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Scientific Basis for Swedish Occupational Standards XXXIV

Aluminium and aluminium compounds
Hydrogen fluoride
N,N-Dimethylformamide
Dichloromethane (Methylene chloride)

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

Translation:
John Kennedy, Space 360 and
Johan Montelius, the Swedish Work Environment Authority.
The consensus reports in this volume are translated from Swedish. If there is any doubt as to the understanding or interpretation of the English version, the Swedish version shall prevail.

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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 34th in the series, and contains consensus reports approved by the Criteria Group from November, 2013 through December 2014. The consensus reports in this and previous publications in the series are listed in the Appendix (page 125).

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of December 2014)

Maria Albin		Dept. Environ. Occup. Medicine, University Hospital, Lund
Cecilia Andersson	observer	Confederation of Swedish Enterprise
Anders Boman		Inst. Environmental Medicine, Karolinska Institutet
Jonas Brisman		Occup. and Environ. Medicine, Göteborg
Per Eriksson		Dept. Environmental Toxicology, Uppsala University
Sten Gellerstedt	observer	Swedish Trade Union Confederation
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Johan Högberg	chairman	Inst. Environmental Medicine, Karolinska Institutet
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Gunnar Johanson	v. chairman	Inst. Environmental Medicine, Karolinska Institutet
Bengt Järvholm		Occupational Medicine, University Hospital, Umeå
Bert-Ove Lund		Swedish Chemicals Agency
Johan Montelius	secretary	Swedish Work Environment Authority
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Per-Åke Persson	observer	SEKO
Agneta Rannug		Inst. Environmental Medicine, Karolinska Institutet
Bengt Sjögren		Inst. Environmental Medicine, Karolinska Institutet
Ulla Stenius		Inst. Environmental Medicine, Karolinska Institutet
Marianne Walding	observer	Swedish Work Environment Authority
Håkan Westberg		Dept. Environ. Occup. Medicine, University Hospital, Örebro

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[1] Drafted by Bengt Sjögren, Inst. Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, and Anders Iregren and Johan Montelius, Swedish Work Environment Authority, Sweden.
[2] Drafted by Birgitta Lindell, Swedish Work Environment Authority, Sweden.
[3] Drafted by Birgitta Lindell, Swedish Work Environment Authority, Sweden.
[4] Drafted by Ilona Silins, Inst. Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Consensus Report for Aluminium and Aluminium Compounds

December 4, 2013

This consensus report is mainly based on a criteria document from 2010 produced collaboratively by the Nordic Expert Group (NEG) and the Dutch Expert Committee on Occupational Safety (DECOS), which covers literature published up to and including April 2009 (30, 98), as well as on an earlier consensus report from 1995 (87) and an earlier criteria document from NEG (132). A final literature search was carried out in Medline in November 2012, but still later studies have in some cases been included. Only aluminium compounds that are used to a significant extent in Sweden have been assessed in this report; see Tables 1 and 2.

Chemical-physical data, Occurrence, Exposure

The oxidation number of aluminium is +3; the chemical-physical data for aluminium and soluble and insoluble aluminium compounds are summarised in Table 1. A long-lived radioactive aluminium isotope, ^{26}Al (half-life 716,000 years), which occurs naturally at very low levels, has been highly important in studying aluminium's toxicokinetics (109). For further Chemical-physical data, see the criteria document (30, 98).

In the Earth's crust aluminium is the most abundant metal, making up ca 8%, and the third most common element. Aluminium is reactive and therefore does not occur as the pure metal in nature, but only in various inorganic compounds. Aluminium oxide (Al_2O_3) is the starting material for the industrial production of the metal in which the oxide is enriched from the mineral bauxite. Pure aluminium is then produced via an electrolytic process (primary smelting) from a mixture of aluminium oxide and cryolite (Na_3AlF_6) (30, 98).

Metallic aluminium is a good conductor of electricity and heat, while its strength, plasticity and low density (ca 1/3 that of iron) mean it has major industrial applications. The metal is found in alloys with, for example, copper, zinc, manganese and magnesium. Aluminium has many areas of application, such as kitchen equipment, bodywork in the automotive and rail industries, aircraft, packaging material and building material. Aluminium powder is used as a pigment, in explosives and in pyrotechnic products (30, 98).

The amounts of aluminium and aluminium compounds used in Sweden in 2009/2010 are shown in Table 2. Sweden's only aluminium smelter produces a total of about 130,000 tonnes per year (personal communication from Eddy Magnusson, Kubal, Sundsvall, March 2011), and ca 50% of production is exported.

Table 1. Chemical-physical data for aluminium and aluminium compounds. For further data see the criteria document (30, 98). nd = no data, subl. = sublimates

Substance/ formula	CAS no.	Molar mass (g/mole)	Melting point (°C)	Boiling point (°C)	Density (kg/m^3, 25 °C)	Solubility
Poorly soluble or insoluble in water						
Aluminium	7429-90-5	26.98	660	2450	2700	Insoluble in water, soluble in bases and acids.
Aluminium oxide, Al_2O_3	1344-28-1 (1302-74-5 corundum)	101.9	2072	2980	3965	Practically insoluble in water, soluble in basic aqueous solution, practically insoluble in non-polar solvents.
Aluminium hydroxide, $Al(OH)_3$	21645-51-2	77.99	300	nd	2420	Insoluble in water and alcohol, soluble in acids.
Aluminium fluoride, AlF_3	7784-18-1	83.98	1291	1537, 1276 (subl.)	2880	Poorly soluble in water: 0.6 g/100 ml at 25°C, slightly soluble in acids and bases, insoluble in alcohol and acetone.
Aluminium phosphate, $AlPO_4$	7784-30-7	121.95	>1460	nd	2560 (23°C)	Insoluble in water, soluble in acids and bases.
Potassium aluminium tetrafluoride, $KAlF_4$	60304-36-1	142.1	560-575	19.5		4.5 g/l in water
Soluble in water						
Aluminium chloride hydroxide, $Al_2Cl(OH)_5$	12042-91-0	174.5	>100	nd	1900	Soluble in water.
Aluminium chlorohydrate, $Al_xCl_y(OH)_{3x-y}$	1327-41-9	nd	ca 80	nd	1340	Soluble in water.
Aluminium nitrate, $Al(NO_3)_3$	13473-90-0	213	73	135 (decom-poses)	nd	Soluble in water: 64 g/100 ml at 25°C; soluble in bases, acetone and HNO_3.
Aluminium sulphate, $Al_2(SO_4)_3$	10043-01-3 (7784-31-8, •18 hydrate)	342.1	700 (decom-poses)	nd	2710	Soluble in water, soluble in dilute acids, practically insoluble in bases.
Aluminium chloride hexahydrate, $AlCl_3•6H_2O$	7784-13-6	241.4	100°C (decom-poses)	-	2390	Soluble in water 477 g/l (20 ºC), decomposes. Incompatible with acids.
Aluminium chloride, $AlCl_3$ anhydrous	7446-70-0	133.3	190 (2.5 atm.)	182, 178 subl.	2440	Reacts explosively with water, with the formation of HCl gas.

Table 2. Amounts of aluminium and aluminium compounds used in Sweden in 2009 and 2010. Data from Kemikalieinspektionen's (The Swedish Chemicals Agency's) database (KemI 2010, http://apps.kemi.se/ kemistat/) and from Statistiska Centralbyrån (Statistics Sweden) (SCB 2010, http://www.scb.se/).

Substance	CAS number	Number of tonnes/year
Al, metallic, incl. alloys, import according to SCB	7429-90-5	285,000
Al, metallic, incl. alloys, export according to SCB	7429-90-5	190,000
Aluminium oxide	1344-28-1	211,600
Aluminium hydroxide	21645-51-2	105,200
Aluminium fluoride	7784-18-1	22,500
Aluminium phosphate (1:1)	7784-30-7	43
Aluminium phosphate (3:1)	1350-50-2	33
Potassium aluminium tetrafluoride	60304-36-1	5
Aluminium chloride hydroxide	12042-91-0	165
Aluminium chlorohydrate	1327-41-9	39,000
Aluminium nitrate	13473-90-0	11
Aluminium sulphate	10043-01-3	136,100
Aluminium chloride·$6H_2O$	7784-13-6	11,500
Aluminium chloride, anhydrous	7446-70-0	112

Pure corundum (alpha-Al_2O_3) is colourless and attractive crystals and are used as precious stones. Lower grade material is used as an abrasive, such as emery, which consists of impure corundum mixed with magnetite, hematite and quartz (30, 98). Aluminium sulphate and aluminium hydroxide have been used for purifying drinking water and waste water. Aluminium hydroxide is used as an antacid for neutralising excess gastric acid. Link, for example, is an acid-binding pharmaceutical; each tablet contains 700 mg or 1100 mg aluminium hydroxide. There is also Novaluzid which contains 140 mg per tablet (40). Aluminium compounds, e.g., Aluminium Starch Octenylsuccinate, can be used to improve consistency in cosmetics (2013-02-14: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple) and medical creams (40).

Aluminium chloride hexahydrate is used in antiperspirant preparations and a solution of aluminium acetotartrate has been used to treat skin conditions. Aluminium salts are now commonly used as adjuvants in a number of vaccines, e.g., against diphtheria, tetanus and hepatitis (30, 98). Aluminium phosphide, which forms phosphine upon contact with water, is used to control insects and rats in grain stores (20).

At pH values over 5.5 natural aluminium compounds mainly occur in insoluble forms, such as $Al(OH)_3$ or aluminium silicate. However, the presence of soluble organic material can affect solubility (67). The concentration of aluminium in naturally occurring water is generally below 100 µg/l unless the water is very acidic. The intake of aluminium from drinking water is therefore normally low in Sweden and, despite the fact that the water is sometimes purified using aluminium salts, the level of aluminium in drinking water is rarely elevated (>100 µg Al/l).

The permitted level of Al in water in the EU and Sweden is 100 µg/l [Livsmedelsverket (National Food Administration) 2013, www.slv.se].

There is no marked difference in the aluminium content of soft drinks and beer in glass or aluminium packaging as the cans are lacquered on the inside to prevent the aluminium dissolving. The concentrations of aluminium in soft drinks and beer are normally below 200 µg Al/l, although levels may increase with very long storage times in aluminium cans (Livsmedelsverket 2011-10-26, www.slv.se).

The aluminium concentration in foodstuffs varies considerably, depending on many factors, such as the agricultural location, fertilisers and additives (30, 98). The highest levels in foodstuffs are usually found in grain products and processed cheese. The calculated daily intake via food has been reported as 5-10 mg (153). Storing or cooking foods, especially acidic foods, in aluminium containers (including aluminium foils and disposable foil trays) can substantially increase the aluminium concentration in the food. So, for example, rhubarb soup boiled for 15 minutes in a new or old aluminium saucepan contained 33 and 39 mg Al/kg, respectively, compared with 0.1 mg Al/kg in rhubarb soup boiled in a stainless steel saucepan [Livsmedelsverket 2013-08-21, http://www.slv.se, "Aluminium i husgeråd" (Aluminium in household utensils)].

Table 3 lists some examples of aluminium concentrations in air, blood and urine, with occupational exposure to aluminium for various activities and occupations. It is evident from the Table that the highest aluminium exposures occur in the manufacture of aluminium powder and in aluminium welding (e.g., MIG- and TIG-welding[1]). The Table also gives some examples of blood and urine concentrations in reference groups.

Uptake, biotransformation, excretion

Studies of individuals occupationally exposed to aluminium have shown that inhaled aluminium is to some extent taken up by the lungs (30, 98). The uptake of aluminium by workers in the aluminium industry and by aluminium welders has been estimated as ca 1.5-2.0% on the basis of air levels and urinary excretion (109, 153).

[1] MIG (Metal Inert Gas) and TIG (Tungsten Inert Gas) are aluminium welding technologies which use inert shielding gases. MIG welding uses consumable electrodes whereas TIG welding uses a non-consumable tungsten electrode. MAG (Metal Active Gas) welding is a variant of MIG welding in which the shielding gas consists to a greater or lesser degree of carbon dioxide. MIG welding of aluminium generates particles with a mass median aerodynamic diameter of about 1.5 µm and the particles generated by TIG welding are of roughly similar size. The same study showed a generally similar proportion of ultrafine particles (<100 nm) with MIG- and TIG-welding of aluminium, 4 and 5%, respectively (29), while in other studies it was observed that the majority of particles with TIG welding of other materials were ultrafine (12, 81). Friction stir welding, which is used to weld aluminium, can generate a similarly high number of ultrafine particles as TIG welding (105).

Table 3. The concentrations of aluminium in air, blood and urine for a number of different activities and occupations, and blood and urine concentrations in some reference groups.

Activity (Ref.)	Air concentration, median (var.; n)		Plasma-/serum concentration, median (var.; n) (µg Al/l)	Urine concentration, median (var.; n)	
	Total dust (mg Al/m^3)	Respirable dust (mg Al/m^3)		(µg Al/l)	(µg Al/mg creat.)
Manufacture of Al powder (83)	– (5-21; –)		8.5 (<1.5-88.8; 52)	69.9 (3.1-1477; 53)	63.0 (8.5-934.7; 53)
Manufacture of Al powder (68)			9.0[1] (dl-21; 16)	83.0 (12-282; 16)	59.0 (12-139; 16)
Manufacture of Al paste (83)	– (1.1-3.8; –)		7.3 (2.3-30.0; 42)	19.4 (1.4-159.4; 47)	22.6 (3.9-159.4; 46)
Al smelter (primary) (119)	0.084 (–; –)	–; 0.031 (–; –)	6.41[2] (SD = 1.61; 28)	49.1[2] (SD = 20.3; 28)	
Al resmelting (57)	0.31[2] (0.04-0.9; 21)[3]				
Al resmelting (144, 145)	0.057[2,4] (0.002-0.54; 73)				
Al moulding (145)	0.029[2,4] (<0.001-0.94; 157)				
Al grinding (55)			11.9[1] (3.1-24.3; 51)	11.6 (1.3-37.1; 48)	6.2 (0.7-21.3; 48)
Al abrading (39)				–; 4 (1-18; 14)	
Al welding (MIG, TIG) (131)	1.1 (0.2-5.3; 16)			82 (6-564; 25)	54 (6-322; 25)
Al welding (MIG) (89)	2.1[2] (0.1-7.7; 34)	0.8[2] (0.2-2.2; 12)			
Al welding (TIG) (89)	0.17[2] (0.07-0.5; 13)	0.29[2] (0.07-0.56; 5)			
Al welding (MIG) (114)	1.1[2] (0.008-6.1; 24)		5.94[2] (0.81-12.4; 12)	91.8[2] (12.4-324; 12)	
Al welding (68)			3.0[1] (dl-27; 38)	22.0 (4-255; 38)	24.0 (4.5-162; 38)
Production of Al sulphate (114)	0.13[2] (0.02-0.5; 10)		3.51[2] (2.16-5.13; 5)	15.7[2]; (4.32-38.1; 5)	
Reference group[5] (83)			4.2 (<1.5-11.0; 39)	9.6 (2.4-30.8; 39)	7.7 (<1.9-20.2; 39)
Reference group[6] (68)			1.0[1] (dl-11; 39)	3.0 (dl-26; 39)	4.7 (dl-25; 39)
Reference group[7] (139)			1.62[2] (0.54-3.51; 21)	8.9[2] (1.89-22.1; 44)	

Var. =range; n=number of measurements; creat. =creatinine; dl=detection limit; – =not measured or not given
[1] Whole blood. [2] Mean value [3] Inhalable dust. [4] Geometric mean. [5] Reference group in the study of Letzel *et al.* (83). The group comprised 39 randomly selected individuals (26 women and 13 men) from the urban district of Erlangen-Nürnberg. [6] Reference group in the study of Iregren *et al.* (68). The group comprised 39 mild steel welders. [7] The group comprised laboratory personnel from three towns in southern Finland who had not been occupationally exposed to aluminium or used antacids. Serum samples were taken from 12 women and 9 men and urine samples from 28 women and 16 men (139).

It is not known what proportion of absorbed aluminium had been absorbed via the lungs or via the gastrointestinal tract after mucociliary transport and swallowing but the rapid increase in urinary concentrations during exposure to welding fumes indicates lung absorption (130, 153). Research subjects were exposed by inhaling aluminium oxide (^{26}Al) particles with an aerodynamic diameter of 1.2 µm. It is estimated that 1.9% of the aluminium initially deposited in the lungs is taken up into the blood (109). In welders and research subjects exposed to welding fumes with particle size varying between 0.01 and 1 µm, uptake was calculated as 0.5-1.5% while the alveolar deposition was estimated at 20% of the inhaled dose (114, 130). This portion of the uptake was based on the urinary excretion of aluminium in the days just after a single exposure. Another fraction of the material taken up was stored in the lungs from where it was slowly distributed into the blood and excreted via the urine. This portion has not been included in the above calculation of uptake (114). Using a similar calculation and an alveolar deposition of 10%, the lung uptake was 7% of the inhaled dose in individuals exposed to particles of soluble aluminium sulphate. Normal urine levels of aluminium were observed after going on holiday which indicates that exposure to soluble aluminium compounds does not result in an accumulation of aluminium in the lungs, despite occupational exposure of more than 20 years (114).

