separate these exposures from exposure to the cutting fluids themselves. A later study of the same cohort found increased mortality from stomach cancer with grinding using emulsions and synthetic cutting fluids. Another study found an association between cumulative exposure to synthetic cutting fluids in grinding and pancreatic cancer. The question of whether exposure to nitrosamines and/or biocides could explain the increased risk was discussed. Subsequent analyses showed an increased risk of bile duct cancer after exposure to mineral oil-based cutting fluids, with a 20-year latency period. There was also a

dose-dependent increase in the risk of prostate cancer 25 years or more after exposure to mineral oil-based cutting fluids or emulsions. The authors interpreted the results as support for the idea that the previous presence of PAH in cutting fluids could explain the association with prostate cancer.

DECOS (19) concluded that the result indicated that one or more components in the used mineral oil-based and ”water-miscible” cutting fluids were probably polyaromatic hydrocarbons (PAH) (DECOS does not describe what it mean by ”water-miscible” cutting fluids, but for the most part it probably means emulsions). PAH occurred at higher concentrations in mineral oils before the 1980s and could possibly explain the increased cancer risk with exposure to mineral oil-based and water-miscible cutting fluids. Those forms of cancer most strongly suspected to be associated with exposure were considered, in the first instance, to be laryngeal, oesophageal, rectal and prostate cancers, but the associations were weak and varied from study to study.

A number of studies from the America automotive worker cohort UAW/GM were published in subsequent years. Cancer in female workers (26) showed an excess risk of colon cancer with exposure to mineral oil-based cutting fluids (HR 3.1, 95% CI 1.71-2.52). There was a discussion about the variability in associations between different exposure metrics and cancer in different studies. It may indicate that exposure metrics other than ”cutting fluids” are relevant, e.g., metal particles or tramp oils (26).

During 1985-2004, 4374 female automobile workers were monitored for cervical cancer (5). A significantly increased standardised incidence rate (SIR 2.96, 95% CI 2.1-4.0) was observed for auto workers. Increased risks (but not significant) were found with exposure to synthetic cutting fluids and cutting fluids of the emulsion-type but there was no increased risk with exposure to mineral oil-based cutting fluids. The analyses did not take into account, for example, smoking or other factors which can influence the risk of cervical cancer.

One study looked at exposure to mineral oil-based cutting fluids, emulsions and synthetic cutting fluids with respect to the components that are common to all these products (25). Exposure-related health risks were more strongly correlated with different components in the cutting fluids than to the type of cutting fluid. Laryngeal and bladder cancer had the strongest association with exposure to PAH. An association was also found between exposure to PAH and prostate and breast cancer, as well as malignant melanoma. Exposure to synthetic cutting fluids and emulsions were found to be associated with colon and rectal cancer. The possibility that there was an effect from combined exposure to, for example, metal particles, tramp oil, etc., was discussed. The incidences of lung and stomach cancer were lower than expected. The study lacked data on smoking.

A study examined the incidence of malignant melanoma in workers exposed to cutting fluids (13). The HR was 1.99 (95% CI 1.00-3.96) in the highest exposure category for mineral oil-based cutting fluids. The risk was lower for emulsions and no association was found with synthetic cutting fluids. The effects of dermal and inhalation exposures were discussed.

A population-based case-control study in the north eastern USA examined the incidence of bladder cancer with different exposures (11). Workers exposed to cutting fluids had an OR of 1.7 (95% CI 1.1-2.5). For individuals not exposed to cutting fluids but exposed to mineral oil the OR was 1.3 (95% CI 1.1-1.7). A thorough assessment of exposure revealed an association between work with mineral oil-based cutting fluids and bladder cancer (OR 1.7, 95% CI 1.1-2.8) (12). The OR for emulsions was 1.5 (95% CI 0.96-2.5) and for synthetic cutting fluids was 1.8 (95% CI 0.6-5.1). The analyses were adjusted for demographic variables such as age, ethnicity, smoking, and area of residence, as well as other known occupational exposure risks with regard to bladder cancer. It was concluded that PAH exposure during the 1970s and 1980s could not be ruled out as a causative factor. In the study from 2014 (12) an attempt was made to separately study the risk of bladder cancer in men who were first exposed in the 1980s when PAH levels were drastically reduced, but too few subjects were available for meaningful analysis.

Reproductive effects

No data on the reproductive toxicity of cutting fluids has been found in the literature.

Dose-effect-/Dose-response-relationships

Respiratory tract

Important dose-response relationships for occupational exposure to cutting fluid aerosols are summarized in Table 2. Air measurements have been carried out using a variety of techniques and it is difficult, for example, to relate short-term measurements with direct-reading instruments to the inhalable aerosol fraction measured by pumped sampling, see below. For the thoracic fraction there is a published conversion factor to the inhalable fraction. One must also bear in mind that cutting fluids are very heterogeneous products comprising many different chemical substances and, for example, microbial content varies considerably.

Increased prevalence ratios for asthma symptoms, work-related asthma symptoms and work-related nasal problems have been reported for exposure to cutting fluid aerosols (semisynthetic), corresponding to an inhalable fraction of around 0.22 mg/m^3 (47), assuming a conversion factor from thoracic to inhalable fraction of 1.4.

Nasal problems and eye irritation have been described with exposure to 0.21 mg/m^3 in the inhalable fraction (emulsion type and synthetic cutting fluids, respectively) (43).

A study has reported effects on pulmonary function over a shift of an exposure to cutting fluids (mineral oil-based cutting fluids and cutting fluids of the emulsion-type) of 0.31 mg/m^3, measured as inhalable aerosols. Effects before a shift on pulmonary function were reported of exposure to cutting fluids of the emulsion-

type at 0.22 mg/m^3 (41). An increased prevalence of chronic cough was also observed with exposure to 0.24 mg/m^3 mineral oil-based cutting fluids.

In two studies exposure was estimated by short-term measurements using a direct-reading instrument, DataRam (33, 52). One of these studies found an increased prevalence of breathlessness, wheezing, cough and nasal problems with exposure to 0.12 to 3.00 mg/m^3 (33). The other study reported an increased prevalence of wheezing with exposure to 0.13 mg/m^3 (52), see Table 2. A third study, which also used a direct-reading instrument (MiniRam), showed an increased prevalence of cough and phlegm production with an exposure level of 0.33 mg/m^3 (61). A factor of 2 has sometimes been used (19) in converting air concentrations measured with direct-reading instruments to the inhalable fraction but the Criteria Group is of the opinion that such a calculation is too unreliable to be used in setting exposure limits.

Cancer

Epidemiological studies, mainly carried out in the American automotive industry (the UAW/GM cohort), revealed an association between exposure to cutting fluid aerosols and the development of cancer. However, this increased risk cannot be linked to any particular type of cutting fluid or substance in cutting fluids, even though PAH, nitrosamines, certain biocides and metals, have been suspected of causing the increase in cancer risk reported in some studies. Additional data, published after DECOS assessment (19), suggest an increased cancer risk, but without consistency in terms of tumour type or additional evidence regarding carcinogenic factors in cutting fluids.

Conclusions

Cutting fluids have very diverse compositions which changes during use. The data do not allow the identification of a critical effect that is valid for all cutting fluids. In epidemiological studies, eye irritation and effects on the respiratory tract (decreased pulmonary function, asthma-like symptoms, cough, nasal irritation) appear to be the health effects observed at the lowest occupational exposure levels. These effects have been reported with several different types of cutting fluids at an exposure level of around 0.2 mg/m^3, measured as inhalable cutting fluid aerosols.

In epidemiological studies it has been shown that work with older types of cutting fluids containing untreated or mildly treated mineral oils can cause cancer. Later studies with newer types of cutting fluids indicate increased cancer risks but without consistency regarding cancer type and it has not been possible to rule out PAH exposure during the 1980s or earlier as the cause. In addition, the newer studies have not been able to identify further carcinogenic components in cutting fluids.

Skin exposure to cutting fluids can cause both allergic and irritant contact dermatitis.

Table 2. Dose-response relationships for occupational inhalation exposure to cutting fluid aerosols. The Table has been modified from ref. (19).

Reference	Air concentrations[a] (mg/m^3)	Inhalable fraction (mg/m^3)	Particle fraction/ sampler	Effect	Outcome	Type of MWF
Fornander *et al.* 2013 (23) Cross-sectional 271 operators 24 controls	0.46	0.92[b]	Total dust	Nasal problems Cough	+ +	L
Meza *et al.* 2013 (47) Cross-sectional 183 operators 224 controls	0.16 (0.11–0.29)	0.22[c]	Thoracic	Work-related asthma symptoms Nasal problems	+ +	semiS
Lillienberg *et al*. 2008, 2010 (42, 43) Cross-sectional 923 men, 125 women Controls: 374 men 77 women	0.2 (0.04-0.57), 0.19 (GM)	0.21	Inhalable, PAS-6 sampler	Asthma Wheezing Chronic bronchitis Influenza symptoms Nasal problems Nasal problems Eye irritation Eye irritation	- - - - - + - +	M,E,S M,S E M,E S
Jaakkola *et al*. 2009 (33) Cross-sectional 726 operators 84 controls	0.12-3.00 breathing zone	-[d]	DataRam 0.1-10 μm	Current asthma Ever asthma Wheezing Breathlessness Cough Nasal problems Chronic bronchitis Chronic bronchitis (metalworking ≥15 years)	- - + + + + - +	M,E, semiS, S
Oudyk *et al.* 2003 (52) Cross-sectional 1334 operators	0.13 0.32	-[d] -[d]	DataRam 0.1-10 μm	Wheezing Wheezing Throat irritation Hoarseness	+ + + +	E,S
Eisen *et al.* 1997 (21) Cross-sectional 1788 operators (cohort analysis)	0.60	0.8[c]	Thoracic, Marple Cascade Impactor	Newly developed asthma	+	S, semiS
Sprince *et al*. 1997 (61) Cross-sectional 183 operators 66 controls	0.33 (GM)	-[d]	MiniRam 0.1-10 μm	Cough Phlegm production	+ +	E, semiS

Table 2. Continued.

Reference	Air concentrations[a] (mg/m^3)	Inhalable fraction (mg/m^3)	Particle fraction/ sampler	Effect	Outcome	Type of MWF
Robins *et al.* 1997 (56) Cross-sectional 83 operators	0.14	0.2[c]	Thoracic	≥10% reduction in FEV_1 and FVC over shift	-	E
34 controls	0.34	0.48[c]		≥10% reduction in FEV_1 and FVC over shift	+[e]	
Kennedy *et al.* 1999 (37) Prospective 2 years 82 operators 157 controls	0.46 0.31 (GM)	0.94[b]	Total dust	Bronchial hyper-responsiveness	+	L,S
Kennedy *et al.* 1989 (36) Cross-sectional	0.2-0.55	0.28-0.77[c]	Thoracic	≥5% reduction over shift ΔFEV_1	+	M,E or S
89 operators 42 controls	>0.55	>0.77[c]		≥5% reduction over shift ΔFEV_1	+	
Kriebel *et al.* 1997 (41) Cross-sectional	0.08-0.15 (mean 0.12)	0.12	Inhalable	≥5% reduction over shift ΔFEV_1	-	M,E
216 operators 170 controls	≥0.15 (mean 0.31)	0.31	Inhalable	≥5% reduction over shift ΔFEV_1	+	M,E
	0.22	0.22	Inhalable	Pre-shift FEV_1 (% expected)	+	E
	0.24	0.24	Inhalable	Chronic cough	+	M
Greaves *et al.* 1997 (27) Cross-sectional 1042 (364 M, 452 E, 226 S) operators 769 controls	0.43	0.60[c]	Thoracic, Marple Cascade Impactor	Current respiratory tract symptoms	+	M
	0.55	0.77[c]			-	E
	0.41	0.57[c]			+	S
	0.41-0.55	0.57-0.77[c]		Physician-diagnosed asthma	-	M,E,S

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; GM=geometric mean; MWF=cutting fluid; M=mineral oil-based cutting fluid; E=cutting fluids of the emulsion type; semiS= semisynthetic cutting fluid; S = synthetic cutting fluid; L = soluble cutting fluid (not defined further)

[a] Arithmetic mean if not otherwise specified.

[b] At concentrations of total dust up to 0.5 mg/m^3 air, a conversion factor 2 can be used for converting to the inhalable fraction (42).

[c] In converting from the thoracic fraction to the inhalable fraction a factor of 1.4 is used (71).

[d] The Criteria Group considers that the conversion of exposure levels measured with a direct-reading instrument (DataRam and MiniRam) to the inhalable fraction is far too unreliable to use in setting exposure limits. A factor of 2 has sometimes been used (19) in converting air concentrations measured with a direct-reading instrument to the inhalable fraction.

[e] Individuals who already had obstructive lung disease before the work shift ($FEV_1/FVC \leq 0.72$).

Potential conflicts of interest

Bengt Järvholm (member) has declared that he has taught at the School of Chemical Engineering (ca once every two years) on the subject of cutting fluids/chemical health risks. The School is run by Castrol Nordic Lubricants AB. Fee invoiced by Umeå University.

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Appendix 1

Abbreviations and clarifications:

AM	Arithmetic mean
GM	Geometric mean
FVC	Forced expiratory volume
FEV_1	Forced expiratory volume in one second.
OR	Odds Ratio
RR	Risk Ratio
CFU	Colony forming units
PAH	Polyaromatic hydrocarbons
PR	Prevalence Ratio
CI	Confidence Interval
HR	Hazard Ratio

The UAW/GM cohort (United Autoworkers/General Motors) comprises a full 46,000 individuals from three production sites for the car industry in Michigan who were employed between 1917 and 1981 and had worked for at least three years before1985.

Inhalable dust is that portion of the airborne particles (particle size 100 μm and less) which is inhaled via the nose and mouth. (http://www.av.se/teman/hygieniska_gransvarden/kontrollera_luften/definiera_damm/)

Thoracic dust is that portion of the inhalable particles (particle size 10 μm and less) which passes through the larynx. (http://www.av.se/teman/hygieniska_gransvarden/kontrollera_luften/definiera_damm/)

Respirable dust corresponds, as before, to that portion of the fraction (particle size 4 μm and less) of inhalable particles which penetrate furthest down through the respiratory tract into the alveoli. Separation into the different fractions also has a mathematical expression, in accordance with the convention in standard SS-EN 481, www.sis.se; (http://www.av.se/teman/hygieniska_gransvarden/kontrollera_luften/definiera_damm/)

The total dust on a filter is not the same as the total amount of airborne particles in the air, but only a certain portion of it.

Consensus Report for Carbon Monoxide

June 16, 2016

This document is based primarily on the evaluation of Carbon monoxide (CO) from the Nordic Expert Group (NEG) for Criteria Documentation of Health Risks from Chemicals 2012 (78) and on evaluations by WHO/IPCS 1999 (40) and ATSDR 2012 (11). Last PubMed search was performed in January 2016.

Physical and chemical properties, Occurrence

CAS number:	630-08-0
Synonyms:	carbon oxide, carbonic oxide
Molecular formula:	CO
Molecular weight:	28.01
Freezing point:	-205 °C (at 101.3 kPa)
Boiling point:	-191.5 °C (at 101.3 kPa)
Vapor density:	0.968
Vapor pressure:	>101 kPa (at 20 °C)
Solubility in water:	2.4 ml/100 ml
Conversion factors at 25 °C:	1 ppm = 1.145 mg/m^3, 1 mg/m^3 = 0.873 ppm

Carbon monoxide (CO) is a colorless, odorless and tasteless gas present in the atmosphere. It originates from both natural and anthropogenic sources. The outdoor ambient concentrations range from around 30 ppb (during summer in the Southern Hemisphere) to around 200 ppb (in the Northern Hemisphere during winter). Volcanic activity, natural and man-made fires and burning of fossil fuels are the main sources of CO in the outdoor ambient air (11, 40).