Uptake of aluminium via the gastrointestinal tract is low, usually less than 1%, and generally soluble aluminium compounds are absorbed better than insoluble ones (30, 67, 98). It is unclear how aluminium is taken up by the gastrointestinal tract (109). Its absorption is influenced by a number of factors. For example, it has been shown that simultaneous intake of organic acids, such as citrate and lactate, increases the absorption of both soluble and insoluble aluminium compounds (76, 153). In a study with two healthy volunteers Priest *et al*. (108) calculated an uptake [after administration of 100 mg isotopically labelled (^{26}Al) aluminium by gastric intubation] of 0.52% for aluminium citrate, 0.01% for aluminium hydroxide and 0.14% for aluminium hydroxide with citrate supplement (108). The absorption of aluminium, administered as a single large dose of $Al(OH)_3$ (antacid tablets, 4 x 244 mg Al) to 10 research subjects, was increased 8- and 50-fold when the aluminium hydroxide was given with orange juice or citric acid solution, respectively, compared with when given in pure water (142). In rats, the absorbed fraction was measured as 0.1, 0.7, 5.1 and 0.1% for aluminium hydroxide, aluminium citrate, aluminium citrate with extra citrate supplement, and aluminium maltolate, respectively, after administration of 40-200 µg isotopically labelled (^{26}Al) aluminium by gastric intubation (125). Iron deficiency has been shown in one study in rats to increase the uptake of isotopically labelled (^{26}Al) aluminium given as $AlCl_3$ by gastric intubation, whereas iron overload reduced uptake (147). Other substances, such as high concentrations of phosphate, fluoride and silicic acid, have been shown to reduce aluminium absorption (153).

Aluminium chlorohydrate is used as an antiperspirant. In one study a single dose of 13 mg aluminium (as ^{26}Al-labelled aluminium chlorohydrate) was applied

to the armpit of two research subjects and after 6 days the aluminium chlorohydrate that had not been absorbed was washed off. Based on urinary excretion, dermal uptake was calculated as ca 0.012% of the applied dose. The authors pointed out that this could not be extrapolated to dermal uptake with repeated application as it is probable that the pathways for uptake of aluminium would become saturated (42). The rate of uptake calculated on the basis of this study has been judged to be in the "extremely low" category (70). Yokel and McNamara (153) have calculated a daily aluminium absorption of ≥ 0.1 µg/kg for dermal exposure to 50-75 mg aluminium/day, with the assumption that the percentage uptake (0.012%) does not change during daily application of antiperspirant. This uptake is of the same order as aluminium uptake via food (153). In a later case report, a concentration of 3.9 µmol (105 µg) aluminium per litre plasma was observed in an individual who for four years applied 1 g antiperspirant cream containing 20% aluminium chlorohydrate to each armpit (53). The amount of aluminium applied each day was 108 mg. When aluminium exposure ended the aluminium concentration fell in both urine and plasma.

Some animal studies have shown that aluminium (in the form of Al-lactate, Al-chloride or Al-chlorohydrate) can be taken up through the nasal cavity and is transported into the brain via the olfactory nerves. The extent and significance of this uptake is not known (152).

The normal body burden of aluminium in non-occupationally exposed individuals is 30-50 mg. The skeletal system contains about 50% of the body burden and the lungs 25% (135). The amount in the lungs can be substantially higher in individuals occupationally exposed to fine, poorly soluble aluminium particles (115). Increased cumulative retention in the lungs has been observed in welders who have experienced long-term exposure (62). Increased cumulative retention in the lungs was also observed in a study in rabbits where the aluminium concentration in the lungs increased 158-fold after inhalation of 0.56 mg aluminium oxide/m^3, 8 hours/day, 5 days/week for 5 months (118). By contrast, long-term exposure to particles of soluble aluminium salts probably does not result in an increase in the lung burden (115).

Different studies have produced widely varying results for the distribution of aluminium between blood cells and plasma or serum (115). In plasma ca 90% of aluminium is bound to transferrin and ca 8% to citrate; less than 1% consists of aluminium hydroxide or aluminium phosphate (109). In the brain's extracellular space aluminium mainly occurs in the form of aluminium citrate (90%) (153).

A total of 0.28 mg isotopically labelled (^{26}Al) aluminium chloride was injected subcutaneously into pregnant rats on day 16 of gestation and various organs were analysed 5 days later. 0.93% of the injected radioactivity was found in the liver of the mother, 0.29% in the placenta, 0.23% in the whole foetus, 0.0038% in the foetal liver and 0.00038% in the foetal brain (154). Lactating rats were injected with 9 µg isotopically labelled (^{26}Al) aluminium chloride daily for 1-20 days post partum. On the 5th day aluminium concentration in the milk peaked at 0.3% of the administered dose/g milk (154).

Rats were exposed to aluminium oxide (Al_2O_3) in the form of nanoparticles (30 and 40 nm) or large particles (50-200 µm) via gastric intubation (500, 1000 and 2000 mg aluminium oxide/kg body weight). At the two highest doses of nanoparticles a statistically significant increase was observed in the uptake of aluminium in the blood, liver, spleen, brain, kidneys, and urine. At the dose 500 mg/kg body weight, an increase was observed in concentrations in the kidneys and urine (only significant for 30-nm particles). With the large particles there was no significant uptake (7).

95% of aluminium is excreted via urine and only a small proportion via faeces (67). Aluminium can also be excreted via breast milk. An average value of 24 µg Al/l (range 7-42 µg/l) was measured in 45 samples of human breast milk (no information is given on the mothers) (41).

Aluminium distributed in various compartments of the body is excreted in a multiphasic process. Using a model based on a research subject injected with ^{26}Al-citrate, a half-life of 0.04 days in blood and extracellular fluid was calculated, and a half-life of 1.43 days in soft tissues (including the liver), 6 days and 45 days in rapid and slow exchangeable pools, respectively, on bone surfaces, 1.4 years in trabecular bone and 29 years in cortical bone (109). Unpublished results with rats reported by Yokel 2000, indicate a long half-life in the brain. In rats given ^{26}Al-transferrin intravenously, no reduction in radioactivity was observed in the brain after 128 days (152). Previously non-exposed volunteer research subjects showed a half-life of about 8 hours for aluminium in urine after exposure to aluminium-containing welding fumes for one working day (130). A half-life of around 9 days was calculated for welders who had been exposed to aluminium for less than one year, while for welders exposed for more than ten years the half-life was 6 months or longer (131). Similar observations have been made in workers exposed to aluminium flake powder. Powder-exposed workers who were examined after a holiday of 4-5 weeks showed a half-life in urine of 5-6 weeks, while retired workers (6 months to 14 years after retirement) had half-lives varying from 1 to 8 years (86).

Biological exposure monitoring

As aluminium is commonly occurring it is very easy for blood and urine samples to be contaminated. This applies to both sampling and analysis. Normal values of around 100 µg per litre plasma or serum reported previously are the result of such contamination (135). A more recent study from Finland gives an average aluminium concentration of 1.6 µg/l (range 0.5-3.5, 95th percentile 2.7 µg/l) in serum of individuals who had not been occupationally exposed (laboratory personnel, n=21) and had not used antacids (139).

The normal concentration of aluminium in urine for non-occupationally exposed individuals is below 16 µg/l (95th percentile) (139). Aluminium in the urine has been proposed, and is used, as a measure of personal exposure but it is not possible to reliably translate urine concentrations into air levels (33, 115). Some equations describing how urine aluminium concentration correlates with exposure

to aluminium particles in the air have been produced for aluminium welding and electrolytic aluminium production (97, 106, 131). The uncertainty in the equations is large as they are based on relatively few individuals. With relevant occupational exposure levels for aluminium-containing welding fumes (about 1 mg Al/m^3, see Table 3) the equations give substantially different calculated urine concentrations, which can differ by a factor of three. The uncertainty is even greater with still lower exposure levels. One of the equations takes into account the number of years of exposure and produces the following empirical relationship: Urine Al (µg/l) = 41.7 x air Al (mg/m^3) + 6.7 x years of exposure – 4.6 (131). The relationship is based on urine samples taken directly after exposure to aluminium welding fumes and the group consisted of three previously non-occupationally exposed individuals who were exposed for one day as well as 22 welders who had been exposed for 0.8-21 years. This equation is used later in the report despite the uncertainty in the calculations in order to estimate air levels from measured urine concentrations in some studies; see below under the heading Dose effect/dose response relationships.

Despite a relatively low absorption of aluminium from the lungs, increased aluminium concentrations have been observed in the urine of a number of exposed occupational groups. Exposed individuals often have levels exceeding 100 µg/l with welding and with the production of aluminium powder and cryolite. Levels can sometimes exceed 100 µg/l in the production of corundum and the electrolytic manufacture of aluminium. It is unusual for levels to exceed 100 µg/l with the smelting, moulding and abrading of aluminium and the manufacture of aluminium sulphate (135), see Table 3.

Germany has a biological exposure limit for aluminium in urine of 60 µg/g creatinine (33). This concentration should be equivalent to 80 µg/l according to an equation presented by Riihimäki and Aitio (115). The Finnish Institute of Occupational Health (Arbetshälsoinstitutet) recommends a urine test in the morning, on the day after a weekend. The recommended upper limit for non-occupationally exposed individuals is 0.6 µmol/l (16 µg/l) and the level at which measures should be taken (the biomonitoring action limit) is 6.0 µmol/l (160 µg/l) (Arbetshälsoinstitutet 2013-10-01, http://www.ttl.fi/en/work_environment/biomonitoring/Documents/Guideline_for_specimen_collection092013.pdf).

Toxic effects

Respiratory system

Restrictive lung disease

Aluminosis, lung fibrosis resulting from aluminium exposure, was reported in Germany in the 1930s and 1940s, as well as in Sweden and England. However, similar cases were rarely reported in North America. The European studies showed that stamped aluminium powder even in the absence of quartz, caused lung fibrosis. Stamped aluminium powder is produced from unsmelted metal. This powder is used in the manufacture of pyrotechnic products as well as pigments.

Stamped aluminium powder has a large surface area because of the flake shape of the particles. Nearly all particles (95%) are less than 5 μm in size (analysis method not specified). The particles react with water, forming hydrogen gas and aluminium hydroxide. Granular aluminium particles which are produced from smelted aluminium, has a more regular particle structure and is not as reactive as stamped aluminium powder. To reduce the risk of explosions different types of lubricant are used in powder production, usually stearine or mineral oils. Lung fibrosis was first reported from industries using mineral oils, but later on cases were also reported from factories that used only stearine (135). In experiments with rats, lung fibrosis was caused to a similar degree by stamped aluminium powder with mineral oil, stamped aluminium powder with stearine and stamped aluminium powder without additives. Granular aluminium particles, on the other hand, did not cause lung fibrosis. According to the authors these results indicates that it was stamped aluminium powder which caused the lung fibrosis rather than any additives (27).

Since the 1990s several new cases of aluminosis have come to light in the German aluminium powder industry (74). A total of 62 workers from two aluminium powder manufacturers, who had been exposed to aluminium at what was presumed to be a high level of exposure, were investigated with respect to effects on the lungs (75). The median age was 41 years (22-64 years) and the median exposure time was 10.3 years (1-30 years). For 20 workers in the group the concentration of aluminium in the urine exceeded 200 μg/l (the biological exposure limit for Germany at that time). High-Resolution Computed Tomography, HRCT) revealed small, rounded changes, mainly in the upper parts of the lungs, in 15 of the 62 participants. Lung function measured as vital capacity was 10% lower in individuals with lung changes. The exposure time for this group was 13 years (6.5-30 years). 9 of the 15 workers had worked as stampers and were exposed to barely greased or non-greased aluminium-flake powder. Three workers had previously been exposed to asbestos and one to quartz. These 15 individuals had higher concentrations of aluminium in plasma and urine than did 47 individuals without any lung changes. 10 of these 15 had urine aluminium concentrations above 200 μg/l. Exposure had probably been higher previously as the median plasma concentration was then 85 μg/l (10-183 μg/l) compared with 28 μg/l (6-256 μg/l) at the time when the lung changes were investigated. The authors think that aluminosis is still an existing lung disease, even though it is now uncommon. With High-Resolution Computed Tomography the disease can be detected at an early stage (75). The Criteria group is of the opinion that there is a lack of clarity concerning the role of aluminium in the occurrence of lung radiological changes due to the absence of control groups, and that the pathological significance of this type of small change in HRCT is uncertain. Three individuals had previously been exposed to asbestos which however does not give these type of lung changes.

Aluminium welding over a long period of time has been associated with isolated cases of chronic interstitial pneumonia (58), pulmonary granulomatosis (23) and pulmonary fibrosis (62, 140).

The abrading and polishing of aluminium can sometimes create an extremely dusty work environment. One case of lung fibrosis (32) and one case of alveolar proteinosis (92) have been described. Interstitial fibrosis has also been reported in connection with the production of abrasives containing aluminium oxide (69).

Obstructive lung disease

Potroom asthma was first described in 1936 in the Norwegian aluminium industry (45). The electrolytic manufacture of aluminium (primary smelting) involves exposure to a large amount of various chemical substances, such as aluminium oxide, cryolite, polycyclic hydrocarbons, fluorides and sulphur dioxide. Asthma still occurs despite improvements in the work environment which have reduced levels of air pollutants. The introduction of prebaked electrodes reduced, for example, exposure to polycyclic hydrocarbons when compared with the earlier Söderberg electrodes.

A number of studies have tried to elucidate which chemical exposure is the main cause of potroom asthma. Thus an Australian study investigated 446 of 583 new employees (77%) at two aluminium smelters over a period of nine years (1995-2003). The group consisted of 326 men and 120 women. Symptoms and lung function were registered (2). Exposure to inhalable dust, fluorides, sulphur dioxide, polyaromatic hydrocarbons (PAH) and oil mist was measured. The occurrence of wheezing increased for men but not women during the measurement period. The increase was correlated with cumulative exposure to PAH, fluorides, inhalable dust (containing aluminium, etc.) and sulphur dioxide, but not oil mist. None of the exposure factors was correlated with FVC or FEV_1 but the ratio FEV_1/FVC was correlated with cumulative exposure to PAH, fluorides and sulphur dioxide. The incidence of bronchial hyperreactivity was significantly correlated with cumulative exposure to PAH, fluorides, inhalable dust and sulphur dioxide. Exposure levels for many chemical substances were strongly correlated with each other. Despite this, many effects were correlated with exposure to sulphur dioxide to a greater extent than exposure to fluorides. The authors conclude that sulphur dioxide, rather than fluorides, is the more likely cause of the symptoms observed (2). The Criteria group's assessment is that the contribution of aluminium to the emergence of potroom asthma cannot be established as it occurs in a very complex environment.

Reversible bronchial obstruction or asthma has been observed in the production of aluminium fluoride and aluminium sulphate (128). Between 1975 and 1976 a total of 13 asthma cases were reported at a Swedish plant which was producing aluminium fluoride; the exposure level was 3-6 mg aluminium fluoride dust/m^3 (measured in the breathing zone, n=15, no further information on dust measurements is given). In 1977 the work environment was improved and exposure was reduced to 0.4-1 mg/m^3. Over the period 1978-1980 there were only two cases of asthma. Over the period 1971-1980 an average of 37 individuals worked on the production of aluminium sulphate. For four workers the development of asthma was mainly associated with times of work when the exposure level was high. The

average level of aluminium sulphate dust varied from 0.2 to 4 mg/m^3 (no further information on dust measurements is given) (128).

According to a case report asthma has been associated with exposure to aluminiumchloride via inhalation in a worker at an aluminium foundry. An asthmatic reaction was observed in the inhalation provocation test with aluminium chloride but no reaction was observed with the same dose of potassium chloride. The report lacked exposure data from the foundry (21).

Potassium aluminium fluoride, including potassium aluminium tetrafluoride ($KAlF_4$), is sometimes used as flux in aluminium soldering (88). This exposure can also trigger asthma and bronchial hyperreactivity (61). A later study investigated 289 exposed individuals from an industry which used potassium aluminium tetrafluoride as flux (80). The control group comprised 118 non-exposed individuals from the same geographical area. Furnace operators and furnace engineers (n=74) had the highest exposure and median exposure was 0.33 mg $KAlF_4$/m^3. The median exposure for low-exposure workers (n=215) was 0.1 mg/m^3. The $KAlF_4$ level was calculated by analysing Al and K in total dust. Compared with the control group, both the low- and high-exposure groups of workers had significantly more frequent symptoms in the form of dry cough, nasal congestion, nosebleeds, and eye symptoms. The high-exposure group had significantly more frequent symptoms in the form of a feeling of tightness in the group, see Table 4, but the difference was only significant in the case of asthma symptoms and nasal congestion. A total of 39 exposed individuals had asthma symptoms and 16 were in the high-exposure group. These symptoms first appeared between a few weeks and 120 months after the start of exposure (median 12 months). None of the individuals with symptoms showed a positive skin prick test against potassium aluminium tetrafluoride (80).