Anthropogenic sources of CO include exhaust of combustion engines and CO production by incomplete burning of wood, coal, charcoal, oil, kerosene etc. Exposure to CO is also common in occupational settings, e.g. as an industrial gas in the production of chemical intermediates. In Sweden most CO in ambient air originates from traffic and transport, incomplete combustion in connection with industry and from energy production (Naturvårdsverket: http://www.naturvardsverket.se/Sa-mar-miljon/Klimat-och-luft/Luftfororeningar/Kolmonoxid/, November 2015). The levels of CO in Stockholm city air have declined during the past 15 years, largely because of the introduction of car catalysts (https://www.naturvardsverket.se/Sa-mar-miljon/Klimat-och-luft/Luftfororeningar/Kolmonoxid/, January 2016). For example, in 2014 the annual average CO at Sveavägen was 0.3 mg/m^3 (0.26 ppm) compared to 1.026 mg/m^3 (0.9 ppm) in 1999. The maximal 8 hours average was 27 ppm in 2014 (http://www.naturvardsverket.se/

Sa-mar-miljon/Statistik-A-O/Kolmonoxid-i-gaturum-och-urban-bakgrund-halter-13/, January 2016).

The concentration of CO in indoor air is influenced by different sources of CO production in the environment. Gas stoves, kerosene heaters and smoking are examples of common sources (11). Another source of CO is portable gasoline-powered generators, which are used in power outages after hurricanes and storms in some parts of the world (35). Higher levels of indoor CO levels are found in homes with gas stoves, compared with homes using electric cooking (58). The average CO concentration measured in indoor air in 400 homes in the US was calculated to 2.2 ±0.17 ppm (83).

Workers exposed to vehicle exhaust, construction workers, firefighters and cooks are at increased risk for CO exposure. Industrial processes producing CO directly or as a by-product include e.g. steel production, nickel refining, coke ovens, production of carbon black and petroleum refining. Examples of exposure levels for some occupations are summarized in Table 1. CO emission from wood pellet storage has been reported as a source of occupational and domestic exposure, and poisonings, sometimes with deadly outcome, has occurred (28, 32, 80, 81). For example, CO levels of 56 (±4) mg/m^3 was recorded in a warehouse and 123 (±10) mg/m^3 in a domestic storage room (81) and CO levels of 180 ppm have been measured in staircases close to cargo holds of ships carrying pellets (80). Cases of CO-poisonings have been reported after acetylene gas welding of pipes, where acetylene gas had degraded to CO in an atmosphere with oxygen depletion (7). In Sweden, the use of "gengas"-generators (generation of combustible gas) caused a CO-poisoning epidemic among taxi drivers during World War II (1939-1945) (49). In indoor arenas, especially where LPG(liquefied petroleum gas)-powered ice machines are used, CO levels are commonly around 2-6 ppm, however considerably higher concentrations (50-400 ppm) have been measured in a few arenas (76). Exhaust emissions from older cars without catalysts may contain high levels of CO, up to 7000 ppm (http://www2.gi.alaska.edu/ScienceForum/ASF5/588.html, May 2016), exposure levels that can cause acute intoxication and death. CO poisoning is still common in some parts of the world, e.g. it was the second most common non-medicinal poisonings death in the USA between 1999 and 2012 (75).

In smokers COHb levels up to 10% is seen, reflecting the absorption of CO from tobacco smoke (40, 78).

Endogenous CO is generated from degradation of hemoglobin by the enzyme heme oxygenase (HO-1). Endogenous CO can be induced by various factors such as oxidative stress, hypoxia, heavy metals, etc., that cause increased HO-1 expression and activity. Also other hemoproteins such as myoglobin, cytochromes, peroxidases and catalase contribute by 20-25% to the total endogenous CO. These sources in combination lead to a normal blood COHb between 0.3 and 1% (61). Women have fluctuating COHb levels during the menstruation cycle. Endogenous CO production also increases during pregnancy because of contributions from fetal endogenous CO production and increased hemoglobin metabolism (61).

Table 1. CO levels measured at different workplaces in Norway 2000-2009. Table modified from (78). NA = not available.

Occupational field	Number of measurements	CO max (ppm)	CO mean (ppm)
Defense activities (incl. submarines)	20	1189	273
Manufacture of carbides	859	NA	124
Scheduled air transport	7	NA	44
Casting of iron	15	375	43
Other preventive health care	6	175	30
Stuff, tunnel, construction site	5	892	19
Manufacture of electrical equipment	4	NA	17
Manufacture of coke oven products	12	NA	14
Wholesale of mining, construction and civil engineering machinery	10	NA	11
Operation of gravel and sand pits	5	NA	11
Construction	107	210	10
Maintenance and repair of motor vehicles	9	37	6
Construction of motorways, roads, airfields, and sport facilities	83	650	5
Installation of electrical wiring and fittings	9	38	4
Manufacture of veneer sheets, plywood, laminboard, particle board	8	682	3
Manufacture of other non-metallic mineral products	30	NA	3
Production of primary aluminium	9	63	2
Aluminium production	4	NA	2
Mining of non-ferrous metal ores, except uranium and thorium ores	7	160	<2
Toll bar stations	15	20	<2
Manufacture of industrial gases	5	9	<2
Manufacture of paper and paperboard	4	3	<2

During pregnancy, the endogenous production of CO can increase as much as three times and maternal COHb levels are usually about 20% higher than in non-pregnant women (87). Endogenous CO production can also be affected by various diseases, for example, hemolytic anemia and other hematological diseases can cause an increase in the CO production (61).

CO can be detected in air samples using techniques based on non-dispersive infrared detection. The most sensitive of these instruments can detect CO levels at around 0.04 ppm. Gas chromatography with flame ionization detector can detect levels down to 0.02 ppm (78). The NIOSH method (method 6604) for occupational hygienic measurements of CO, recommends a portable direct-reading monitor (limit of quantification around 1 ppm and detection range of 0-200 ppm) (59).

Production and use

In the industrial production of CO the initial product is usually a gas mixture containing CO. CO is frequently used as a reducing agent in the production of inorganic chemicals. The major use of CO in industry is in the production of acetic acid. In 2009, the reported use of CO in Sweden, Norway and Finland was 2.4 million tonnes. The main use categories included manufacture of basic metals, chemicals, and chemical products, scientific research, as well as the category "electricity, gas, steam and air condition supply" (78). In Sweden, more than 700 000 tonnes were used in 2013 (http://www.kemi.se/hitta-direkt/statistik, February 2015).

Uptake, biotransformation and excretion

Inhaled CO diffuses from the alveolar gas phase to the red blood cells, and to other tissues. Binding of CO to hemoglobin (Hb) in blood to form COHb contributes to CO transfer from alveolar air to blood. The affinity of human Hb for CO is more than 200 times that for oxygen (11, 40).

In addition to Hb, CO also binds to other heme-containing molecules, like myoglobin and cytochromes. Studies have shown that CO binds reversibly to myoglobin (the main binding protein for CO in cardiac and skeletal muscle) with an affinity constant approximately 8 times lower than for Hb (34). However, because of myoglobin's abundance in muscle, inhaled CO can transfer in substantial amounts into muscle tissue (11). This could lead to a reduced oxygen supply to tissues as the CO-myoglobin decrease the storage capacity of oxygen in myoglobin. The transfer of CO into muscle tissue is generally larger in males than in females, probably due to differences in muscle mass and capillary density (14). Higher concentrations of CO found in blood, heart, skeletal muscle, and spleen, which have been observed in human autopsy studies, probably reflect the large quantity of CO binding proteins in these organs (Hb in erythrocytes and spleen and myoglobin in cardiac and skeletal muscle) (11).

Recent studies have proposed that the elimination of CO is biphasic, initially involving a rapid decrease, followed by a slower phase (15, 73). The initial elimination of CO is rapid ($t_{½}$ = 50-70 minutes) (82). Fetal hemoglobin has higher affinity for CO than maternal hemoglobin and compared to maternal elimination, removal of fetal CO is slower, involving half-times of COHb of 7.5 hours compared to 4 hours for maternal COHb, resulting in a prolonged fetal exposure (78). A gender difference in the elimination rate of CO has also been observed, where non-pregnant females have faster COHb reduction, compared to males (90).

Biomonitoring

Exposure to CO can be estimated by measuring COHb in blood. Clinical analyses to detect COHb often use direct-reading spectrophotometers. Pulse oximeters can be used for non-invasive measurements of COHb. The most sensitive technique

to measure COHb is based on gas chromatography (limit of detection 0.005% COHb) (78). CO in exhaled breath can be measured to assess CO levels in blood. This approach involves portable analyzers with electrochemical detection, infrared spectrometry, gas chromatography etc. The limit of detection is low, down to 1 ppb (78).

COHb levels for different CO exposure concentration and time combinations and workloads can be calculated with the Coburn-Forster-Kane (CFK) equation (78), see figure 1.

Diffusion of CO into tissue can be calculated using the Haldane equation. After COHb is formed, CO diffuses from the capillaries into the tissue compartments. Tissue tension of CO is determined by COHb concentration, partial pressure of oxygen, the affinity of hemoglobin for CO and the concentration of oxyhemoglobin (50).

The slow turnover of COHb makes it a suitable biomarker of exposure to CO. However, due to variable background levels (Table 1), COHb is not a suitable exposure marker for low ambient CO levels. Furthermore, COHb is not a good effect biomarker. This is because the toxicity of CO occurs not only from the hypoxia caused by reduced capacity of the blood to transport oxygen but also via other mechanisms that are related to the intracellular concentration (partial pressure) of CO (36, 50, 69, 82).

COHb levels in workers from different occupations are summarized in (78) and ranged from 0.7% (production of chemicals) to 5.2% (foundry workers).

Toxic effects

The binding of CO to Hb, replacing oxyHb with COHb was long considered the main mechanism underlying CO toxicity. However, newer studies of low exposures suggest that CO may induce toxicity via several mechanisms including COHb formation, increased nitric oxide (NO) levels, oxidative stress, inhibited apoptosis, and effects on ion channels (69). For example, cellular energy metabolism is affected long after levels of COHb are decreased to normal. This can explain the lack of correlation observed between measured COHb levels and the severity of clinical effects (13, 50, 69, 82).

CO binding to other heme-containing proteins, such as cytochromes and myoglobin can result in cellular toxicity. Clinical outcomes include arrhythmias and cardiac dysfunction, direct skeletal muscle toxicity and loss of consciousness. Increased NO levels are believed to cause loss of consciousness and as an important factor leading to oxidative damage. Oxidative damage can cause increased brain lipid peroxidation and delayed neurological effects (69, 78).

The pathophysiological effects seen after CO-poisoning show similarities to effects observed with post-ischemic reperfusion injuries. Formation of reactive oxygen radicals during reperfusion has been suggested as the major cause of post-ischemic brain injury caused by CO (11, 84).

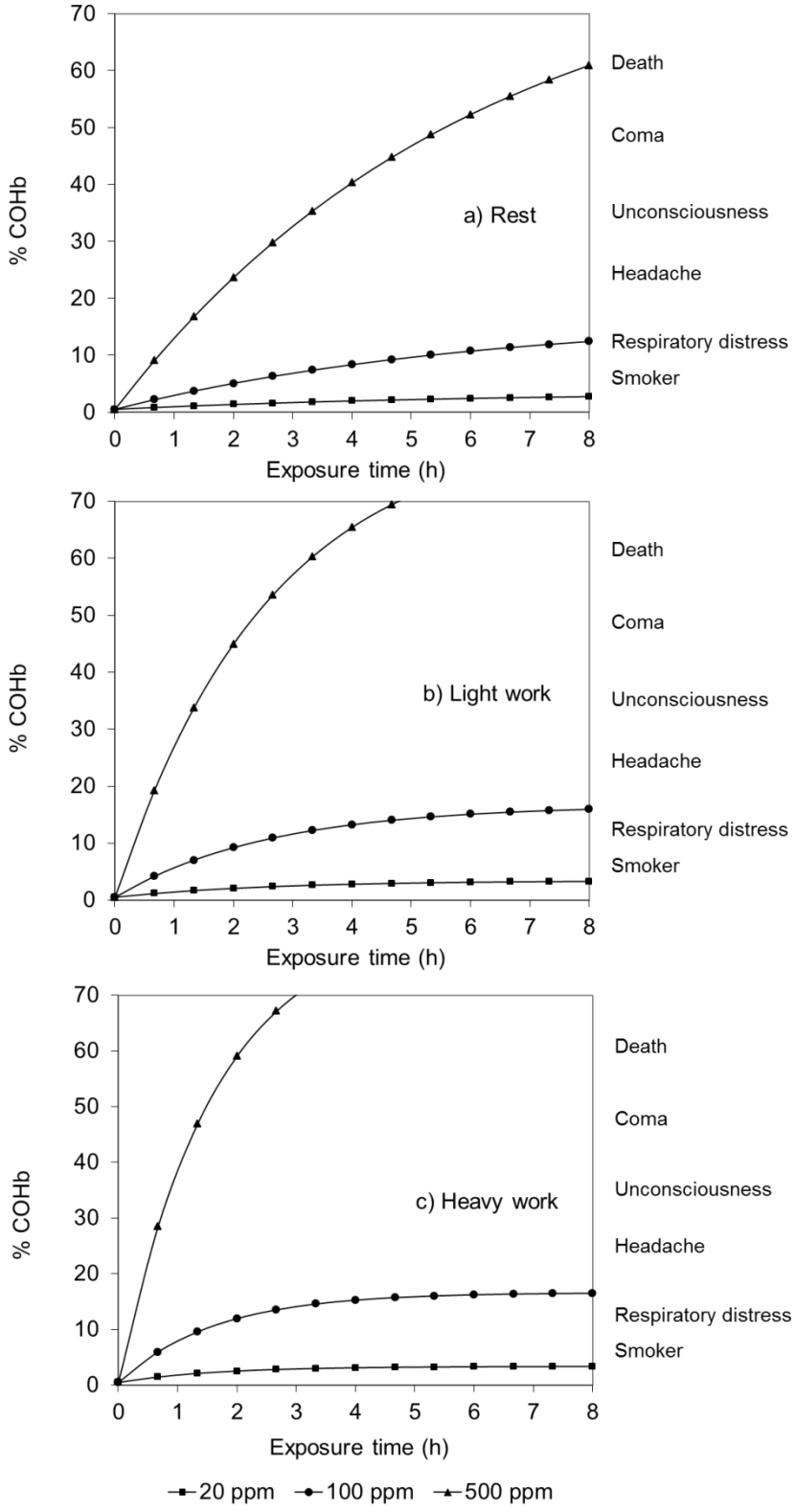

Figure 1. Calculated COHb levels for different CO exposure concentration - time combinations based on the Coburn-Forster-Kane (CFK) equation. COHb-levels at rest (a), light work (b) and heavy work (c) are shown. Figure modified from NEG (78). The relation between COHb and given health effects is approximate.

Halomethanes, such as dichloromethane, dibromomethane and diiodomethane, are metabolized to form CO. Co-exposure to halomethanes and CO could consequently lead to enhanced toxic effects. Inhalation of 100 ppm dichloromethane for 7.5 hours (at rest) can result in ca 4% COHb (57).