A study of 50 aluminium-exposed workers was carried out at a shipyard in Sicily (1). The group mainly comprised welders (n=38) who worked with MIG- and MAG-welding. They were compared with a homogeneous control group of 50 non-exposed workers, all of whom had a serum aluminium concentration below 7.5 µg/l (mean value 6.4 µg/l). The average age of the groups was 31.8 and 31.5 years, respectively. The average exposure time was 11.8 years (range 5-21). Stationary measurements of dust concentrations in the air varied from 6 to 20 mg/m^3. The mean serum aluminium concentration in the exposed group was 32.6 µg/l. Data from spirometry was evaluated for VC, FEV_1, and $FEF_{25-75\%}$. Significant differences between the groups were observed for all variables that indicated restrictive and obstructive changes, and the effects were correlated with aluminium concentrations in serum.

Ozone is formed during gas metal arc welding (MIG/MAG) of aluminium. A previous study of aluminium welders showed that respiratory tract symptoms were related more to ozone exposure than to particle exposure (129). A case of asthma related to aluminium welding has also been described (141).

Table 4. Symptoms in controls and individuals exposed to potassium aluminium fluoride. Air levels (median) give the amount of potassium aluminium tetrafluoride measured in total dust (80).

Symptom	Cont-rols (%) N=118	Low exp. (%) median 0.1 mg/m^3 N=215	Odds ratio* low exp./ controls (95% CI)	High exp. (%) median 0.33 mg/m^3 N=74	Odds ratio* high exp./ controls (95% CI)
Chest tightness and wheezing	5.1	10.2	2.2(0.8-5.9)	23.0	6.3(2.3-17.3)
Breathlessness	3.4	7.0	2.2(0.6-7.3)	12.2	4.3(1.2-14.7)
Dry cough	3.4	14.9	4.6(1.5-13.9)	21.6	7.7(2.4-24.3)
Nasal congestion	13.6	26.5	3.5(1.7-7.0)	43.2	6.2(3.0-13.0)
Nosebleeds	2.5	21.9	11.0(3.2-38.1)	28.4	14.6(4.1-52.1)
Eye symptoms	4.2	18.1	6.3(2.3-17.8)	25.7	9.3(3.2-26.8)

*After adjustment for gender and age.

Central nervous system

There are several possible mechanisms for aluminium neurotoxicity. Exposure to aluminium has, amongst other things, been linked to increased oxidative stress, the formation of reactive oxygen species (ROS) and an increase in lipid peroxidation (78); see also below, under the heading Animal data. Aluminium increases the formation and cumulative storage of insoluble amyloid beta-protein and hyperphosphorylated tau-protein. It has been proposed that these changes are associated with the development of Alzheimer's disease (78, 152).

Haemodialysis

In the 1970s some haemodialysis patients contracted severe encephalopathy (5, 6), which proved to be due to a combination of aluminium in the dialysis fluids, the intake of aluminium-containing pharmaceuticals (to prevent hyperphosphataemia) and an inability to excrete aluminium because of renal insufficiency (15). Dialysis encephalopathy is a very serious disease from which 90% of patients die within 12 months of the first symptoms appearing if the condition is not treated. Dialysis patients with a serum aluminium concentration below 40 µg/l did not show an excess mortality rate but patients with serum concentrations in the range 41-60 µg/l had a 20% excess mortality rate and patients with serum concentrations above 200 µg/l had an excess mortality rate of nearly 70% (22). A dose-response relationship has also been observed between cumulative aluminium dose and the incidence of encephalopathy. In dialysis patients exposed to aluminium doses lower than 4 g the incidence of encephalopathy was less than 0.7%. A dose of 4-8 g resulted in 10% of patients developing encephalopathy whereas more than 18% of patients developed encephalopathy with a dose of over 12 g (124).

Aluminium powder

In a cross-sectional study (110) Rifat *et al*. assessed the cognitive functions of 261 Canadian mine workers (mainly uranium and gold mine workers) who had been exposed to ”McIntyre powder”. The control group comprised 346 non-exposed mine workers. ”McIntyre powder” was used in Canada during the period 1944-1979 as a prophylactic for preventing silicosis in mine workers. The mine workers inhaled the powder for 10 minutes [10-20 minutes according to ref. (111)] in the changing room before each shift. It was stated that the finely ground powder contained 15% aluminium and 85% aluminium oxide (Al_2O_3) and it was recommended that the concentration in the changing room should be ”20,000 to 34,000 parts per ml”. The participants were interviewed at home and were subjected to three cognitive function tests: Mini-Mental State Examination (MMSE), Raven's Coloured Progressive Matrices test (CPM) and Symbol Digit Modalities Test (SDMT). Adjustments were made to take into account completed degrees and immigration status; see Table 5. The exposed mine workers had significantly worse average results (total results for the three tests) than controls and a significantly greater proportion of them underperformed in one or more of the three tests. A dose-response relationship was observed between the proportion of mine workers with intellectual impairment and treatment time; see Table 5 (110). It is uncertain what levels of aluminium the mine workers were exposed to in this study as no air measurements were made. In a criteria document from 1992 Sjögren and Elinder give a calculated concentration of 30 mg/m^3 and refer to a personal communication by with David Muir (133). With this information, 10 minutes of exposure time and the stated composition of ”McIntyre powder”, an 8-hour time-weighted average of 0.375 mg aluminium/m^3 was calculated. The results reported in Rifat's study from 1990 (110) have been criticised for, amongst other things, the cross-sectional design in which inclusion in the study group and exclusion from the study group may have affected the result (24, 34, 76). In a proceeding from 1992 (111) Rifat commented on difficulties in the study, but also writes that differences in native language and in the level of education alone could

Table 5. The dose-response relationship (exposure time and intellectual impairment) was reported for mine workers exposed to ”McIntyre powder” and for those not exposed (110).

Treatment time (years)	Number	Prevalence* of intellectual impairment (%)	p-value**
0	346	5	
0.5-9.9	105	10	0.087
10-19.9	106	14	0.003
≤20	50	18	0.002

*Adjusted for age at the time of the test, years as a mine worker, native language, level of education, head trauma, tremor, blood pressure, and loss of vision and hearing.
**Exposed group compared with non-exposed group.

not explain the observed effects. Rifat later carried out a follow-up study which was recorded in the form of a report in 1997 (112) to Occupational Disease Panel (ODP) (the Criteria group has not had access to the report), which is commented on in ODP's annual report for 1997/98 (100). In this follow-up study no difference was observed in cognitive functions between mine workers exposed to the powder and those who were not exposed. The group with the longest exposure showed a small but non-significant increase in the risk of dementia. It is worth noting that some members of ODP urged caution in the interpretation of the data because the study suffered from a lack of power to detect risk due to the small sample size caused by the poor response rate. Therefore no definitive conclusion can be made from the follow-up study (100).

A German study (84) reported data on 32 workers exposed in the manufacture of aluminium powder. The control group from the same industry comprised 30 individuals. The study involved two measurement sessions separated by five years. At the second session the group numbers had been reduced to 21 and 15, respectively. The missing individuals had either declined to take part or were no longer employed in the industry. The subjects underwent a comprehensive battery of psychological tests and event-related P300 potentials were examined. At the first session median aluminium concentrations in urine were 109.9 µg/l (range 5.0-336.6) for exposed workers and 7.6 µg/l (range 2.6-73.8) for controls. At the second session the urine concentrations were 24.1 µg/l (3.4-218.9) and 6.5 µg/l (2-25.4), respectively. No effects of exposure were observed at either the first or second session (84).

Aluminium welding, see also Table 7

A study examined 17 aluminium-exposed welders (63), aged between 24 and 48 years (average 37 years), with rating scales for symptoms and mood, neuropsychological tests, EEG and auditory evoked responses. They had been welding for 5-27 years (average 15 years), but had been exposed to aluminium in MIG welding for only ca 4 years. The average aluminium concentrations in urine and serum were 75.5 (median 64.8) and 5.7 µg/l (median 4.9), respectively. All the welders performed normally in the psychological tests when compared with the standards used at the institute in Helsingfors, but the results from four memory tests were negatively correlated with the measure of biological exposure. The variability in reaction time also increased with increased exposure. There was a relationship between results for certain parameters from the quantitative EEG recording and the measure of exposure, but auditory evoked responses showed no such relationship.

A report from 1996 describes a cross-sectional study of welders exposed to aluminium (n=38) (68, 133). The results for the exposed group were compared with those for a matched control group comprising of mild steel welders (n=39). The median concentration of aluminium in urine was 22.0 µg/l (range 4 - 255) for those exposed; see Table 3. The research included questionnaires on symptoms a, comprehensive battery of psychological tests, EEG recordings and brainstem auditory evoked potentials. The group of aluminium exposed welders reported more

CNS symptoms (especially fatigue) than the control group. Four motor function parameters were also affected in aluminium-exposed welders. EEG or "evoked potentials" revealed no differences between aluminium-exposed welders and controls. A significant deterioration in motor functions was observed in a subgroup (n=19) consisting of aluminium welders with high concentrations of aluminium in the urine (median 59 µg/l, range 24-255 µg/l), when compared with a group (n=39) with low urine concentrations (average urine concentration ≥8.0 µg/l) (133). An examination of the original data in the study showed that the duration of exposure was 6 years for the individual who had 59 µg Al/l urine; i.e., the median concentration (the exposure time varied within the group between 1.4 and 10.5 years).

Two Finnish cross-sectional studies report data from partially overlapping groups of welders (4, 113). The report of Akila *et al*. presents data for a control group of 28 individuals (mild steel welders), a low-exposure group of 27 individuals, and a high-exposure group of 24 individuals. The two exposed groups welded aluminium. Average urine aluminium concentrations for the three groups were 12.4, 60.7, and 269.2 µg/l, respectively, and serum concentrations were 2.4, 4.6, and 14.3 µg/l, respectively (exposure time not given in the study). The groups were investigated using a comprehensive test battery. Significant differences between the groups were observed in several of the tests of attention and memory, and slower responses were also seen in a verbal test. Certain dose-effect relationships were also observed (4). The study by Riihimäki *et al*. reports the total estimated aluminium body load for 65 aluminium welders and 25 mild steel welders. All the welders were classified according to aluminium concentrations in urine and serum, respectively, and were divided into three groups: 25 controls, 29 low exposure and 30 high exposure. The median urine concentrations in these groups were 11, 49, and 192 µg Al/l, respectively, and the median serum concentrations were 2.2, 3.8, and 12.4 µg Al/l, respectively. The median exposure time was 4.7 years in the low-exposure group and 13.75 years in the high-exposure group. The groups were examined using a symptom questionnaire as well as psychological and neurophysiological tests. Significant differences were observed between the groups with respect to fatigue, memory and concentration, as well as emotional lability. No differences were observed in reported sensory and motor symptoms. Significant exposure-related negative effects were seen in the psychological tests for attention and memory in the high-exposure group when compared with the control group. The quantitative assessment of EEGs showed no differences between the groups but the visual assessment of EEG curves showed several small non-specific abnormalities in the exposed groups. Dose-effect relationships were observed for all psychological tests, apart from memory span. The authors concluded that the effect threshold for aluminium concentration in urine was 110-160 µg/l and in serum 6.7-9.4 µg/l (113).

A Norwegian study was published in 2000 which compared 20 aluminium welders with age-matched construction workers. Measurements included a symptom questionnaire and a psychological test battery consisting of a well-

established tremor test (Kløve-Matthews Static Steadiness test) plus tests of simple and complex reaction times from the computer-administered NES battery. The median concentrations of Al in urine were 41.6 µg/l (average 50.2 µg/l), with a range of 18.9-129.6. The urine samples were taken both before and after shifts (personal communication Rita Bast-Pettersen, 2013-05-13). Air levels of aluminium were measured using personal monitors with sampling in the breathing zone under the fresh air-fed welding helmet. Positive pressure supplied air respirators had been in use for ca 4 years before the study was carried out. A total of 69 full days of monitoring were carried out for 17 welders. The median concentration of aluminium in air was 0.91 mg/m^3 (average concentration 1.18 mg/m^3), with a range of 0.57-3.77 mg/m^3. For five of the welders, air and urine concentrations were measured two years before the study was carried out and it was observed that urine concentrations for these five had fallen from 94 µg/l to 67 µg/l (averages) and the equivalent measurements of average air concentrations had fallen from 2.05 mg/m^3 to 1.46 mg/m^3. The welders performed better than the construction workers in the tremor test but within the welding group there was a significant relationship between tremor (both dominant and non-dominant hand) and the number of years spent in aluminium welding. This relationship was statistically significant even when age was included in the regression analysis. There was no difference in performance between the groups with regard to reaction time but in welders a statistically significant relationship was observed between the concentration of aluminium in air and impaired performance (10).

Two longitudinal studies of aluminium welders in Germany were carried out in the car industry and amongst train and truck manufacturers. One study included 98 aluminium welders in the car industry and 50 assembly workers not exposed to aluminium (18, 73). The groups of aluminium welders and assembly workers were comparable with regard to gender (all men), age, education, physical workload and social background. Three repeated measurements were made at intervals of two years. After four years results for the symptom questionnaire and psychometry were compared for 92 welders and 50 controls. The median values for aluminium in urine after the shift were 48, 40 and 16 µg/l, respectively, for the three different measurement occasions and the corresponding plasma concentrations were 8, 4 and 4 µg/l, respectively. After two years the reaction time was longer for welders than for controls and aluminium concentrations in urine were correlated with reaction time (18). In the follow-up examination after four years, no significant differences between the exposed and non-exposed groups were observed in the various tests of psychological performance (73). In another study 44 aluminium welders working for train and truck manufacturers were compared with 37 non-exposed workers (19, 72). The number of participants had fallen to 33 welders and 26 controls after two years and to 20 welders and 12 controls after four years. The median values for urine aluminium concentration after the shift were 130, 146 and 94 µg/l, respectively, at the different measurement occasions and the corresponding concentrations in plasma were 12, 14 and 13 µg/l, respectively. The welders produced significantly worse performances in the Symbol Digit Modalities test,

the Block Design test, and to some degree in an attention test, but not in a reaction time test. The welders' reaction times improved from the first to the second examination (19). At the third examination the welders' average exposure time was 15 years. There were no differences between welders and controls with regard to psychological performances and there was no association between biological exposure indicators and psychological test results (72). Exposure levels were low in some of the studies and the other studies had shortcomings in the form of a substantial reduction in participation over the course of the examinations and the shortness of the follow-up period. The authors did not comment on the possibility that the effects might be reversible.

Exposure-related effects have been demonstrated in the four studies (10, 63, 113, 133), see above, which compare welders who work with aluminium with other welders or compare welders with high aluminium exposure to welders with low exposure, see Table 7.

An Italian cross-sectional study found a significant deterioration in cognitive performance (attention and memory) in aluminium welders (n=86) when compared with an occupationally non-exposed control group (office workers, n=90). A significant association was also observed between serum aluminium concentration in welders and effect on cognitive performance (14). The study was inadequately reported, including estimates of exposure, and therefore no conclusions can be drawn about effect levels.

A meta-analysis of 9 studies [two of the studies in Table 7 were included in the meta-analysis, refs. (10, 133)] was carried out, with psychological test results as the outcome examined. This analysis included a total of 449 exposed individuals and 315 controls, with the aluminium exposed subjects working as welders, foundry workers and electrolysis workers in aluminium production. The average urinary aluminium concentration in the different studies varied between 13 and 133 µg/l. The studies included used 6 different psychological tests which included a total of 10 performance variables. Exposed workers performed worse in nearly all the tests. They also recorded significantly worse results in the digit symbol test, which measures speed-dependent cognitive and motor performance (90).

Alzheimer's disease

Alzheimer's disease is the most common form of dementia. A relationship between aluminium and Alzheimer's disease was proposed after the discovery of higher levels of aluminium in the brain of deceased Alzheimer's patients when compared with levels in the brains of patients who had died from other causes (28). However, later results have been incongruent (152).

A case-control study examined 130 patients with Alzheimer's disease and the same number of controls. As the disease affects memory function, information was obtained from relatives. Controls were primarily selected from the patients' circles of friends. Patients and controls had to be married and to have been married for 10 years before the first symptoms of dementia had appeared. A relationship was found between the use of aluminium-containing antiperspirants and

Alzheimer's disease (OR 1.6, 95% CI 1.04-2.4) after adjustment for age, Alzheimer's disease in the family and previous head injuries (51).