Human data

Exposure to high CO levels, leading to CO poisoning and resulting in COHb levels of 50-60% is often lethal. However, for susceptible groups such as persons with coronary heart disease and fetuses, CO may be lethal at lower concentrations (40). Symptoms after high exposures include severe headache, dizziness, nausea, vomiting, mental confusion, visual disturbances, reddening of the skin, compartment syndrome, fatigue, hypotension and coma. Effects seen after exposure to high levels of CO are summarized in (78).

Children are regarded as being more sensitive to the hazardous effects of CO. 177 children (4-12 years) by accident exposed to CO were examined in hospital. The children reported headache (139/177), nausea (61/177), dizziness (30/177), dyspnea (19/177), vomiting (13/177), abdominal pain (11/177) and drowsiness (9/177). The average COHb level was 7.0%. COHb was measured between 60-120 minutes after the exposure, which is a limitation of the study according to the authors (44). In another study 16 children with CO poisoning (COHb levels ranging from 17 to 44%, mean 27%) reported nausea (16/16), headache (13/14), vomiting (12/16), lethargy (11/16), syncopal episodes (9/16) and visual problems (3/14) (22). The time periods between the CO exposure and COHb measurements are not known.

Exposure to lower levels of CO may cause symptoms such as changes in time discrimination, visual vigilance, and choice response, although results are conflicting below 10% COHb (40). Levels of COHb as low as 3.4-4.3% have been associated with decreased physical work capacity (38), see below.

Cardiovascular effects

Studies reporting cardiovascular effects are summarized by Stockmann-Juvala (78).

Three persons out of 15 exposed to 15 ppm CO (COHb 2.4%) showed P-wave deviations in the electrocardiograms. Similar observations were found in 6 of 15 subjects that were exposed to 50 ppm (COHb 7.1%). However, there were no reports on smoking status of the subjects (23). The authors concluded that P-wave abnormalities found in the study probably were due to interference by CO with normal atrial pacemaking or conducting tissue activity, and that CO has a specific toxic effect on such tissue.

Four healthy volunteers were exposed to 75 or 100 ppm CO with corresponding COHb levels of 3.4 and 4.3%, respectively. In an exercise test after the exposure both levels of CO caused decreased lung ventilation at maximum performance and decreased maximal aerobic capacity was observed after exposure to 100 ppm CO (38).

Fifteen healthy men exposed to a mixture of air and CO, resulting in COHb levels of 5.1%, had decreased exercise duration and maximal effort after CO exposure. No ischemic electrocardiographic changes or disturbances in myocardial perfusion were found (2). In another study, CO concentrations resulting in COHb levels of 5-20% in 16 young healthy males did not cause any effects on cardiovascular functions (43).

Several studies have investigated the potential for CO exposure to enhance the development of myocardial ischemia during exercise in patients with coronary artery disease. In one study, decreased time to development of angina symptoms and ischemic ST-segment changes was observed after an exercise test at COHb levels of 2 and 3.9%. The CO exposure levels were set individually to reach the target COHb levels and ranged from 42 to 202 ppm (target 2% COHb) and from 143 to 357 ppm CO (target 4% COHb). The study involved men with coronary heart disease (3, 4). Other studies on patients with angina pectoris have shown similar results at COHb levels between 2.9 and 5.9% (1, 6, 8, 45). Significantly increased number of ventricular arrhythmias and increased heart rate during exercise were observed in patients with documented coronary artery disease (COHb levels 5.9%) (72).

Electrocardiographic changes among indoor barbeque workers occupationally exposed to CO were investigated. The average COHb level among the exposed was 6.5 and in the unexposed control group 2.2%. Several electrocardiographic parameters differed between the groups (with increased values for maximum P-wave duration, P-wave dispersion, maximum QT interval, QT dispersion and corrected QT dispersion in the exposed group). These parameters are known as predictors of atrial fibrillation, ventricular arrhythmias, and sudden death (71).

CNS effects

CNS effects are common health implications observed after acute CO poisoning and have been demonstrated in humans at COHb levels >20%. A decrease in visual and auditory vigilance and visual tracking have been observed in studies of healthy volunteers (COHb levels 5-20%) (83). A meta-analysis of the literature concerning CO exposure and behavior effects estimated that COHb levels of 18-25% are needed to cause a 10% effect in behavior (12). However, a recent review emphasizes that cognitive function may be impaired at COHb levels as low as 5% (82). In chronic CO poisonings exposure (over weeks to years), patients have experienced symptoms such as memory loss, dizziness, tremors, changes in sleep patterns, headaches, and emotional lability (82).

An increased risk of Parkinson disease has been observed in patients hospitalized for CO-intoxication (47). The study included 9 012 patients with and 36 048 without CO-poisoning, where the CO-intoxicated patients exhibited a 9.1-fold higher risk of developing Parkinson disease (95% CI 6.2-13.3) compared to the reference group (after adjusting for age, sex and several comorbidities). After 12 years of follow-up the cumulative incidence of Parkinson disease among the CO intoxicated was 1.5% higher than in the cohort of non-CO intoxicated. The cohort

of CO-intoxicated comprised mostly younger people and persons with more co-morbidities than those in the general population; however the CO-intoxicated patients with no comorbidity were more likely to develop Parkinson disease than the reference subjects. Thus, the authors conclude that the disease was caused mainly by CO itself (47).

Forty-five volunteers were exposed to CO from kerosene stoves (1.5-2.5 hours) at an average concentration of 61 ppm (SD 24, range 17-100 ppm). The average COHb-level was 4% (SD 3, range 1-11%) and correlated with air CO ($r = 0.39$). In neurophysiological tests (including tests for memory, attention and concentration, new learning ability etc.) the exposed group had lower scores compared to a control group of 47 subjects matched for age and sex. The exposed subjects had significantly lower test scores on 7 subtests, slightly lower on 4 (not significant), and slightly higher scores on 3 subtests (not significant) (5).

There are several case reports linking CO-poisoning with hearing loss in humans (41, 48, 56, 64). However, it is not clear if noise exposure is a prerequisite for the auditory effects seen after long-term occupational exposure to CO, as has been seen in some animal studies, because noise exposure estimates are normally lacking.

In a study from 1948, 700 patients suspected of having a CO-poisoning were examined. Most cases had been exposed to CO from gas generators used in automobiles. The average exposure duration was 6 years. Based on medical examinations and interviews, 263 of the patients were diagnosed with chronic CO-poisoning and among those 78% (205 patients) had hearing loss (reduced to 68% when other risk factors were considered). 63% of the patients with hearing loss reported tinnitus. The authors concluded that CO-intoxication was associated with hearing loss despite the lack of noise exposure. The results are presented in a Finnish thesis 1948, and reviewed in (41).

A database containing information on occupation, noise level, number of years of noise exposure, audiometric data and medical history (collected by Quebec National Public Health Institute 1983-1996) was examined. CO exposure for each occupation was estimated by 5 experienced industrial hygienists and audiologists. The exposure was not quantified; workers were assessed to be exposed or non-exposed based on their occupation. Workers were grouped into 4 different groups depending on their previous exposure: 1) CO + noise $\geq$90 dBA ($n = 1872$), 2) noise alone $\geq$90 dBA ($n = 2383$), 3) CO + noise <90 dBA ($n = 1031$) and 4) noise alone <90 dBA ($n = 1526$). Audiometric data was used to link exposure groups with effects on hearing. There was no effect of CO plus noise <90 dBA. Workers exposed to CO and noise $\geq$90 dBA had significantly poorer hearing thresholds at high frequencies than workers without CO exposure but with similar noise exposure. The shift in hearing threshold was dependent on years of noise exposure. The results imply that CO exposure increases the magnitude of hearing loss caused by noise. This study was presented as a conference proceeding and is reviewed in (41).