Several epidemiological studies have found a relationship between the concentration of aluminium in drinking water and the occurrence of Alzheimer's disease, but these studies also do not present congruent results. Epidemiological studies have not been able to show a relationship between occupational exposure to aluminium and Alzheimer's disease. There is currently no scientific consensus on a relationship between aluminium exposure and the development of Alzheimer's disease (30, 44, 98, 121).

Bone

Aluminium-exposed workers (n=32) who produced aluminium powder were compared with non-exposed workers (n=29) at the same plant. The median aluminium concentration in urine was 110 µg/l in the exposed workers. No difference between the groups was found for bone density in the lumbar vertebrae (123).

Skin

There are only a few isolated case reports of sensitisation to aluminium caused by occupational exposure to aluminium and aluminium compounds. Bearing in mind that aluminium is a commonly occurring substance with many industrial applications, it is judged that the risk of sensitisation to aluminium with occupational exposure is very small (30, 76, 98).

Cases of aluminium-induced sensitisation and allergic contact dermatitis have been reported with repeated long term exposure of the skin to aluminium-containing antiperspirants and pharmaceuticals for topical use (30, 76, 98). A more common cause of sensitisation is when the metal has been injected, e.g., in vaccination with aluminium-adsorbed vaccines and aluminium-containing extracts for hyposensitisation (30, 76, 98), and studies in recent years show a relatively high frequency of aluminium sensitisation (11, 99). Of a total of 76,000 children 645 (0.85%) developed persisting itching nodules around the injection site (subcutaneous or intramuscular) after vaccination with aluminium hydroxide-adsorbed vaccines. The symptoms appeared 2 weeks to 5 years (median 3 months) after the vaccination and were prolonged (months, years). Of the children who developed itchy nodules 77% were patch test positive for aluminium (11) which according to the authors was an unexpectedly high incidence. An abstract reported that ca 10% of children (6-16 years) who had received subcutaneous immunotherapy with aluminium-precipitated antigen extract, developed contact allergy to aluminium (148). Aluminium compounds are added to vaccines and extracts for hyposensitisation because they prolong the adsorption time and increase the immunological response (adjuvant effect) (122). The most commonly used aluminium-based adjuvants are aluminium hydroxide and aluminium phosphate (17).

Heart disease

A study of quartz-exposed gold mine workers (n=1894) in Australia found that exposure to aluminium powder (inhaled to prevent the development of silicosis) possibly increased fatalities from heart disease (104). Some studies have shown an increased prevalence of heart disease amongst workers in the electrolytic production of aluminium (120, 136). This disease may be caused by the inhalation of particles and other airborne contaminants that are known to cause heart disease in urban environments (16). The main theory for explaining this relationship is that inhaling particles creates a low-grade inflammation in the lungs which increases the concentration of inflammatory markers and coagulation factors in the blood (16). One of these coagulation factors is fibrinogen. A slightly higher concentration of fibrinogen was observed in workers at an aluminium smelter who worked with Söderberg furnaces when compared with others who worked with prebaked electrodes. The median concentration of particles was higher with the Söderberg furnaces (1.9 mg/m^3) than with the furnaces which used prebaked electrodes (0.6 mg/m^3) (134). A Canadian study of aluminium exposed individuals who worked with Söderberg furnaces showed a relationship between cumulative exposure to benzo(a)pyrene and the prevalence of ischaemic heart disease (43). The Criteria group concludes that there is an association between ischaemic heart disease and the complex chemical environment, in which aluminium is one of many components, and that the contribution of aluminium cannot be determined.

Other effects

A 43-year-old woman sought medical care for leg pains and extreme fatigue. Over a period of 4 years she had used 2 g/day antiperspirant cream which contained 20% aluminium chlorohydrate. The aluminium concentration in plasma was 105 µg/l. After she stopped using the cream plasma concentrations returned to normal within 8 months and urine concentrations within 3 months, and her symptoms disappeared (53).

Genotoxicity, Carcinogenicity

Human data

IARC concluded in 1987 that there is sufficient evidence that certain exposures occurring during aluminium production cause lung and bladder cancer (64), and the same assessment was made in 2010 (Group 1, "Occupational exposures during aluminium production are carcinogenic to humans") (65). Armstrong *et al*. performed meta-analyses of several cohort studies. The pooled risk estimate for lung cancer was 1.16 (95% CI 1.05-1.28) with an exposure to benzo(a)pyrene of 100 $\mu g/m^3$ x years and was based on eight studies of workers at aluminium smelters. The risk estimate for bladder cancer, based on six studies, was 1.42 (95% CI 1.23-1.65) with a benzo(a)pyrene exposure of 100 $\mu g/m^3$ x years (65). The Criteria group is of the opinion that this excess risk of cancer of the lungs and urinary bladder is probably associated with exposure to polyaromatic hydrocarbons that

are produced by the electrodes in the electrolytic process and the group also concludes that the contribution of aluminium cannot be determined.

Synthetic abrasives which contain aluminium oxide, silicon carbide and other ingredients have been used for more than 70 years (143). Exposure to aluminium occurs both in the manufacture of these products and during their use in grinding and polishing. An increased risk of stomach cancer was observed in two studies (71, 143) and an increased risk of lung cancer in another study (127). To summarise, it is difficult to assess the importance of aluminium in the development of cancer with exposure to aluminium-containing synthetic abrasives.

Some have found an association between aluminium sand casting and an increased prevalence of lung cancer. This process involves exposure to several chemical substances. Quartz-containing sand is the material most suspected of causing lung cancer in these environments (126, 145, 146).

Animal data

Rats were exposed orally (gavage) to 212-2120 mg aluminium sulphate [$Al_2(SO_4)_3 \cdot 18H_2O$]/kg body weight per day (according to the Criteria group's calculations this corresponds to 17-172 mg Al/kg body weight per day) for 7, 14 and 21 days. Cells from bone marrow were examined and a dose-dependent reduction was found in the number of dividing cells, together with a dose-dependent increase in chromosomal aberrations, with chromosomal breakages predominating (116).

For 12 weeks rats were exposed via gavage to 10 mg Al/kg body weight per day in the form of aluminium lactate. An effect on the energy metabolism of mitochondria was observed in many parts of the brain, with a reduction in ATP, glutathione and superoxide dismutase and an increase in reactive oxygen species (ROS) in the hippocampus and corpus striatum (77). In another study using the same exposure, elevated levels of 8-OHdG (8-hydroxy-2-deoxyguanosine) were found in mitochondrial DNA in many parts of the brain. As a further measure of oxidative DNA damage, fragmented DNA was found in the genome. Increased expression of p53 protein was also observed in the hippocampus and corpus striatum in the aluminium exposed animals (77). It was concluded that aluminium caused oxidative DNA damage and an increase in p53 which may be involved in neurodegeneration (78).

Mice were exposed to aluminium chloride 10, 50 and 300 mg/kg body weight/day in the diet (corresponding to 2.02, 10.1 and 60.6 mg Al/kg body weight/day, respectively) for 100 days. Even with the lowest dose there was a decrease in superoxide dismutase in the hippocampus and cortex as well as an increase in malondialdehyde in the cortex. This study also revealed, at the lowest dose, higher levels of 8-OHdG in mitochondrial DNA and genomic DNA damage measured using the comet assay (117).

Aluminium chloride has been shown to be positive in a dominant lethal test in mice (54). Aluminium chloride at doses of 7 or 13 mg Al/kg body weight per day

was administered subcutaneously to male mice. For further details, see section Effects on Reproduction.

In vitro

A previous review of standardised mutation tests, in which bacteria or mammalian cells were used, sums up aluminium compounds as non-mutagenic (82). However, a number of studies with plants referred to in the review showed that aluminium salts can inhibit cell division and cause chromosomal aberrations. A recently published Chinese study with broad beans (*Vicia faba*) reports that aluminium chloride causes a significant increase in micronuclei and chromosomal aberrations at concentrations from 10 to 1000 µM (151).

In human peripheral blood lymphocytes aluminium chloride ($AlCl_3 \cdot 6H_2O$) causes oxidative DNA damage, increased micronuclei frequency, reduced repair of radiation-induced DNA damage, reduced cell division and apoptosis (9, 79). From 8.3 µM (224 µg Al/l) upwards a dose-dependent increase was observed in DNA damage measured using the comet assay, but at the highest concentration tested, 104 µM, there was a decrease (79). Also, the frequency of micronuclei increased in a dose-dependent manner over the concentration range 4.2-40 µM (112-1080 µg Al/l) but fell with the highest concentration (9). An increased frequency of DNA damage in the comet assay and of chromosomal aberrations was also observed when human blood lymphocytes were exposed to 5, 10, 15 and 25 µM aluminium chloride (corresponding to 135-675 µg Al/l). The increase was significant even at the lowest concentration (85).

Peripheral lymphocytes from healthy research subjects were exposed to aluminium sulphate at concentrations of 0.5-4 mM (14-108 mg Al/l). An increased number of micronuclei were observed even at the lowest concentration (91).

Micronuclei in lymphocytes and peripheral lymphocytes are significantly more common in Alzheimer's patients than in disease-free control individuals. When peripheral lymphocytes were treated with 1 mM aluminium sulphate (27 mg Al/l) the number of micronuclei increased significantly in lymphocytes from healthy individuals but not in lymphocytes from Alzheimer's patients (137).

Nanoparticles

Nanoparticles of Al_2O_3, 30 or 40 nm in size, did not induce any mutations in the Ames test with or without metabolic activation (8).

Hamster cells (Chinese hamster ovary cells, CHO-K1) were exposed *in vitro* to nanoparticles of Al_2O_3 (average size 28 nm). An increased frequency of micronuclei was observed at 0.5-10 µg/ml but no effect on the frequency of sister chromatid exchange was noted in the dose range 1-25 µg/ml (35).

Rats were exposed once via gavage to 500, 1000 and 2000 mg/kg body weight of aluminium oxide (Al_2O_3) with various particle sizes (30 nm, 40 nm and large particles, 50-200 µm). Exposure to the two highest doses of nanoparticles caused an increase in micronuclei in polychromatic erythrocytes from bone marrow, regardless of particle size. The total number of chromosomal aberrations increased

after 1000 and 2000 mg/kg of 30-nm particles and after 2000 mg/kg of 40-nm particles. Large particles had no effect on either the number of micronuclei or the number of chromosomal aberrations (7).

In the so-called ”19-dust-study” female rats were exposed to ultrafine particles of aluminium oxide and aluminium silicate, and to other granular biopersistent particles (GBP) with low specific toxicity (95). 29/44 (number of tumours per number of rats) malignant lung tumours developed after five weekly intratracheal administrations of 6 mg aluminium oxide, and 22/47 tumours developed after ten administrations of 6 mg, compared with 0/46 in controls. With the same doses of aluminium silicate 18/47 and 19/45 malignant lung tumours, respectively, developed, compared with the same control group. The outcome was similar with other GBP. In an unpublished report from industry (107) an almost identical experiment (probably the same study) gave median values of: 111 and 97 weeks, respectively, for the calculated survival time after the first exposure to aluminium oxide; 107 and 108 weeks, respectively, after the first exposure to aluminium silicate; and 111 weeks for controls (30, 98).

It is presumed that the development of lung tumours after intratracheal instillation is caused by particle overload in the rat's lungs. Overload means that the amount of particles exceeds the lung's ability to remove the particles (52, 66).

The ”9-dust-study” has been criticised on a number of points (138). The authors state that several factors indicate that the rat's clearing system is overloaded at the high dose rates used. With high dose rates the particles are distributed differently than with the low dose rates to which humans are normally exposed. In rats particle overloading leads to inflammation in a way that is not relevant to humans. The inflammation, rather than any specific toxicity, can explain the occurrence of cancer. For a further discussion of the lack of relevance to humans of particle overload in rats see ref. (103).

Effects on Reproduction

No information has been found on the reproductive toxicity of metallic aluminium, either for humans or for animals. There are few studies on the reproductive toxicity of aluminium compounds in humans and those that have been carried out are of doubtful relevance (30, 98) or have inadequate recording of exposure. In addition, no inhalation studies have been found in the literature which report the reproductive toxicity of aluminium compounds in animals.

The results of studies which examine the effects of aluminium compounds on reproduction are difficult to evaluate for a number of reasons. Those doses which affect fertility and have developmental toxicity effects often have general toxic effects in the parental generation. Also, the uptake of aluminium in the gastrointestinal tract is low, 1% or lower (31). The uptake varies according to which aluminium compound (soluble or insoluble) is administered and the manner of exposure (via gavage, drinking water or feed). Another factor which affects uptake is whether the diet contains substances that affect bioavailability, e.g., organic acids such as citrate, tartrate and lactate, or minerals such as calcium, magnesium

and iron (37, 47, 48). A comparison of studies in rats showed that orally administered insoluble aluminium hydroxide did not induce maternal toxicity or foetotoxic effects at doses (133 mg Al/kg body weight per day) which were ten times higher than doses of water-soluble aluminium nitrate which did induce such effects (47, 102). When aluminium hydroxide was administered concomitantly with citrate, maternal and foetotoxic effects were observed (50). Indications of similar effects were observed in mice when aluminium hydroxide was administered concomitantly with lactate (25).

Studies published over the period 1966-2008 were evaluated in a recently published assessment and classification of the effects on reproduction of aluminium and aluminium compounds by a Dutch expert committee (56). The committee concluded that there was insufficient data to classify metallic aluminium and insoluble aluminium salts according to their effects on fertility, their developmental toxicity and their effects on children via breast milk. Insoluble aluminium compounds did not induce maternal toxicity or effects on the foetus at those doses that were tested (however, see above for the concomitant administration of high doses of citrate or lactate). In these studies aluminium hydroxide was administered via gavage on day 6-15 of gestation, in doses up to ca 100 mg Al/kg body weight per day in mice (26, 36) and 266 mg Al/kg body weight per day in rats (49). It was concluded that there were insufficient data to assess the effects of soluble aluminium compounds on fertility but the committee did recommend that, with regard to developmental toxicity, water-soluble aluminium compounds should be placed in category 2 in accordance with DECOS's classification (”substances which could be regarded as if they cause developmental toxicity in humans”). The committee also recommended that soluble aluminium compounds be labelled with ”may cause harm to breastfed babies”. Table 6 presents the central studies, i.e., studies with relevant routes of exposure (via the gastrointestinal tract) and the absence of clear maternal toxicity, on which the expert committee bases its assessment of the developmental toxicity of soluble aluminium compounds (56). In summary, six studies showed neurotoxicity in offspring when mothers were exposed to soluble aluminium compounds during gestation and lactation.

Insoluble aluminium hydroxide is an acid-binding agent that is used in antacids and is placed in Category A in accordance with FASS's classification with respect to pregnancy, i.e., no known risks when used during pregnancy, and in Group I with respect to breastfeeding, i.e., no active substances pass over into breast milk (40).

In a recently published two-generation reproductive toxicity study (carried out in accordance with OECD's guideline 416) male and female rats (the F_0- and F_1-generations, 24 animals per gender per exposure group) were exposed to 0, 120, 600 or 3000 ppm aluminium sulphate in drinking water for 10 weeks up until mating. Exposure continued during mating, gestation and lactation. Aluminium exposure reduced water intake in all three groups and a transient weight loss was observed in the highest exposure group. Reduced body growth before weaning

Table 6. Summary of studies in the DECOS document which demonstrate the developmental toxicity of soluble aluminium compounds without any apparent maternal toxicity. The Table was modified from ref. (56). Expo. = exposure, GD = gestation days, PN = postnatally.

Dose, mg Al/ kg body weight per day	Species, Number of animals, Al salt, expo. route	Study design	General maternal toxicity	Effects on development	Ref.
0* 160 200	Rats, 12-14/ group, $AlCl_3$, feed	Expo. GD 8-21	None (feed intake, weight, behaviour)	No effect on litter size at birth. Increased mortality in both exposed groups PN days 1-18 and lower body weight days 1-7. Impaired neuromotor development up to day 9 PN in both groups.	13
0* 18 36 72	Rats, 4/group, $AlCl_3$, gavage	Expo. GD 8-20	None (body weight, behaviour, reproductive parameters)	Effect on neuromotor development in the two highest exposure groups.	93
0* 400	Rats, 6-9/group, Al lactate, feed	Expo. GD 1-7, GD 1-14, or GD 1-21	GD 1-7 and 1-14: None. GD 1-21 reduced feed intake and growth	No effect on litter size, mortality or birth weight. Impaired performance (GD 1-7 and 1-14) in negative geotaxis test, locomotor coordination test and operant conditioning test.	96
5-10 (control) 100-210 200-420	Mice, 16 divided into three groups, Al lactate, feed	Expo. during gestation and lactation	None (feed intake, weight, signs of toxicity)	No effect on pregnancy rate, litter size, gender distribution, and birth rate. Significant neuromotor effects in offspring were observed in both exposure groups at weaning and 14 days later.	38
1.4-2.9 (control) 100-210 200-420	Mice, 40/group, Al lactate, feed	Expo. during gestation and lactation. At weaning the young were given the adult diet or the control diet	None (weight)	No effect on length of gestation, litter size or birth weight. Increased aggressiveness in the highest dose group. Non-dose-dependent long-term effects on ”neurobehaviour”. Reduced grip strength days 150-170 PN (both exposure groups).	46
<1 (control) 10 50 100	Mice, 30-40/ group, Al lactate, feed	Expo. during gestation and lactation. At weaning the young were given the same diet as the adults up to day 35 PN, after which they received control diet.	None (weight)	No effect on litter size or birth weight. The 50- and 100-groups: reduced growth during suckling. 100-group, >90 days PN: impaired performance in Morris Maze test and motor activity test.	48

* The amount of Al in the standard diet was not given.