The effects of low levels of CO and noise exposure on hearing status were investigated in a group of workers. The participants were divided into 4 groups based on their exposure: 1) CO only (n = 2), 2) CO plus noise 85-90 dBA (n = 2), 3) noise only 90-91 dBA (n = 3) and 4) unexposed controls (n = 21). CO levels ranged from 16 to 35 ppm and COHb levels were between 2 and 3%. The combination of CO and noise exposure had an effect on hearing at 8 kHz (measured via both pure-tone audiometry and distortion product optoacoustic emissions). However, these results were based on data from two workers only. The results were presented in a French thesis and are reviewed in (41).

Effects on lung function

Among children in Taiwan and Germany positive associations between long-term exposure to CO and asthma have been observed (37, 39). However, as traffic air pollution contains several pollutants that may have strong correlations, it is hard to separate the effects ascribed to individual pollutants.

Animal and in vitro data

Exposure to high CO levels is lethal. The NEG document lists a number of lethality studies where COHb levels in rats that died were 50-80% and 57-90% in guinea pigs. CO concentrations of 4 000-5 000 ppm during 30 minutes in rats caused death in 50% of animals exposed (78).

Alterations of a number of hemodynamic parameters, such as increased heart rate, cardiac output, coronary perfusion pressure and contractility, and decreased tissue oxygen tension were observed in rats at CO exposure of 150-250 ppm (29, 42, 86). Ventricular fibrillation has also been found in dogs and monkeys exposed to CO, at corresponding COHb levels of 6.4% (dogs) and 9.3% (monkeys), respectively. A threshold reduction for ventricular fibrillation was found in dogs and in monkeys with acute myocardial injury. Exposure to 100 ppm for 2-6 hours (COHb 6.5%) reduced the ventricular fibrillation threshold in anesthetized normal dogs (9, 10, 25).

Results from repeated-dose short term (up to 13 weeks) animal studies are reviewed in the NEG document (78). The most common effects studied are hematological, pulmonary and cardiovascular effects. Hematological alterations occur as compensatory mechanisms as a result of the hypoxia induced by CO. These effects include increased blood volume, hemoglobin-, hematocrit-, erythrocyte count, and erythrocyte volume. Such changes have been observed in rats (≥7.5% COHb) and in monkeys (≥10% COHb) (78).

Intermittent (6 h, 5 days/week) or continuous (24 h, 7 days/week) exposure of healthy dogs to 50 ppm CO for 6 weeks caused histopathological changes (mobilization of glial cells and thinning of white matter) in the brain (1/7 dogs in the intermittent group, and 5/8 dogs in the continuous group). 100 ppm (intermittent and continuous groups) affected a greater proportion of dogs. These changes could be related to similar but more severe CNS changes seen at much higher exposures. Alterations in cardiac rhythm, heart dilation, and fatty degeneration of the heart

muscle were also observed after exposure to 50 and 100 ppm (65). The authors suggest that the CNS effects are secondary to cardiac effects, and that 50 ppm is an unacceptably high exposure.

Cardiac effects were also seen in monkeys exposed to 100 ppm (23 hours/day, 12 or 24 weeks, COHb 12%). Electrocardiograms showed higher P-wave amplitudes in both infarcted and non-infarcted monkeys, and higher incidence of T-wave inversion in infarcted monkeys (26).

Two recent reviews conclude that CO cause a potentiation of noise-induced hearing loss as observed in several animal studies (41, 89). The majority of the reviewed studies were performed in rats, a species less sensitive to acute CO intoxication compared to humans (41).

Genotoxicity

Genotoxicity caused by CO was studied in pregnant mice. One group of animals was given a single CO dose of 0, 1500, 2500 or 3500 ppm for 10 minutes on gestation days 5, 11 or 16. The other groups were exposed to 0 or 500 ppm CO for 1 hour/day on gestation days 0-6, 7-13 or 14-20. A dose-dependent induction of micronuclei and sister chromatid exchanges were found in bone marrow cells in maternal and fetal cell samples from animals in the first group. The same effects were observed in both maternal and fetal cell samples from the group exposed to 500 ppm at different gestation intervals (46). The Criteria group notices that the exposure levels used were high, and concludes that such high concentrations probably cause general toxicity, including oxidative stress.

Carcinogenicity

No studies were found.

Effects on Reproduction

There are several studies linking CO in ambient air to preterm birth, developmental disorders, reduced fetal growth or fetal death. However, in cases when CO in ambient air has been linked to health effects in epidemiological studies it is not possible to assess the contribution of CO to these effects, as these exposures were mixtures of compounds. The NEG document lists a number of studies on developmental effects of CO exposure during the gestational or early postnatal period (78). Here only the results and studies most relevant for setting an occupational exposure limit will be presented.

Human data

CO is transferred to the fetus via the placenta. Fetal hemoglobin has higher affinity for CO than maternal hemoglobin and pregnant women have a higher production of CO. Exposure to CO in ambient polluted air has been associated with preterm birth, developmental disorders, reduced fetal growth or fetal death,

also at relatively low CO levels, ranging from 1 ppm up to 12 ppm (11, 40, 50). However, air pollution contains several chemicals that may have similar effects, so the effects ascribed to individual pollutants has not been possible to separate.

A review article from 1990 summarizes a number of CO-poisoning cases of pregnant mothers, which resulted in fetal mortality or neurological complications in fetuses who survived (60). There was no information on exposure levels, but fetal outcome was poorer when maternal symptoms increased. In cases when the mother was conscious, fetal outcome was generally better. Furthermore, markedly elevated COHb levels were associated with adverse fetal outcome. In all but one case maternal COHb levels of 48% and higher resulted in maternal and fetal death (60).

Several retrospective cohort studies suggest that ambient CO exposure during the first trimester could be linked to preterm birth and reduced fetal growth (78). In a study from 1999 CO levels in California were measured at 18 stationary monitors. The cohort included more than 125 000 births (1989-1993) of mothers residing within 2 miles radius of the monitors. Exposure to >5.5 ppm CO in the outdoor air during the last trimester was associated with a significantly increased risk of low birth weight (OR 1.22, 95% CI 1.03-1.44). After adjustment for concurrent exposures to NO_2, PM10 and ozone the OR for CO effects increased to 1.38, but was not significant (95% CI 0.86-2.22) (67). The risk estimate was controlled for maternal education, and according to the authors there was an indirect adjustment for smoking because maternal age, race, and education are factors influencing the smoking behavior of pregnant women. A follow-up study in 2005 (1994-2000, cohort size 106 000 births), obtained a relative risk of 1.10 (95% CI 1.03-1.18) per ppm increase in air CO during the last 6 weeks of pregnancy. However, after adjustment for PM10 no significant association was seen (relative risk 0.98, 95% CI 0.83-1.16) (88). The risk estimate was controlled for maternal education but not for active or passive smoking. The effect of CO on preterm birth in a cohort including >97 000 births was evaluated by Ritz and colleagues in 2000. The relative risk was estimated to be 1.12 (95% CI 1.04-1.21) per 3 ppm increase in CO during the last 6 weeks of pregnancy, after adjustment for other risk factors and ambient air concentrations of NO_2, O_3 and PM10 (68). The study was insufficiently controlled for tobacco smoking and educational level, and the actual exposure of mothers could have been higher than the concentrations measured by stationary monitors.