(day 21 postnatally) was observed in the highest exposure groups of the F_1- and F_2-generations and there was a reduction in relative spleen and liver weights at weaning as well as a delay in the opening of the vagina in F_1 females. At this point in time (ca day 30 postnatally) the females had a slightly higher body weight (non-significant) than the control group. No other exposure-related negative reproductive or developmental effects were noted, including mating parameters, fertility, gestation index and length, number of implantations and number of pups delivered, incidence of pups with malformations or variations, oestrous cyclicity and sperm parameters, anogenital distance, histopathology of sex organs in the parental generations or effects on neurobehavioral development. The authors concluded that 600 ppm aluminium sulphate in drinking water (equivalent to a total intake of 8.06-14.0 mg Al/kg body weight per day from drinking water and feed) is a NOAEL (no observed adverse effect level) in the study of parental systemic toxicity and reproductive/developmental toxicity. A dose of about 50 mg Al/kg body weight per day had no effect on the reproductive performance of the males (59). Regarding the delayed opening of the vagina in F_1 females, the authors point out that further studies are required before drawing any reliable conclusions on the effect on sexual maturity (59). The same research group also investigated aluminium ammonium sulphate (0, 50, 500 or 5000 ppm in drinking water) in a two-generation study which yielded largely the same results as the study with aluminium sulphate, see above. The NOAEL in the study of parental toxicity and reproductive/developmental toxicity was 5.35-9.36 mg Al/kg body weight per day (60).

The reproductive performance of male mice following exposure to aluminium was examined in a dominant lethal test (54). The study took place over 11 weeks and aluminium chloride was administered subcutaneously in doses of 0 (control), 7 or 13 mg Al/kg body weight per day, for the first 14 days. After 3 and 5 weeks of treatment the serum concentration was ca 200 µg Al/l in the low-dose group and ca 375 µg Al/l in the high-dose group (control group, ca 90 µg Al/l). After 11 weeks these concentrations had almost returned to control levels. No effect on weight or signs of general toxicity were observed in males during the period of the study. The relative weights of testes, epididymides and seminal vesicles were reduced by week 5 in the high-dose group. After exposure the males were mated with untreated females and the females which became pregnant were replaced by new females. The pregnant females were killed on day 16 of gestation and the uterus and foetus were examined. There was a substantial reduction in mating frequency and fecundity in both dose groups, most particularly around week 5. Significantly more post-implantation losses were seen in the treated groups, as well as increased foetal mortality and foetal haemorrhage, and reduced weight in live foetuses (weeks 3-8). The dominant lethal factor (post-implantation losses/ total implantations) was significantly elevated in week 5 (low-dose group) and weeks 5 and 6 (high-dose group). All effects were reversible and by the end of the study (week 11) had mostly returned to control levels. The authors concluded that aluminium affected the reproductive function of the males and may have caused

genotoxic abnormalities in sperm (spermatids and spermatozoa) (54). The authors did not comment on the high serum levels of aluminium in the control group but according to Krewski *et al.* (76) a reasonable approximation of normal serum levels is 10 times higher in research animals than in humans, i.e., 10-20 µg Al/l. Similarly high levels in control groups have been reported previously (94, 101, 149, 150).

Female mice were exposed to aluminium chloride via drinking water (calculated dose 300 and 600 mg Al/kg body weight per day) from day 1 of gestation until day 15 postpartum. Exposure resulted in a significant dose-dependent reduction in growth rate in offspring, along with a delay in opening of eyes and fur growth, and reduced reflexes during the suckling period. In addition, a significant dose-dependent reduction was observed in brain dopamine measured from day 7 to day 36 postnatally and serotonin was significantly reduced at the highest dose. After weaning (from day 22 postnatally, only male animals were studied) a reduction was observed in locomotor activity, learning capability and cognitive behaviour (3).

Dose-effect/dose-response relationships

Central nervous system

At high doses aluminium damages the central nervous system (CNS). In the 1980s haemodialysis patients developed severe encephalopathy. In dialysis patients exposed to aluminium doses lower than 4 g the prevalence of encephalopathy was less than 0.7%. A dose of 4-8 g resulted in 10% of patients developing encephalopathy whereas more than 18% developed encephalopathy with a dose of over 12 g. Dialysis patients could have very high serum levels of aluminium, over 100-200 µg Al/l (22, 124).

At lower exposure levels CNS effects (impaired cognitive and neuromotor functions) have been observed in individuals who have been engaged in welding aluminium. This has been examined in a limited number of studies most of which measured aluminium concentrations in urine but not levels in air, and the basis for establishing a relationship between air levels and effects on the CNS is very uncertain. Aluminium accumulates in the body, e.g., in lungs and bone tissue, and is released slowly from these storage sites. This makes it even more difficult to determine an air level at which CNS effects occur after occupational exposure to aluminium.

The Criteria group has focused on those studies that have compared aluminium welders with other welders or have compared high-exposure- with low-exposure-aluminium welders, see Table 7. Studies, e.g., refs. (72, 73), which compared aluminium welders with other occupational categories were regarded as less reliable because the selection criteria for worker inclusion in (and exclusion from) various occupations, as well as educational effects, could result in these other groups being substantially different from welders with regard to subtle psychometric variables.

One study found a significant relationship between tremor and the number of years of welding aluminium; also there was a deterioration in reaction time with increasing levels of aluminium in the urine (10). The median concentration of aluminium in air was 0.91 mg/m^3 (average 1.18 mg/m^3) with a range of 0.57-3.77 mg/m^3 and the median concentration of aluminium in urine was 41.6 µg/l (average 50.2 µg/l) with a range of 18.9-129.6. Urine samples were taken both before and after the shift. It is reasonable to assume that the urine samples taken after the shift would have higher concentrations than those taken before the shift. Welding helmets with positive pressure supplied air respirators were introduced four years before the study was carried out and measurements for some of the welders indicate that air and urine concentrations had been 40% higher two years previously (10). If one assumes that the reduction in exposure was the same for the entire group, then the exposure would have been about 1.3 mg/m^3 two years earlier.

Using an equation which took into account the number of years of exposure, the Criteria group calculated approximate aluminium concentrations in air from those in urine for three studies which lacked air concentrations as well as for the study of Bast-Pettersen *et al* (10), see Table 7: Urine Al (µg/l) = 41.7 x air Al (mg/m^3) + 6.7 x years of exposure – 4.6 (131). As this relationship is based on only one study (131) with few participants (n=25) there is a large degree of uncertainty in the calculated air concentrations, especially with low urine levels; this is reflected in the fact that several of the urine concentrations given in Table 7 result in calculated air concentrations that are below zero. No subsequent research has been carried out to validate this relationship. In addition, the equation presumes that urine samples are taken directly after exposure. This relationship was valid for one of the three studies which only gave urine levels (133); in this study the urine concentration was converted to a concentration after the work shift. This correction was not made in the other two studies (63, 113). As it is likely that the urine aluminium concentration was highest after the work shift the calculated air concentrations in these two studies underestimate the actual air concentrations. In summary, the three studies (in which the air concentration is estimated from urine levels) show CNS effects at air concentrations of 0.5-2.5 mg Al/m^3; see Table 7.

A cross-sectional study with highly uncertain exposure levels reported possible effects on the cognitive functions of Canadian mine workers who had been treated with aluminium powder ("McIntyre powder") (110).

No information has been found in the literature on CNS effects in occupational exposure to soluble aluminium salts.

Respiratory system

Some aluminium compounds, such as aluminium fluoride, aluminium sulphate, aluminium chloride and potassium aluminium tetrafluoride, have been linked with asthma:

Aluminium fluoride. 13 cases of asthma per 65 person-years were reported at an average exposure of 3-6 mg aluminium fluoride dust/m^3 (measured in the

Table 7. Air and urine aluminium concentrations in studies which compare aluminium welders with other welders or compare high-exposure- to low-exposure-aluminium welders.

Air concentration, mg/m^3 (range)	Urine concentration, µg/l (range)	Exposure time, years (range)	Calculated air concentration[1], mg/m^3 (range)	Number of exposed/ controls	Effect	Ref.
0.9 median, 1.2 average, (0.6-3.8), measured underneath respiratory protection	42 median, 50 average (19-130)	7 median, (2-21)	0[2] (0[2]-2.1)	20/20	Prolonged reaction time correlated with air concentration. Impaired motor function correlated with years of welding work.	10
	59 median, (24-255)	6 median, (1.4-10.5)	0.6 (0[2]-5.5)	19/39	Impaired motor function.	133
	192 median, (86-745), 110-160 effect threshold	13.75 median, (3.6-23)	2.5 (0[2]-15.8) 0.5-1.7	30/25	Impaired memory and concentration.	113
	65 median, 76 average, (24-165)	ca 4	1.0 (0.04-3.4)	17/-	Impaired memory correlated with urine concentration. Prolonged reaction time correlated with serum concentration.	63

[1] The aluminium concentration in air was estimated using the relationship Urine Al (µg/l) = 41.7 x air Al (mg/m^3) + 6.7 x years of exposure – 4.6 (131); see the text for further details. The median urine concentration was used in calculating the air concentration.
[2] The calculated air concentration was negative.

breathing zone). After the implementation of environmental improvement measures, average air concentrations fell to 0.4-1 mg/m^3 and the number of asthma cases fell to 2 per 129 person-years (128).

Aluminium sulphate. In the manufacture of aluminium sulphate the average exposure was 0.2-4 mg aluminium sulphate dust/m^3. A total of 4 individuals per 370 person years developed asthma. The asthma mainly occurred in association with work tasks known to involve high levels of exposure (128).

Aluminium chloride. A case of asthma was reported that was related to exposure to aluminium chloride in a foundry. No air concentrations were presented in the study (21).

Potassium aluminium fluoride. Exposure to potassium aluminium tetrafluoride ($KAlF_4$) has been associated with symptoms of the respiratory system and the eyes. In a low-exposure group (0.1 mg $KAlF_4$/m^3, in total dust) a significant increase was reported in the symptoms dry cough, nasal congestion, nosebleeds and eye problems when compared with a control group. With higher exposure

(0.3 mg $KAlF_4/m^3$) a significant increase was reported in asthmatic symptoms in the form of wheezing, tightness of the chest and breathlessness (80).

Genotoxicity, Carcinogenicity

Micronuclei were found in red blood cells of rats exposed to nanoparticles of aluminium oxide administered via gavage at 1000 or 2000 mg/kg body weight (7). Intratracheal exposure to nanoparticles of aluminium oxide or aluminium silicate (6 mg on 5 occasions) caused an increase in the number of malignant lung tumours in rats but no dose-response relationship was observed (95). The lung tumours may be explained by a rat-specific reaction to overloading of the clearing function.

Oxidative DNA damage and increased levels of p53 in the brain were observed in rats exposed for 12 weeks to aluminium lactate at 10 mg Al/kg body weight per day via the gastrointestinal tract (77).

A dose-dependent reduction in the number of dividing cells and an increase in chromosomal aberrations, with chromosomal breakages predominating, were observed in bone marrow cells from rats exposed orally to 17-172 mg Al/kg body weight per day (in the form of aluminium sulphate) for 7, 14 and 21 days (116).

Oxidative DNA damage was also observed in mice exposed to 10 mg aluminium chloride in the diet (equivalent to 2 mg Al/kg body weight per day) for 100 days (117). A dose of 2 mg Al/kg body weight per day is equivalent to inhalation exposure of humans to an air concentration of 0.2 mg Al/m^3, assuming a body weight of 70 kg, a caloric factor of 7 (the metabolic rate of mice in relation to body weight is ca 7 times higher than in humans), ca 1% absorption in the gastrointestinal tract, ca 10% absorption in the lungs, and an inhaled air volume of 10 m^3 over 8 hours. The calculation is very unreliable because it involves several approximated assumptions.

Aluminium chloride was shown to be positive in a dominant lethal test in mice (54) at doses of 7 or 13 mg Al/kg body weight per day administered subcutaneously.

Oxidative DNA damage (comet assay), micronuclei and chromosomal aberrations have been observed *in vitro* in human blood lymphocytes at aluminium chloride concentrations as low as ca 5 µM (ca 135 µg Al/l) (9, 79, 85).

To sum up, there is no basis on which to assert that aluminium and aluminium compounds cause cancer in humans.

Effects on Reproduction

Developmental toxicity was observed postnatally in animal studies in the form of increased mortality, reduced body weight gain, and impaired neuromotor and behavioural development when soluble aluminium compounds were administered via the gastrointestinal tract during gestation. In rats, effects on neuromotor development were observed in young when 36 mg Al/kg body weight per day (as aluminium chloride) was administered to the mother via gastric intubation on days 8-20 of gestation (93), and increased mortality, reduced weight and impaired weight

development were observed when 160 mg Al/kg body weight per day (as aluminium chloride) was given via feed on days 8-21 of gestation (13); see Table 6. Reduced growth was observed in suckling mice when 50 mg Al/kg body weight per day (as aluminium lactate) was administered via feed during gestation and lactation (48), as well as reduced grip strength in offspring when they reached adulthood if the mother was given 100-210 mg Al/kg body weight per day (as aluminium lactate) via feed during gestation and lactation (46); see Table 6. Two studies indicate that orally administered aluminium hydroxide, which is insoluble in water, can also induce maternal and foetotoxic effects in animals that are given citrate or lactate concomitantly (25, 50).

Effects on the reproductive performance of male mice (dominant lethal test) were reported after subcutaneous injection of 7 mg Al/kg body weight per day for 14 days (given as aluminium chloride), which resulted in serum levels of up to 200 µg Al/l (54).

A two-generation reproductive toxicity study in rats indicated that a total intake of 8.06-14.0 mg Al/kg body weight per day [via drinking water (aluminium sulphate) and feed] did not produce toxic effects in the parental generation or developmental toxicity in the offspring. It was concluded that the reproductive capacity of the males was not affected at a dose of around 50 mg Al/kg body weight per day (59).

Conclusions

The critical effect of occupational exposure to aluminium is the effects on the central nervous system (CNS). These effects (impaired cognitive and neuromotor function) have been observed in aluminium welders and are associated with exposure to sparingly soluble, fine aluminium particles, mainly in the form of aluminium oxide. There is no reliable data on which to determine at what levels of exposure these effects occur. In one study that reported CNS effects at a median air concentration of about 1 mg Al/m^3 air and a urine concentration of 42 µg Al/l, the exposure had previously been higher. In other studies of aluminium welders CNS effects have also been seen with roughly the same and higher urine levels. Reproductive toxicity studies in animals have also observed neurotoxic effects (effects on neuromotor development in offspring) after administering soluble aluminium compounds.

Aluminium compounds have been shown to be genotoxic in animal experiments. Aluminium compounds cause oxidative stress which can result in the genotoxic and neurotoxic effects that have been observed. Genotoxic effects have been reported at a dose of around 2 mg/kg body weight per day.

Asthma is the critical effect of occupational exposure to soluble aluminium sulphate and aluminium chloride, and to sparingly soluble aluminium fluoride and potassium aluminium tetrafluoride. Occasional cases of asthma have been reported in association with exposure to aluminium fluoride dust, when the average air concentrations were 0.4-1 mg/m^3, and to aluminium sulphate dust, when the average air concentrations were 0.2-4 mg/m^3. An association has been

seen between exposure to potassium aluminium fluoride compounds and respiratory symptoms at potassium aluminium tetrafluoride concentrations of around 0.1 mg/m^3 in total dust.

Potential conflicts of interest

Agneta Rannug (member) has declared that she has received some funding from L'Oreal which markets antiperspirants that contain aluminium compounds.

Gunnar Johanson (member) has declared that he contributed to The Nordic Expert Group's criteria document on aluminium, published in 2010.

The authors of the draft, Anders Iregren, Johan Montelius and Bengt Sjögren, have worked as authors of a chapter on aluminium in the book "Handbook on the Toxicology of Metals" (135).

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Consensus Report for Hydrogen fluoride

September 1, 2014

The subject of this consensus report is hydrogen fluoride. When taken up by the body hydrogen fluoride is converted to fluoride and data on the effects of other fluorides (principally sodium fluoride) have therefore been included in those cases where it is judged to be relevant. The report is mainly based on a previous consensus report on fluorides (61). Complementary data searches for hydrogen fluoride have been carried out in PubMed and Toxline, up to and including March 2014.

Chemical-physical data and occurrence

CAS no.	7664-39-3
Formula	HF
Synonyms	hydrofluoride
Molecular weight	20.01
Boiling point	19.5 °C
Melting point	-83 °C
pKa	3.45
Vapour pressure	90 kPa
Conversion factors	1 mg/m^3 = 1.2 ppm, 1 ppm = 0.8 mg/m^3 (20 °C, 101.3 kPa)

Anhydrous hydrogen fluoride is a colourless, pungent gas which mainly occurs as $(HF)_6$, but at higher temperatures is usually in monomer form (HF). Anhydrous hydrogen fluoride reacts strongly with, for example, sodium hydroxide, sulphuric acid and many organic compounds, and readily dissolves in water to form hydrofluoric acid. Commercial hydrofluoric acid usually contains hydrogen fluoride at concentrations up to 53%. Aqueous solutions of hydrogen fluoride fume at concentrations over 40-48%. Hydrofluoric acid salts are known as fluorides (11, 61).

Anhydrous hydrogen fluoride is used as a starting material in the production of various organic and inorganic fluoride compounds such as carbon-fluorine compounds, aluminium trifluoride, synthetic cryolite (Na_3AlF_6), alkylates in petrol, and also in the production of elementary fluorine. Hydrogen fluoride is also used in the synthesis of uranium tetrafluoride and uranium hexafluoride, both of which are found in the nuclear power industry. Hydrofluoric acid is used in, for example, pickling stainless steel (removal of surface impurities), derusting and cleaning of brass and cleaning of crystals, the manufacture of circuit boards and other electronic component and for etching enamel. Hydrofluoric acid has previously been used in glass etching. Other areas of use for hydrofluoric acid include

as a catalyst in condensation reactions, in oil refining (not in Sweden) and tanning hides (not in Sweden). In addition, hydrofluoric acid is used as a preservative and in dentistry (61, 68, 77, 86). A total of ca 2680 tonnes was used in Sweden in 2011 in 124 different chemical products, mainly in the metals industry (SPIN database 2013, www.kemi.se).

In the 1960s a survey of drinking water was carried out in Sweden which showed that about 500,000 individuals drank water with a fluoride concentration of over 0.8 mg/l (40 µmol/l) (61). A subsequent study reported that 18.2% of ca 30,000 sampling locations had fluoride concentrations between 1.5 and 4 mg/l and that 1.7% had concentrations ≥4 mg/l. High fluoride concentrations were primarily found in ground water in permeable rocks, particularly in private wells sunk into rock (69). Livsmedelsverket's (Swedish National Food Administration's) threshold limit for fluoride in mains water is 1.5 mg/l (60).

It is estimated that in 1981 adults in Sweden took in an average of 0.4 mg/day from food (e.g., from vegetables, fish and tea). In addition, it was estimated that 0.3 mg/day came from water and other drinks with low fluoride concentrations (≤0.2 mg/l) and 1.5 mg/day from water and other drinks with a fluoride concentration of 1 mg/l. The total intake was estimated at below 1 mg/day for large parts of the population (60).

Uptake, biotransformation, excretion

Hydrogen fluoride was absorbed almost 100% after inhalation by rats exposed to 36-176 mg F/m^3. It is thought that this is also the case in humans (61). Hydrofluoric acid has a permeability coefficient close to that of water, measured in a lipid membrane composed of lecithin and cholesterol. The skin and other tissues are rapidly penetrated by the diffusion of undissociated hydrogen fluoride and the same systemic effects can occur as with inhalation (11, 61). The rapid absorption of hydrofluoric acid seen after dermal exposure may also be due in part to the corrosive properties of the substance (61, 80). There is a lack of data on quantitative calculations of dermal uptake (61).

When fluorides, e.g., sodium fluoride, are administered perorally, hydrogen fluoride is formed in the acid environment in the stomach (80). Almost all the fluoride (99%) exists as hydrogen fluoride at pH 1.4 (68).

Following uptake there is an increase in fluoride levels in blood. Fluoride is not metabolised but can form complexes with, for example, calcium and magnesium. The substance is distributed to all the body's organs via the blood and binds reversibly to bone in the form of fluorapatite. Almost the entire body's fluoride content (99%) is found in bone and teeth (61). A study in humans showed that 1 hour after intravenous injection of ^{18}F, 40% of the administered dose was found in extracellular fluid; 20% had been excreted and 40% had been taken up by tissue (including 2.5% in the red blood cells) (61). The kidney is the most important organ of excretion, with 40-60% of the daily fluoride intake being eliminated renally. 5-10% of the daily intake of fluoride is excreted via faeces (61).

Fluorides can cross the placental barrier. There is a direct relationship between the mother's and the foetus' serum concentration (measured in umbilical cord blood), equivalent to 75% of the mother's serum concentration. Fluoride is taken up into mineralised tissues in the foetus, such as bone and teeth. Fluorides appear only to a limited extent in breast milk (61).

Biological exposure monitoring

Studies using different routes of exposure (oral and inhalation) have shown a relatively good correlation between exposure and fluoride concentrations in urine and blood in both experimentally exposed and occupationally exposed subjects (61). It has been reported that urine concentration increased by 4.6 mg/l (urine concentration measured after shift) when the fluoride concentration increased by 1 mg/m^3 during exposure to hydrogen fluoride from a bath containing hydrofluoric acid (61). In workers at an aluminium smelter there was an increase of 3.9 mg/l in the total amount of fluorides in urine over a 24-hour period, during which the fluoride concentration increased by 1 mg/m^3 (61).

Germany has a biological threshold limit for inorganic fluorides and hydrogen fluoride in urine of 4 mg/l (measured as fluoride after the end of exposure/after the shift) (20). Arbetshälsoinstitutet (The Finnish Institute of Occupational Health) in Finland recommends taking one urine sample in the morning after two days without exposure or one urine sample after work at the end of the working week and, as a concentration that should not be exceeded, gives 200 µmol/l (3.8 mg/l) in the morning sample and 350 µmol/l (6.6 mg/l) in the sample taken at the end of the working week. The upper limit for non-exposed workers is given as 100 µmol/l (1.9 mg/l) (2, 70). The concentration of fluorides in the urine of non-exposed workers is normally roughly the same as the fluoride concentration in drinking water (61).

Toxic effects

Effects on the skin, eyes and respiratory tract

Hydrogen fluoride and hydrofluoric acid have an irritant and corrosive effect on the skin, eyes and mucosa. Tracheobronchitis, pulmonary oedema and pulmonary haemorrhage, sometimes with fatal outcome, have been reported in accidents were hydrogen fluoride has been released and inhaled at high concentrations (61). Corrosive injuries in the respiratory tract (and metabolic disorders) can occur immediately or after a period of time (77). NIOSH has specified 30 ppm as an exposure level which is immediately dangerous to life or health (IDLH) (23).

Single exposures to high doses of irritative substances can trigger an asthma-like disease – RADS (Reactive Airways Dysfunction Syndrome) – in persons with previously healthy respiratory systems. A 26-year-old formerly healthy woman was exposed to hydrogen fluoride when she cleaned her toilet with a rust removing aqueous solution containing 8-9% hydrogen fluoride. After scrubbing for

1.5-2 minutes she experienced a burning sensation in her eyes, nose and mouth, as well as breathing difficulties. Her condition was diagnosed as RADS and involved permanent health problems in the form of breathing difficulties at exertion (61). So-called "potroom asthma" and other effects on the respiratory tract have been reported in workers involved in the electrolytic production of aluminium (aluminium smelter). An association with fluoride exposure has been demonstrated in a number of studies, but because of exposure to many other (irritant) substances, such as sulphur dioxide, it has not been possible to determine exactly what role fluoride compounds play in the development of such health problems. No sensitising mechanism has been described (61). Taiwo *et al*. (76) reported that fluoride in gaseous form (average exposure) and smoking were independent risk factors (multivariate regression analysis) for the development of medically diagnosed asthma in aluminium smelter workers (76). However, the study has been criticised with regard to the selection of participants and exposure data (1). Abramson *et al*. (1) showed in a relatively new study that sulphur dioxide may be more important than fluorides as a cause of at least some effects on the respiratory tract, e.g., asthma, in smelter workers.

An increased risk of nosebleeds was reported in a cross-sectional study of industrial workers exposed to hydrogen fluoride at a facility for flame brazing. Nine individuals in the exposed group (n=31) and 4 individuals in the control group (n=44) stated in a questionnaire that they had experienced blood in nasal discharge or nosebleeds almost daily. RR (relative risk, adjusted prevalence) was given as 3.6 (95% CI 1.1-11.0). For 2 of the 9 hydrogen fluoride-exposed individuals with nosebleeds, the problem had arisen after 1-3 months of exposure during the summer when hydrogen fluoride levels were low (it was not stated how many in the control group developed nosebleeds during this period). Examination of the nasal mucosa of 28 exposed individuals by rhinoscopy revealed scabs and bloody mucosa in 11 individuals. Eight of these had reported problems with nosebleeds in the questionnaire. The prevalence of medically diagnosed asthma was nominally increased, though not significantly, in the exposed group (adjusted RR=2.6, 95% CI 0.47-14.5). Air measurement showed that the concentration of hydrogen fluoride in the workplace was on average 1.0 mg/m^3 (0.8-1.1 mg/m^3, 2 samples in February) during the winter period (ca 4 months) and 0.15 mg/m^3 (0.05-0.4 mg/m^3, 16 samples in May/June) during the warmer period (ca 8 months). The authors stated that there were also irritant substances other than hydrogen fluoride in the facility but that the concentrations were low. They, therefore, concluded that the effects on nasal mucosa were caused by hydrogen fluoride (26). Most of those cases with nosebleeds appeared to be associated with the higher concentration which, however, was based on only two measurements. The Criteria Group is of the opinion that the causative association is unclear. The study, which was initiated because the industrial healthcare unit of the factory noted an increased occurrence of nosebleeds amongst employees, barely managed to produce significant results and had quite a high level of uncertainty in its risk assessment.

In an exposure chamber study 20 healthy research subjects were exposed to hydrogen fluoride for 1 hour. The participants were divided into three different exposure groups: 0.2-0.6 mg/m^3 (n=9), 0.7-2.4 mg/m^3 (n=7) and 2.5-5.2 mg/m^3 (n=7). Most were exposed on only one occasion (3 individuals on two occasions separated by three months). Two individuals had hay fever and one of them had a high level of IgE (the exposure group of these two was not specified). Symptoms of the eyes and of the upper and lower respiratory tract were recorded before, during and after exposure using a questionnaire in which the symptoms were graded from 0 (”no symptoms”) to 5 (”most severe”). Pulmonary function was measured before and after exposure. Symptoms of the upper respiratory tract (itching/irritation/soreness in the nose and throat) increased with greater exposure. In the group with the lowest exposure mild symptoms were reported in 4 out of 9 individuals (p=0.06) and in the medium-exposure group in 6 out of 7 (p=0.10). In the highest-exposure group all the research subjects reported symptoms (4 had mild and 3 had strong symptoms) (p=0.02). No clear dose-response relationship was observed for symptoms of the eyes (itching/irritation, soreness) and of the lower respiratory tract (soreness, cough, coughing up sputum, tightness of the chest, wheezing). Almost all symptoms had disappeared 4 hours after exposure. No change in FEV_1 was observed in the study. A small (significant) reduction in FVC was observed in the lowest-exposure group but not in the other groups. This finding can therefore not be interpreted as an effect of exposure (52). There were only a few research subjects and they were not subjected to zero exposure to accustom them to the chamber. It is, therefore, difficult to assess the effect of the lowest exposure. The most probable LOAEL in the study was evaluated as 0.7-2.4 mg/m^3 (61).

In a later study (53) in which research subjects (n=19) were exposed to hydrogen fluoride (<0.6, 0.7-2.4 and 2.5-5.2 mg/m^3) for 1 hour, there was a significant increase in the proportion of CD3-positive cells in the bronchoalveolar portion of the bronchoalveolar lavage fluid at the highest exposure and in the bronchial portion at the two highest exposures. At the highest exposure there was also an increase in myeloperoxidase and interleukin-6 in the bronchial portion of the bronchoalveolar lavage fluid. The result was interpreted as the expression of an inflammatory reaction. Bronchoalveolar lavage was carried out 3 weeks before exposure and 23 hours after the end of exposure (53).

In another study the same authors reported symptoms of the upper respiratory tract as well as signs of an inflammatory reaction in the nasal mucosa at exposure for 1 hour to 3.3-3.9 mg HF/m^3 (n=10). 7 out of 10 healthy research subjects reported problems in the upper respiratory tract associated with exposure (two individuals grade 1, three individuals grade 2, one individual grade 3 and one individual grade 4). With nasal lavage it was shown that, amongst other things, there was a gradual increase in neutrophil granulocytes and in the total number of cells. An effect on the concentrations of TNF-α and various eicosanoids was also reported. Nasal lavage was performed immediately before exposure, directly after exposure and 1.5 hours after exposure (54). In a further study (55) bronchoalveo-

lar lavage (n=10) was carried out two hours after the end of exposure (3.3-3.9 mg HF/m^3, 1 hour). A significant reduction was observed in neutrophil granulocytes, lymphocytes and the total number of cells in the bronchoalveolar portion (no significant changes in the bronchial portion). Significant reductions were also reported in the concentrations of, for example, interleukin 6 (bronchoalveolar portion and bronchial portion) and interleukin 8 (bronchial portion only). TNF-α was not found in any sample and no significant changes were observed in analysed eicosanoides or antioxidants. Nor were any significant changes seen in FVC or FEV_1. The authors concluded that exposure did not cause acute inflammation in the lungs after 2 hours and that the results indicated different time periods for the development of inflammation in the nose and lungs after exposure to hydrogen fluoride (53, 54, 55).

In a small chamber study 5 research subjects were exposed for 6 hours/day, 5 days per week for 10-50 days to individually varying air concentrations of hydrogen fluoride, at average values (n=6, i.e., for one person 2 average values were given) of ca 1.1-3.8 mg/m^3. The research subject who had an average exposure of ca 1.1 mg/m^3 (range 0.7-1.6 mg/m^3) for 15 days reported a mild tingling sensation in the face (skin, eyes), but experienced no skin flushing (Table 1). At somewhat higher air concentrations all research subjects developed symptoms in the form of a mild tingling sensation in the skin, eyes and nose, as well as skin flushing and peeling, as with mild sunburn. No effects in the lower respiratory tract were reported (46, 61). Exposure of the eyes to higher concentrations leads to reddening, oedema, photophobia and corneal necrosis (61).

Hydrofluoric acid can be highly corrosive on the skin. In the first instance localised burns arise as a result of hydrogen ions being released. Penetration of fluoride ions down into the underlying tissue then causes more deep-seated damage (local cell death, systemic toxicity). This gives rise to intense pain after a dose-dependent latency period. Concentrations >50% (including anhydrous hydrogen fluoride) result in immediate, severe pain and a whitish discolouration of the skin. Concentrations <20% cause virtually no acute pain upon contact, but can cause severe delayed injury 12-24 hours later. Injuries can occur in deep-seated tissue and bone, even if the overlying skin has not been markedly affected (5, 61, 73, 86). Absorption through the skin can lead to serious, sometimes fatal, poisoning (Table 2).

When 0.05, 0.1, 0.2 and 1% hydrofluoric acid was tested on mouse skin *in vivo* (effects on the skin were evaluated after 2 and 24 hours) signs of localised inflamamation were observed and in 5/6 animals focal erosions of the epithelium were seen after 24 hours of exposure to a 1% solution. No burns were observed with 2 hours exposure to a 1% solution (34). Another study (19) reported that hydrofluoric acid was corrosive on rabbit skin in patch testing (occlusion) with 0.01, 0.1, 0.5 and 2% hydrofluoric acid for 5-60 minutes (rinsed with water for 30 seconds). The skin was studied for 4 days and an increased incidence of animals with skin damage was observed at all concentrations after just 5 minutes of application (non-dose-dependent), whereas no damage was observed with a

1-minute application of 2% solution (the only concentration tested). A previous study reported no discernible skin reaction upon application of ≤4% hydrofluoric acid in rabbits for 5 minutes and a subsequent rinse for 15 minutes (43).

Dose-dependent irritation was shown in an *in vitro* test in hens eggs (HET-CAM, an *in vitro* alternative to the Draize test on rabbit eyes), using 0.05, 0.1, 0.2 and 1% hydrofluoric acid. The 0.1, 0.2 and 1% solutions were classified as strong eye irritants (34).

In a test on rabbit eyes in accordance with OECD guideline 405, a slight reddening of the eye's conjunctiva was reported upon application of 0.13% hydrofluoric acid, but 0.13% hydrofluoric acid was not considered to be a primary eye irritant. 1.06% hydrofluoric acid was judged to be a moderate eye irritant (swelling, reddening) and to pose a risk of corneal opacity (ECHA, 2013: http://echa.europa. eu/web/guest/information-on-chemicals/registered-substances). Another similar study reported that 0.2% hydrofluoric acid (pH ~1) caused slight corneal opacity, mild-to-moderate transient iritis and mild-to-moderate conjunctivitis in rabbits. 0.5% and 1% hydrofluoric acid have been declared to be corrosive (ECHA, 2013: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances).