Guatemalan children that were exposed in utero to indoor wood smoke in the third trimester had impaired neurophysiological performance at 6-7 years of age (27). CO was measured using passive 48-hours Gastec tubes fixed to the participants clothing and was 3.0 ±2.5 ppm (range 0.8-11.6, n = 20 mothers) during the second trimester and 3.8 ±3.0 ppm (range 0.6-12.5, n = 39 mothers) during the third trimester. CO levels were also measured from the mothers' infants during the first 9 months of life (2.2 ±2.0 ppm, range 0.3-9.8, n = 39 children). The mothers were interviewed (using questionnaires) to gather demographic and health information, including age when child stopped breastfeeding, home assets,

maternal education, environmental tobacco smoke exposure during the first year of life, mothers and child exposure histories etc. At the child's neurophysiological assessment (at age of 6-7 years) the exhaled breath CO was measured (averaged 2.3 ±0.9 ppm, all below 5 ppm) to detect any acute exposure. The neurophysiological assessment was built on several tests and included e.g. gross motor, fine motor speed and coordination, working memory and attention, short and long-term memory, visuo-spatial integration etc. The scores were compared to raw and age-standardized mean scores from developed countries. Child scores on 4 out of 11 neurophysiological tests were significantly inversely associated with maternal third trimester CO and included visuo-spatial integration, short-term memory recall, long-term memory recall and fine motor performance. The third trimester CO exposure appeared to influence the neurophysiological performance more than the second trimester or infant CO exposure. The authors suggest this may be due to that the (mothers') mean CO exposure and range of exposure was higher during third trimester compared to the exposure during the second trimester or infant period (27). The study, however, has several issues, e.g. that other potential risk factors in wood smoke were not measured. In addition, the mothers removed the measurement equipment before entering the sauna house (approximately once per week) and short term peak exposure, e.g. up to 150 ppm during cooking, was not captured by the passive monitoring method used. Furthermore, the households included in the study were located at >2600 meters above sea level and children living in this area are already under stress from lower oxygen levels, a factor that could affect the outcome (27). Possible confounders include other exposures (PAH, lead, pesticides) and maternal intelligence, which were not measured (27). According to the authors the birth cohort is ethically and age homogenously unique.

Studies have shown that prenatal and postnatal exposure to tobacco smoke (which contains CO) increases the risk of behavioral and cognitive effects in humans (91). Prenatal exposure to tobacco smoke has also been linked to hearing loss, for example as decreased performance in auditory tasks in the neonatal period, and unilateral hearing loss in adolescents. Hearing deficits caused by prenatal exposure may also contribute to cognitive and behavioral effects observed (91).

Animal data

Rabbits exposed to 90 ppm CO during gestation showed decreased birth weights and increased neonatal mortality (62). Rats exposed to 150 ppm CO during the gestational period showed reduced birth weight and decreased weight gain. Neurobehavioral and biochemical testing of the offspring revealed lower behavioral activity levels through the pre-weaning period, altered central catecholamine activity, and reduction in total brain protein at birth (30).

A study on rat pups exposed to 75-300 ppm CO during gestation until postnatal day 10, showed a decrease in body weights (79). Furthermore, CO caused lower cerebellar weight and decreased total cerebellar content of gamma-aminobutyric

acid (GABA) in rats at 10 and 21 days after birth. These results suggest that developmental processes involving GABAergic neuronal maturation and development of cerebellum as vulnerable to early CO exposure (79).

Effects of CO on the development of the CNS have been observed in a number of studies. Effects on aerial righting reflex (recovering from an upside-down to a dorsoventrally upward position during a linear downward free fall) were observed at postnatal day 14 in mice pups exposed to 65 or 125 ppm CO during pregnancy. Impairment of the righting reflex and negative geotaxis (an automatic orienting response and movement directionally against gravitational cues, used as a diagnostic of vestibular and/or proprioceptive function) were observed in pups exposed prenatally to 125 ppm on postnatal day 1 and 10, respectively (74). Delays in the development of negative geotaxis and homing behavior were also observed in rat pups of dams exposed to 150 ppm CO during gestation (31).

Learning and memory impairment was seen in an avoidance task at postnatal days 30-31 in male rat pups exposed to 150 ppm CO during gestation (55). Impairment of active avoidance behavior in a two-way active avoidance task was seen in 90-day-old rats and in 18-month-old rats after exposure of the mothers to 150 ppm CO during gestation. No effects were seen in a lower dose group (75 ppm) (24).

Chronic exposure to CO (12, 25 and 50 ppm) postnatally from day 8 to day 27 caused a decrease in c-Fos expression in central inferior colliculus (an area in the brain with auditory functions) in rats. They were fed automatically to minimize individual variation. c-Fos was used as a marker of neural activation as c-Fos has functional importance, and results were evaluated using an automatic tool for image analysis of immunohistology (85). The authors emphasize the importance of long term exposure and concluded that mild CO exposure (as low as 12 ppm) could permanently impair the developing auditory system of the rat (85). Semi-quantitative immunocytochemical methods were used and clear effects were seen at all three doses but no dose-response.

In newborn rats exposed to CO (12, 25, 50 or 100 ppm, days 6-22) attenuated amplitude of action potential of the eighth cranial nerve (vestibulocochlear nerve) was observed. The otoacoustic emission amplitude was reduced after exposure to 50 ppm, but not at lower concentrations (77).

Another study exposed CD-1 mouse pups to CO (0, 5, 100 ppm) for 3 hours on postnatal day 10. A total of 348 pups, both males and females, were evaluated (20). Extrapolation of postnatal day 10 in mice to the human timing in brain development is uncertain (21); however the authors suggested that this may correspond to an early postnatal time point or the end of the third trimester in humans (20). The authors found that CO exposure as low as 5 ppm caused an inhibition of developmental neuroapoptosis in hippocampus and neocortex (inhibited cytochrome c release, decreased caspase-3/7 activity, decreased number of activated caspase-3 positive cells and TUNEL positive nuclei). Learning, memory and social behavior were tested on the mice 4-5 weeks post-exposure, where exposed mice (5 and 100 ppm) showed signs of impaired memory retention and spatial

working memory. Exposed mice (5 and 100 ppm) also demonstrated signs of reduced social approach and greater avoidance (20). Release of cytochrome c from the mitochondria intermembrane space into cytosol is one of the most upstream events to initiate the intrinsic apoptosis pathway (20). Two more recent papers by the same research group, using a similar experimental setup, showed that CO levels as low as 5 ppm, given to 7 days old male mice for 1 hour, caused oxidative stress and affected apoptosis in certain regions of the brain (18, 19).

In a study on the developing peripheral auditory system of rats exposed to CO on postnatal days 8-22, swollen nerve terminals of the inner hair cells were observed at 25 ppm. No effects were seen at 12 ppm (51). Prenatal (day 5-20) or pre- and postnatal (day 5-20) exposure to 25 ppm CO caused decreased neuroglobin levels (quantified with an immunocytochemistry method) in the spiral ligament cells and spiral ganglia neurons in cochlea. Cytochrome c levels were also decreased in the spiral ligament, spiral ganglia neurons and in supporting cells. No significant changes were observed in rats only exposed postnatally (54).

Rats exposed prenatally, pre- and postnatally, and postnatally to 25 ppm CO showed signs of oxidative stress in the cerebellum. This included increased levels of superoxide dismutase (SOD1 and SOD2), and heme oxygenase (HO-1) in the cerebellar cortex, and an increase in inducible nitric oxide synthase (iNOS) and nitrotyrosine in blood vessels and Purkinje cells. Most significant effects were seen after prenatal and pre- and postnatal exposure (53). SOD1 and HO-1 levels were also increased in stria vascularis and in blood vessel walls of pups exposed to 25 ppm CO pre- and postnatally but not in those exposed only during gestation. iNOS and nitrotyrosine levels were increased in blood vessels of the cochlea of rats in both exposure groups (52).

Reduction of myelin sheath thickness of sciatic nerve fibers was found in both 40- and 90-day-old rats exposed in utero to 75 and 150 ppm CO (16). Another study on rats exposed to 75 or 100 ppm on day 0-20 of pregnancy showed effects on sodium channel development (17).

CO exposure (60-157 ppm) during pregnancy resulted in a dose-related increase in absolute and relative heart weight of newborn rat pups (63, 66).

Dose-effect/dose-response relationships

High concentrations of CO, leading to COHb levels around 50-60% is often lethal. However, lower levels of CO can lead to severe effects in susceptible groups such as fetuses or in persons with coronary heart disease (40). Symptoms at high concentrations of CO include e.g. headache, dizziness, nausea, mental confusion, and coma.