Systemic effects

Hydrogen fluoride has high acute toxicity. One study reported death from ingesting a tablespoon (15 ml) of 9% hydrogen fluoride solution. In another case an individual died from heart failure resulting from myocardial necrosis 12 days after ingestion of half a snaps glass of 17.3% hydrofluoric acid. Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea) and systemic toxicity can occur rapidly. Signs of serious systemic toxicity after exposure (with various routes of exposures) include CNS depression, seizures, cardiac effects/cardiac arrest and coma. Cardiac arrhythmia and cardiac arrest are thought to be related to the development of hypocalcaemia and/or hyperkalaemia. Acute pulmonary oedema may also be one of the toxic effects (even without clear inhalation exposure). Cardiac effects (and deaths) after skin exposure to hydrogen fluoride have been reported in a number of cases. One case of serious poisoning involved electrolyte imbalances, bradycardia and cardiac arrest (asystole after 16 hours) after exposure of 3% of the skin surface to 20% hydrofluoric acid. The skin had been washed with water and treated with calcium gluconate gel immediately after the accident had occurred and had only been mildly affected, with first-degree burns (11, 25, 61, 83).

Prolonged high uptake of fluorides leads to skeletal fluorosis which is characterised by increased bone mineralisation, i.e. osteosclerosis. Skeletal changes appear to be slowly reversible, at least in part, after the end of fluoride exposure. Osteosclerosis itself rarely causes any problems but it can lead to osteoporosis and an increase in the incidence of fractures. Concomitant tendon calcification can cause pain and restriction of movement (61). A Finnish study (n= 144 627) which examined the relationship between hip fractures and fluoride concentrations in

drinking water reported a significantly increased relative risk in women aged 50-65 years in the highest-exposure group compared with the lowest-exposure group. The total uptake in the cohort was estimated at 0.6-3.7 mg F/day (including food and other fluoride sources, such as toothpaste). However, the participants were divided into groups according to fluoride concentration in drinking water (61). WHO has concluded that studies from India and China indicate an increased risk of bone effects with an intake (mostly via food and drink) of over 6 mg F/day. Significant effects were seen with an intake of 14 mg F/day (61, 80).

Very few studies have reported on skeletal effects in individuals occupationally exposed to hydrogen fluoride specifically. An older study reported osteosclerotic changes in a man who had worked for 16 years in the production of hydrofluoric acid. The urine concentration (24 hours) was given as ca 15 mg F/l (81). However, many studies have been published which involve individuals occupationally exposed to various fluorides (fluorides in gas form and in particulate form), e.g., in association with aluminium production. Several older studies are presented in a publication from 1977 (35). The overall conclusion was that workplaces with air concentrations <2.5 mg F/m^3 (as time-weighted average) and which are associated with urine concentrations <5 mg F/l are not thought to cause osteosclerosis. On the other hand, the risk of demonstrable osteosclerosis occurring was high if the air concentration in the workplace was >2.5 mg F/m^3 and/or the urine concentration was >9 mg F/l for extended periods (35, 61). No definite cases of skeletal fluorosis were reported in a study of workers (n=2066) at a Canadian aluminium smelter. Mild x-ray indications of increased skeletal density were found in a few workers who had been exposed for more than 10 years (gender not specified). However, there was poor agreement between the various radiologists in their interpretations of the x-ray images. The highest exposure was to ca 0.48 mg F/m^3 (personal monitor measurements, total airborne fluorides, i.e., in particulate form and in gas form) for at least 50% of the work time and in this group urine concentrations of 1.9 and 2.7 mg F/l (average values) were measured before and after the shift. It was stated that urine concentrations >9 mg F/l after the shift were not measured in any worker. Blood tests showed no signs of renal, hepatic or haematopoietic effects (13). In another study skeletal changes amongst 2258 workers at a Polish aluminium smelter were clinically and radiologically matched with a qualitative "exposure index", calculated on the basis of period of employment and the extent to which exposure limits were exceeded (measurements showed values up to 4 times higher than the Polish exposure limit of 0.5 mg HF/m^3). The prevalence of skeletal changes was positively correlated to the "index of exposure years" (gender not recorded). More pronounced changes were observed in older workers (16). A Slovakian study reported 14 cases of skeletal fluorosis (stages 1-3). All 14 (men) had worked in electrolytic production of aluminium (8 had been pensioned off) and the average period of exposure was 17.7 years. The group average value for urinary fluorides was 254.5 µmol/l (ca 4.85 mg F/l) with a range of 32-491 µmol/l (ca 0.6-9.3 mg F/l), while normal values in the region were ≤50 µmol/l (≤0.95 mg F/l). Irregular measurements at the production

location indicated average air concentrations of 3.7 mg F/m^3 for 1960-1968. Values between 0.16 and 13.7 mg F/m^3 were reported for 1987-1989 (8). A Chinese case-control study (119 cases, 126 controls) in workers at two aluminium smelters examined fluoride exposure, calcitonin-receptor gene polymorphism and the risk of fluoride-related effects on bone (Chinese diagnostic x-ray criteria for fluorosis). The participants were divided into three groups (gender not specified) based on urine fluoride concentrations: <2 mg/l (low), 2-4 mg/l (medium), >4 mg/l (high), respectively. OR (effects on bone) was 4.1 (95% CI 1.9, 8.7) and 14.1 (95% CI 6.5, 30.6) for the groups with medium and high exposure, resepectively, compared with low exposure. Individuals with the "TC/TT"-genotype in the calcitonin receptor gene (uncommon genotype in Asians) had a significantly greater risk than those with the "CC" genotype (common genotype in Asians but uncommon in Caucasians). According to the authors the "TC/TT" genotype increases the risk of developing dose-dependent fluoride-induced bone injury (79).

A review and meta-analysis (14) included 27 studies which had investigated the relationship between fluoride exposure and cognitive function in children. The data search covered the period 1980-2011. The 27 studies (25 from China, 2 from Iran) that were included in the meta-analysis had "high-exposure" groups and reference groups and most used fluoride concentration in drinking water as the measure of exposure. The fluoride concentration varied substantially in the "high-exposure" groups, while the reference groups had drinking water concentrations ≤1.1 mg/l (a small number of studies reported higher concentrations). In almost all the studies the IQ score of children/young people was lower for the "high-exposure" groups than for the reference groups. The authors of the review stated that the available exposure information did not allow a formal dose-response analysis and that there were also other weaknesses in the included studies. Nevertheless, they concluded that the data did support the suggestion that "high fluoride exposure" could affect the development of the brain and nervous system. The authors do not comment on whether the exposure occurred via the mother or the effects had resulted from direct exposure of the children. An assessment of epidemiological studies of industrial chemicals identified 6 substances/substance groups with neurotoxic developmental effects. Fluoride was amongst these (29). Six other substances/substance groups with neurotoxic developmental effects had previously been identified in the same manner (29).

Studies in research animals have reported that repeated prolonged exposure to sodium fluoride via gavage or via drinking water affects behaviour and cognitive function. Impaired cognitive ability when compared with a control group (one test) was reported in a study in rats which for 3 months had been fed daily by gavage with 0.5 ml water containing NaF (100 mg/l). Two weeks before the gavage feeding started the rats weighed ca 50 g and on the basis of this weight the dose could be calculated as 1 mg NaF/kg body weight/day (0.45 mg F/kg body weight/day). It was stated that the drinking water contained <0.07 mg/l NaF; the fluoride concentration in the feed was not specified. Histological examination of the hippocampus showed a significant reduction in the number of neurones

compared with the control group. A significant increase in the level of malondialdehyde (a marker for lipid peroxidation) was also reported as well as a significant reduction in the level of glutathione peroxidase and in superoxide dismutase activity in the hippocampus. If rats were also given an analogue of a Ginkgo biloba extract perorally this partly counteracted the effects of NaF (84). In a Chinese study (49) young mice were given 0, 2, 5 or 10 mg NaF/l in drinking water (distilled water) for 4 weeks and were then subjected to a number of tests for memory/learning and behaviour. Dose-dependent effects (significant at the two highest dose levels) were demonstrated for cognitive deterioration and depressive behaviour. The animals in the high-exposure groups were less active than those in the other groups and showed signs of fluorosis (light yellow plaque on the teeth). Effects on body weight were not observed in any exposure group. The study did not give the fluoride concentration in the feed. In a second Chinese study (50) rats were given <0.5 (control group), 5 or 50 mg NaF/l drinking water for 6 months. A dose-dependent deterioration was observed in a test which measured memory/ learning (significant in both high- and low-dose groups), when compared with the control group. The study also showed dose-dependent and significant changes in protein expression in brain tissue (certain proteins that are important in cognitive function). Fluoride concentration in feed was not reported. In a number of other studies in which research animals experienced repeated/prolonged exposure to NaF via drinking water (e.g., refs. 4, 33, 39) showed a deterioration in cognitive function at exposures levels ≥100 mg/l in drinking water. An effect on behaviour was reported at exposure levels ≥25 mg/l in drinking water. In these studies low doses of NaF were not given to research animals.

Genotoxicity

Little data has been found on hydrogen fluoride. Lee *et al*. (47) reported in a review that, with inhalation exposure, hydrogen fluoride was mutagenic in gametes in a sex-linked recessive lethal (SLRL) test in fruit flies. ECHA stated that the original study was poorly reported and that the significance of the result could not be assessed. ECHA reported further that hydrofluoric acid (ca 75%) was not mutagenic in bacteria (Salmonella typhimurium TA1535, TA100, TA98, TA1537) when tested *in vitro* (Ames test), with or without metabolic activation (ECHA 2013: http://echa.europa.eu/web/guest/information-on-chemicals/ registered-substances).

However, the ability of other fluorides, principally sodium fluoride, to damage genomes has been tested extensively in various systems, both *in vitro* and *in vivo* (61*)*. Gene mutations have not been shown in *in vitro* tests in bacteria, but mutagenic effects were observed in cell studies, particularly at high fluoride concentrations. Chromosomal aberrations and sister chromatid exchanges (SCE) have also been demonstrated in cell studies (human cells, hamster cells) with sodium fluoride, but the results are not consistent. Negative results have even been obtainned at high doses. Nor is the situation unequivocal with regard to *in vivo* studies in mice and rats. Most studies show no effects (micronuclei, SCE, chromosomal

aberrations), even after high exposure, but there are also reports of effects even with moderate sodium fluoride intake (61).

Few studies have examined the genotoxic effects of fluorides in humans (61). A Chinese study of fluoride-exposed workers involved in phosphate fertiliser production showed a significant increase in the average frequency of SCE in peripheral blood lymphocytes from 40 workers when compared with a matched control group. Production started with a fluoride-containing mineral. Measurement data indicated that the workers were mainly exposed to hydrogen fluoride and silicon tetrafluoride; air concentrations were given as 0.5-0.8 mg/m^3. However, no further details were given on the measurements nor any information on the total amount of fluoride. There was also some exposure to phosphate vapour, ammonia and sulphur dioxide (it was stated that the latter two could induce chromosomal aberrations). A further study of the same workers showed a significant increase in both chromosomal aberrations and micronuclei in peripheral blood lymphocytes, compared with controls (58, 59, 61). In a study of postmenopausal women with osteoporosis who were given calcium and sodium monofluorophosphate (average dose 23 mg F/day) for 4.2 years (range 1.4-12.6 years) no increase was observed in the frequency of SCE in lymphocytes, compared with the control group (38). The association between fluoride concentration in drinking water and the frequency of SCE in lymphocytes was examined in a number of other studies, but no increase that could be related to fluoride exposure was observed (61).

The Criteria Group had previously concluded that the data on the genotoxicity of fluorides were insufficient to come to a definite conclusion (61).

Carcinogenicity

No studies of cancer associated with exposure to hydrogen fluoride have been found.

A cohort study of Danish cryolite workers exposed to cryolite dust (average dust levels 30-40 mg/m^3, estimated as equivalent to the absorption of 14-70 mg F/day) and traces of quartz, reported an increased incidence of cancers, e.g., lung-, larynx- and bladder-cancers. Many had probably been smokers and lifestyle factors such as smoking and alcohol consumption could probably explain the increases in lung- and larynx-cancer, but only partly explain the increased occurrence of bladder cancer. Seventeen case of bladder cancer (423 cryolite workers (men), period 1943-1987) were reported, compared with the 9.2 that would have been expected (SIR 1.84, 1.08-2.96). It was inferred from the results that occupational exposure to fluorides could have contributed to the increased incidence of bladder cancer (27). A follow-up study (422 cryolite workers, period 1943-1999) reported 43 new cancer cases, including 12 cases of primary lung cancer and 3 cases of bladder cancer. The SIR for bladder cancer was 1.67 (95% confidence interval 1.02-2.59). The authors concluded that these new data strengthened the results from the previous study. They emphasised that they had not found any clear exposure (occupational) to other known carcinogens and concluded that

fluoride should be regarded as a possible cause of bladder cancer and as a contributory cause in lung cancer (28). Several epidemiological studies of workers in aluminium smelters also showed an increased death rate from various types of cancer, e.g., lung and bladder cancer. However, it is uncertain whether one can link the increased risk to fluoride exposure because of concomitant exposure to other substances (e.g., polyaromatic hydrocarbons) and the lack of a consistent pattern (61).

Hydrogen fluoride is formed when fluorides, e.g., sodium fluoride, are administered perorally (80) and relevant studies are referred to here. Various studies have examined possible associations between cancer and fluoride exposure via drinking water. The large majority of these studies showed no such association (61). The importance of fluoride exposure in osteosarcoma has been studied specifically (particularly in children/young people). In many studies no relationship was observed between non-work-related fluoride exposure (e.g., via drinking water) and the risk of osteosarcoma (24, 48, 61). However, a literature review which examined the possible risk factors for bone tumours in children and young people revealed that a positive correlation between fluoride in drinking water and an increased incidence of osteosarcoma had been observed in three ecological studies (one study specifically in boys) and an increased incidence of all bone cancers combined was observed in one study. Furthermore, it was stated in the review (24) that a case-control study (7) showed an association between increased fluoride levels in drinking water and increased incidence of osteosarcoma in boys, but not in girls. However, further data from the subsequent study (not further specified) is not thought to support a link between fluoride and osteosarcoma (21). In a later case-control study the authors concluded that there was no association between fluoride levels in bone and the risk of osteosarcoma (42). Sandhu *et al.* (66) reported that a significant increase in average fluoride concentration in serum had been observed in a group of patients with osteosarcoma, when compared with two matched control groups (one group had other types of bone tumours).

A study by NTP in research animals exposed via drinking water (25, 100 or 175 mg/l NaF, 2 years) reported a small, non-significant increase in tumours in bone tissue (osteosarcoma) in male rats (0/50, 1/50, 3/80 vs 0/80 in controls, significant dose-response trend). The estimated total fluoride intake (feed, drinking water) in the groups (male rats) was ca 0.8, 2.5 and 4.1 mg/kg body weight/day, respectively. The association between fluoride intake and osteosarcoma in male rats was regarded as doubtful (”equivocal evidence of carcinogenic activity”). Corresponding results were not obtained in female rats or mice (”no evidence of carcinogennic activity”) (61, 80). A subsequent NTP study reported no increase in osteosarcoma with exposure to sodium fluoride. In the study male rats were exposed to 250 mg/l NaF in drinking water (ca 4.5 mg F/kg body weight/day) for 2 years. The incidence of osteosarcoma was 1/49 (extraskeletal form) in exposed rats and 2/49 in controls. The incidence of sarcoma in bone was 1/49 in both groups (63). A study in which rats of both sexes were given a diet with added NaF equivalent to 4, 10 and 25 mg NaF/kg body weight/day, respectively (ca 1.8, 4.5 and 11.25 mg

F/kg body weight/day, respectively) for up to 99 weeks, showed no significant increase in the incidence of osteosarcoma or other bone tumours, nor of any other types of tumour (56).

The Criteria Group has previously concluded that there was insufficient data on cancer and fluorides to draw any definite conclusions (61). In the 1980s IARC (36) concluded that fluorides (inorganic, in drinking water) cannot be classified with regard to carcinogenicity in humans (Group 3).

Effects on Reproduction

There is mostly a lack of data on the effects on reproduction of exposure to hydrogen fluoride.

Human data

An increased occurrence of spontaneous abortions was reported amongst female factory workers in the semiconductor industry and, as well as glycol ethers, fluorine compounds (hydrofluoric acid and ammonium fluoride) were found to be risk factors. However, the authors pointed out that the relationship might be a chance correlation or that significant, unidentified substances that covary might be involved (67, 75). Measurements in 35 production facilities in the semiconductor industry (personal monitor measurements) showed low average exposure levels for fluorides, 0.001 mg/m^3 (82). A case-controlled study showed no association between fluoride in drinking water and increased risk of spontaneous abortions (3).