Genotoxicity has been observed in animals exposed to high CO-concentrations (500-3500 ppm) (46).

At lower levels several adverse effects appear and include e.g. cardiovascular and neurodevelopmental effects.

Cardiovascular effects

P-wave deviations have been observed in healthy individuals after exposure to 15 and 50 ppm (2.4 and 7.1% COHb, respectively) (23). However, the health relevance of these changes is uncertain as both statistical analyses and control for confounding factors were lacking, and the CO-induced vector changes were very small and not consistent between subjects. Furthermore, P-wave deviations are not uncommon and may occur as a result of stress. However, cardiac effects have been seen in monkeys exposed to 100 ppm (daily during 12 or 24 weeks, COHb 12%). Electrocardiograms showed higher P-wave amplitudes in both infarcted and non-infarcted monkeys, and higher incidence of T-wave inversion in infarcted monkeys (26).

Decreased lung ventilation at maximal performance has been observed in healthy volunteers after exposure to 75 and 100 ppm (3.4 and 4.3% COHb). A decreased maximal aerobic performance was observed at a level of 100 ppm CO (4.3% COHb) (38). Furthermore, decreased maximal effort and exercise duration at COHb levels of 5.1% has been observed in healthy subjects (2).

CO exposure has been observed to enhance the development of myocardial ischemia in patients with coronary artery disease. Decreased time to onset of angina symptoms and ischemic ST-segment changes was seen after an exercise test at COHb levels of 2 and 3.9% (CO exposure levels ranged from 42 to 202 ppm and from 143 to 357 ppm, respectively) (4).

Ventricular fibrillation after CO exposure has been observed in several animal studies (9, 10, 25). Furthermore, effects on several hemodynamic parameters such as increased heart rate, cardiac output, coronary perfusion pressure and contractility have been shown in rats after CO exposure (29, 42). P-wave deviations has also been observed in monkeys (26). In dogs, exposure to CO levels of 50 and 100 ppm caused alterations in cardiac rhythm, heart dilation and fatty degeneration of the heart muscle. Effects on CNS was also observed, but the authors suggest these being secondary to the cardiac effects (65).

Developmental effects

As CO is transferred to the fetus via the placenta, and because fetal Hb has higher affinity for CO than maternal Hb, and because pregnant women produce more CO endogenously, the fetus is considered to be more susceptible to environmental CO compared to adults. Preterm birth, reduced fetal growth and neurodevelopment has been associated with increased CO levels in ambient air pollution (50). However, ambient air pollution contains many components which co-variates and with similar effects, making the assessment of individual substances uncertain. Nevertheless, similar neurodevelopmental effects have been observed in animal studies, e.g. in rats exposed to 150 ppm CO during the gestational period (30). Lower behavioral activity during preweaning period, effects on cerebellum and delays in the development have been shown in animals exposed to CO. Learning and memory impairments has been seen in male rats exposed to 150 ppm CO during gestation (55). In mice exposed 3 hours on postnatal day 10 to low levels of CO (5 ppm),

inhibition of developmental neuroapoptosis was found in the brain and later impaired learning, memory and social behavior (20). Two additional studies by the same research group, where 7 days old mice were exposed to 5 ppm CO for 1 hour, supports the results (18, 19). The Criteria group notes that these three studies are performed by the same research group and using the same experimental setup.

Permanent changes in the developing auditory system of rats were observed in pups exposed to 12, 25 and 50 ppm CO postnatally (day 8-22) (51, 85) and in rats exposed to 50 ppm on postnatal days 6-22 (77). Rat pups exposed to 25 ppm CO prenatally (day 5-20) and pre- and postnatally (day 5-20) had effects on nerve cells in the cochlea (54).

Neurodevelopmental effects have been observed in Guatemalan children and significantly correlated to indoor CO from wood smoke (on average exposed to 0.6-12.5 ppm CO) in the third trimester (but not in the second trimester or in the infancy period). Postnatal exposure to CO was thus less well correlated and considering kinetics for CO it can be argued that a causative role for CO is favored in comparison to other factors in wood smoke and mentioned in the study. These children had impaired neurophysiological performance at 6-7 years of age (27). The authors conclude that although not by itself conclusive, this study suggests that a WHO 24-h Air Quality guideline of 7 mg/m^3 (6.1 ppm) may not be sufficiently protective. The study has several issues, e.g. other potential risk factors in wood smoke were not measured. Possible confounders include other exposures (PAH, lead, pesticides) and maternal intelligence, which were not measured. In addition, short term peak exposures were not captured by the monitoring method used. Furthermore, children living at >2600 meters above sea level are already under stress from lower oxygen levels, a factor that could affect the outcome.

Ototoxicity

Several studied have shown effects of CO on hearing loss, often in combination with noise. For example, CO levels ranging from 16-35 ppm in combination with noise caused audiometric hearing loss in two persons (41). Several animal studies have also shown combined effects with CO and noise (41).

Conclusions

Based on animal data, the critical effect of CO is neurological developmental effects. Effects on neuroapoptosis, brain development, learning and memory have been demonstrated in mice exposed postnatally (day 10) to 5 ppm CO for 3 hours or (day 7) to 5 ppm for 1 hour. Permanent changes in the developing auditory system of rats have been observed in pups exposed postnatally (day 8-27) to 12 ppm. There is a small observational study where an effect was seen in neurodevelopment in children whose mothers had been exposed to CO from wood smoke during pregnancy. The fetus is considered to be more susceptible to CO compared to adults.

At somewhat higher exposure levels CO causes cardiovascular effects. For example, decreased lung ventilation at maximal performance has been observed in

healthy volunteers after exposure to 75 and 100 ppm and decreased time to onset of angina symptoms and ischemic ST-segment changes have been observed in patients with coronary artery disease in an exercise test at exposure levels from 42 to 202 ppm CO (2% COHb) and from 143 to 357 ppm CO (3.9% COHb). In dogs, exposure to 50 ppm CO caused alterations in cardiac rhythm, heart dilation and fatty degeneration of the heart muscle.

CO exposure in combination with noise could lead to hearing loss.

Fatalities have occurred from extremely high short term exposure to CO.

Potential conflicts of interest

Gunnar Johanson (member) has declared that he contributed to The Nordic Expert Group's criteria document on Carbon Monoxide, published in 2012.

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Summary

Montelius J (ed). Swedish Criteria Group for Occupational Standards. *Scientific Basis for Swedish Occupational Standards.* XXXV. Arbete och Hälsa 2017;51(5):1-61. 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 January, 2015 through June, 2016.

Key Words: Carbon monoxide, Consensus report, Cutting fluid aerosols, Metal working fluid, MWF, Occupational exposure limit (OEL), Risk assessment, Scientific basis, Toxicology.

Sammanfattning

Montelius J (ed). Kriteriegruppen för hygieniska gränsvärden. *Vetenskapligt underlag för hygieniska gränsvärden.* XXXV. Arbete och Hälsa 2017; 51(5):1-61. 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 januari 2015 till och med juni 2016.

Nyckelord: Hygieniskt gränsvärde, Kolmonoxid, Riskvärdering, Skärvätskeaerosol, Toxikologi, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2017;51(4):1-60.

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
Aluminium	April 21, 1982	1982;24	III
revised	September 14, 1994	1995;19	XVI
Aluminium and aluminium compounds	December 4, 2013	2017;51(3)	XXXIV
Aluminium 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
revised	June 16, 2016	2017;51(5)	XXXV
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
Cutting fluid aerosols	June 16, 2016	2017;51(5)	XXXV
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
revised	December 10, 2014	2017;51(3)	XXXIV
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
revised	December 10, 2014	2017;51(3)	XXXIV
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
revised	September 1, 2014	2017;51(3)	XXXIV
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
Metal working fluid	June 16, 2016	2017:51(5)	XXXV
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
revised	December 10, 2014	2017;51(3)	XXXIV
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

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