It was stated (61) that "certain effects" on the concentrations of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) had been observed in men who had been diagnosed with skeletal fluorosis and had worked in the cryolite industry for 10-25 years (the original studies were Russian and there are no further details).

Animal studies

When 2% hydrofluoric acid was applied to the skin of rabbits for 4 hours (occlusive, wiped off after exposure) an increase in fluoride concentration in the blood was reported, along with corrosive injuries on the skin and a significant reduction in relative and absolute testicular weight. No significant effect on testicular weight was observed with the corresponding exposure for 1 hour. Body weight was not significantly affected in any group and no clinical signs of systemic toxicity were observed (the animals were killed after 4 days) (19).

Well executed studies carried out by the FDA (Food and Drug Administration) in the USA, gave negative results for perorally administered sodium fluoride. In these studies (15, 71, 72) NaF was given in drinking water and there was good control with regard to background levels of fluoride (distilled water with <0.2 mg/l fluoride, low-fluoride diet with 8 mg fluoride/kg). Sprando *et al.* (71) reported no significant, dose-related effects on testes, sperm and endocrine function, nor on body weight, in male rats (multi-generation study, male and

female rats) when 25, 100, 175 or 250 mg/l NaF (approximately 1.5-12 mg F/kg body weight/day) was given for 14 weeks to a parent generation and the F_1 generation was exposed via the mothers (in the womb and during lactation) and directly via drinking water (14 weeks). Body weight, organ weights (including reproductive organs), number of sperm in the testes and serum levels of testosterone, LH and FSH were determined for all groups. Histopathological examination of the testes was carried out in the control and high-dose groups (71). The testes from animals in the F_1 generation (all dose groups) were examined in a further study. For the most part no significant effects were observed in morphometric examination of the testes (significantly reduced volume and volume percentage of lymphatic endothelium at 175 and 250 mg/l) and the authors concluded that the data as a whole did not indicate negative effects on testicular structure or spermatogenesis at the doses used (72). The same authors later published fertility data (e.g., fertility index, number of litters produced) for male rats and female rats who were given NaF in drinking water (3-generation study, doses as above) and reported no indication of negative effects in either the parent generation or the F_1 generation (15).

However, effects on the testes and on spermatogenesis have been observed in many other studies in research animals (various species) given sodium fluoride perorally (by gavage, in drinking water, in feed) at high or relatively high doses (51, see also references in ref. 23 and 71). For example, abnormal sperms were observed in rabbit who were given sodium fluoride in distilled water for 18 or 29 months. After 29 months of exposure spermatogenesis ceased. The dose was 10 mg NaF/kg body weight/day (4.5 mg F/kg bw/day). The fluoride concentration in the feed was not given but the fluoride concentration in drinking water was <0.5 mg/l (44, 74).

A recently published study (85) reported effects on spermatogenesis in rats given 25, 50 or 100 mg/l NaF via drinking water (tap water) 10 days before mating (male and female animals) and during gestation and lactation, and in offspring given the same dose in drinking water for 5 weeks after weaning. The drinking water contained <1.0 mg/l fluoride before NaF was added. The fluoride concentration in feed was not given. At the dose level of 25 mg/l histopathological and ultrastructural examination revealed minor changes in the testes of offspring. At 50 and 100 mg/l major (dose-dependent) changes were observed in the testes (including atrophy, damaged sperm, reduced sperm count). Testicular homogenate was examined for signs of oxidative stress. When compared with the control group a significant reduction in the activity of an antioxidant enzyme (superoxide dismutase) was observed at all doses along with a significant increase in levels of a lipid peroxidation marker (malondialdehyde) at both the higher doses. In a study of markers for endoplasmic reticulum stress in testicular tissue (expression of mRNA and protein) a significant upregulation was observed at all dose levels (not for all markers at 25 mg/l). The gene expression of inflammatory enzymes (iNOS, COX-2) was also significantly upregulated in the testes at all doses. The expression of cytokinins was also significantly upregulated (TNF-α at 50 and 100 mg/l,

IL-1β at 25 and 50 mg/l). Activation of the transcription factor NF-κB, which plays an important role in regulating inflammatory response, was observed at 50 and 100 mg/l. The authors concluded that endoplasmatic reticulum stress and inflammation in testicular tissue, together with oxidative stress, are probable causes of fluoride-induced disruption of spermatogenesis and reduced sperm count (85).

Some Indian studies reported effects in male rats even at low exposure levels. Gupta *et al*. (32) showed concentration-dependent degenerative changes and reduced spermatogenesis in the testes (histological examination) of male rats after 6 months administration of 2, 4 or 6 mg/l NaF in drinking water (distilled water). In the testes the numbers of gametes (e.g., spermatogonia, secondary spermatocytes), Sertoli cells and mature Leydig cells were reduced, as were levels of serum testosterone. Lower relative weight of testes and other sex organs, reduced sperm motility, etc., were also observed. All effects were dose-dependent and significant, even in the low-dose group. Significant dose-dependent results were also obtained in the biochemical analysis (including levels of protein, glycogen, cholesterol in testes). A dose-dependent reduction in fertility was reported but no further details were given. No effect on body weight was observed in any dose group. The animals were given standard feed but the fluoride concentration was not reported (32). In another study (64) in which 4.5 and 9 mg/l NaF was added to drinking water (tap water) given to male rats for 75 days (this was stated to be equivalent to 0.7 and 1.3 mg NaF/kg body weight/day in reference 23) showed a significant (at both dose levels) and dose-dependent reduction in the number of sperm as well as reduced sperm motility and viability. A dose-dependent reduction in the activity of 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) in testes was also reported. A significantly lower body weight was observed in male rats in the high-dose group (64). The fluoride concentration in feed was not given; the control group was given "tap water without NaF". The same authors also examined effects on sperm and sex hormones in adult offspring exposed via mothers during gestation and lactation. The mothers were given 4.5 and 9 mg/l sodium fluoride in tap water. The background level of fluoride was 0.7-1.0 mg/l in drinking water (tap water) and 0.2-0.3 mg/kg in the diet. Significant dose-dependent reductions were observed in sperm motility (not significant at 4.5 mg/l), sperm viability and number of sperm. A significant dose-dependent reduction in testosterone and increase in FSH and LH levels in serum were also observed, as well as a significant dose-dependent reduction in 3β-HSD and 17β-HSD activities in testicular tissue. Histological changes in the testes were also reported, but no data supporting this assertion were recorded. There were no significant differences in body weight between the groups, neither for mothers nor offspring (65). The studies (32, 64, 65) are difficult to assess. Uncertain effect levels (doses given as concentration in drinking water) as well as other weaknesses in the studies (e.g., incompletely reported results, incomplete information on background levels of fluoride) make it difficult to assess dose-response relationships.

Data on reproductive and developmental toxicity has been summarised in a review by Ema *et al.* (23) and in a previous report from the Criteria Group (61). Particularly relevant amongst these are studies in rats given drinking water with added sodium fluoride (including multi-generation studies). Ema *et al.* (23) reported that renal damage was observed in offspring at the dose level 6 mg NaF/kg body weight/day (30 mg/l in drinking water). It was stated that the feed contained <4 mg fluoride/kg (23, 41). Lower body weight and degenerative changes in heart muscle and lungs were also reported in offspring at 10 mg NaF/kg body weight/day (50 mg/l in drinking water) (23). Earlier studies in rats showed no effects on bone in offspring (though this was not the case in the parent generation) given 150 mg/l fluoride (as NaF) in drinking water (61). In more recent studies (dose levels 25, 100, 175 or 250 mg/l NaF in drinking water) the only effect was reduced ossification in the hyoid bone of offspring (rats) at the highest dose (equivalent to 28 mg NaF/kg body weight/day). No effects were seen in the groups with a lower intake (23, 61). In a study which examined the morphological development of rat foetuses from mothers given ≥250 mg/l NaF in drinking water (≤25 mg NaF/kg body weight/day) on days 0-20 of gestation, an increase was observed in skeletal variations at the highest dose level (at which the mothers had reduced body weight gain). Otherwise, no negative effects on foetal development were observed (23, 61). No effect on foetal development was reported in another study in rats given 300 mg (27 mg/kg body weight) on days 6-15 of gestation and rabbits given 400 mg (29 mg/kg body weight) on days 6-19 days of gestation (23).

Effects on the brain were investigated in a multi-generation study in rats continuously exposed to sodium fluoride. In the study, rats were given drinking water (tap water) without fluoride (< 1 mg/l) or with added sodium fluoride (100, 200 mg/l) during gestation and lactation; offspring were then given fluoride at the same concentrations in drinking water. The animals were given standard feed, but the fluoride concentration was not specified. Memory/learning and related parameters were studied in the offspring (3 generations) at 1 month of age. A significant (not entirely dose-dependent) reduction in serum thyroid hormones (free T3, free T4) was observed, principally in the F_2- and F_3-generations. Reduced activity of the enzyme acetylcholinesterase was also observed in different brain regions and the effect became more pronounced with each generation. Histopathological examination revealed dose-dependent changes in various brain regions (including the degeneration of neurones in the hippocampus and signs of necrotic changes in the cerebral cortex); the effects were most pronounced in the third generation. The third generation was also most affected when tested for deterioration in memory/learning (both dose levels) (6). In another study 25, 50 or 100 mg/l NaF in tap water was given to rats before, during and after gestation (lactation period), and subsequently to offspring. The tap water contained 0.34 mg F/l before fluoride was added; fluoride concentration in the feed was not specified. When the offspring was 2 months old, various parameters were studied to evaluate brain function. A significant (all doses) and, for the most part, dose-dependent

deterioration was observed in results from a test measuring cognitive function. Neurodegenerative changes were observed in the hippocampus at both the highest dose levels. There was also a significant reduction in brain glucose consumption at 50 and 100 mg/l. A significant effect on the expression of three functional proteins in the brain was observed at all dose levels. Both body weight and brain weight were significantly lower in the 50- and 100-mg/l groups (40).

Dose-effect-/dose-response relationships

Human data

Hydrofluoric acid can be highly corrosive on the skin. In addition, damage can occur in underlying tissue. Concentrations >50% (including anhydrous hydrogen fluoride) result in immediate, severe pain and a whitish discolouration of the skin. Concentrations <20% cause virtually no acute pain upon contact but can cause severe delayed injury 12-24 hours later. Injuries can occur in deep-seated tissues and bone, even if the overlying skin has not been markedly affected (5, 61, 73, 86). Absorption of hydrogen fluoride through the skin can lead to serious poisoning and death (Table 2). In one case electrolyte imbalance, bradycardia and cardiac arrest occurred after exposure to 20% hydrofluoric acid over 3% of the skin surface. The skin was only slightly affected, with first-degree burns (83).

Tracheobronchitis, pulmonary oedema and pulmonary haemorrhage, sometimes with fatal outcome, have been reported in accidents were hydrogen fluoride has been released and inhaled at high concentrations (61). A concentration of 30 ppm has been declared as the level at which there is an immediate danger to life or health (23). Acute effects in the form of a burning sensation in the eyes, nose and mouth, and breathing difficulties (diagnosed as RADS), as well as persistent problems in the form of breathing difficulties upon exertion, were reported in one case involving exposure to hydrogen fluoride (air concentrations not specified) associated with cleaning with an aqueous solution containing 8-9% hydrogen fluoride (61).

Irritation of the respiratory tract has been reported in a controlled study involving short-term exposure to hydrogen fluoride. At exposure levels of 0.7-2.4 mg HF/m^3 6 out of 7 individuals reported mild symptoms of the upper respiratory tract. An increase was observed in the proportion of CD3-positive cells in the bronchial portion of the bronchoalveolar lavage fluid. At exposure levels of 0.2-0.6 mg/m^3 4 out of 9 individuals reported mild symptoms of the upper respiratory tract (52, 53). There were only a few research subjects and they were not subjected to zero exposure to accustom them to the chamber. It is, therefore, difficult to assess the effect of the lowest exposure. The most probable LOAEL in the study was evaluated as 0.7-2.4 mg/m^3 (61). An increased risk of nosebleeds was reported in a cross-sectional study of occupationally exposed subjects. Average levels of exposure to hydrogen fluoride were given as 0.15-1.0 mg/m^3 (26). The study, which was initiated because the industrial healthcare unit of the factory noticed an increased occurrence of nosebleeds amongst employees, produced barely significant

results (and a fairly large degree of uncertainty in the risk assessment). Most of those cases with nosebleeds appeared to be associated with the higher concentration which, however, was based on only two measurements. The Criteria Group concludes that the causative relationship is unclear. Effects on humans in chamber exposure is given in Table 1.

Long-term exposure to fluorides can result in skeletal fluorosis (osteosclerosis). Osteosclerosis was observed in an individual who had worked for 16 years in hydrofluoric acid production. The urine concentration (24 hours) was given as ca 15 mg F/l (81). An older review article (35) states that osteosclerosis was not thought to be found in workplaces with air concentrations <2.5 mg F/m^3 (as time-weighted average) and where urine concentrations were <5 mg F/l, whereas a high risk of diagnosable osteosclerosis was reported at air concentrations >2.5 mg F/m^3 and/or urine concentrations >9 mg F/l for prolonged periods (35, 61). No definite case of skeletal fluorosis was reported amongst a small number of individuals at an aluminium smelter who had been exposed for >10 years, though there were possibly slight x-ray indications of increased skeletal density. Workers with the highest exposure were exposed to ca 0.5 mg F/m^3 for at least 50% of the work period and had urine concentrations of 1.9 and 2.7 mg F/l (average values) before and after their shift, respectively (13). Another study reported 14 cases of skeletal fluorosis at an aluminium smelter. Group average values for urinary fluorides were 255 µmol F/l, with a range of 32-491 µmol F/l (4.85 mg F/l, range 0.6-9.3). Irregular measurements indicated average concentrations in air of 3.7 mg F/m^3, 1960-1968. Values between 0.16 and 13.7 mg F/m^3 (8) were later reported. In a Chinese study of workers at two aluminium smelters, the risk of fluoride-related effects on bone (Chinese diagnostic criteria for fluorosis) was higher with urine fluoride concentrations of 2-4 mg/l and >4 mg/l than with urine fluoride concentrations <2 mg/l (OR 4.1 and 14.1). Polymorphic analysis of the calcitonin-receptor gene gave further support to the assertion of a dose-response relationship (79).

WHO (80) has concluded that there is some increase in the risk of skeletal effects with an intake (mainly via food and drink) of over 6 mg F/day. Significant effects were observed with an intake of 14 mg F/day. With a dose of 6 mg F/day as the starting point (assuming 100% uptake and inhalation of 10 m^3 air, 5 days/week) it can be calculated that an air concentration of 0.8 mg F/m^3 will produce this daily dose. If a corresponding calculation is made for the dose of 14 mg F/day, this gives an air concentration of 2.0 mg F/m^3 (61). However, when assessing the health effects of fluorides (including hydrogen fluoride) background exposure should be taken into account. Swedish National Food Administration's (Livsmedelsverket) threshold limit for fluoride in mains water is 1.5 mg/l (60). The background intake is nearly 3 mg F/day if, on the basis of data from ref. (60), one assumes that the intake of fluoride from water and other drinks is ca 2.3 mg/day at this concentration in drinking water and that the intake of fluoride via food is 0.4 mg/day. It should, therefore, be possible for the risk level of 6 mg F/day to be reached by occupational exposure to around 0.4 mg F/m^3.

An increase in, for example, lung and bladder cancer, has been observed in epidemiological studies of individuals occupationally exposed to fluoride at aluminium smelters. However, these data do not allow a valid conclusion to be drawn, in part because of concomitant exposure to other substances, e.g., polyaromatic hydrocarbons, and the lack of a consistent pattern (61). An increase in, for example, lung cancer and bladder cancer has also been observed in cryolite workers (one cohort) without any obvious occupational exposure to other known carcinogens (27, 28). According to the authors, the result indicated that fluoride might possibly cause bladder cancer and be a contributory factor in lung cancer development (28). The association between fluoride in drinking water and cancer has been examined further but the large majority of these studies have failed to demonstrate such a link (27, 61).

The importance of fluoride exposure specifically with regard to osteosarcoma (principally in children/young people) has also been studied (7, 21, 24, 42, 61, 66), but the results are inconsistent.

Animal data and in vitro studies

Results have been contradictory with regard to the effects of fluoride (NaF) administration on testes and sperm in research animals and it is uncertain whether there is a dose-response relationship (see below). This could be due in part to species differences and different modes of administration (gavage, in drinking water, in feed, etc.). But results could also have been affected by other differences between the studies, for example, the composition of feed/drinking water (e.g., the content of fluoride and of nutrients such as antioxidants and minerals). Concomitant administration of vitamins D and E and calcium has, for example, been reported to counteract the negative effects of sodium fluoride on testes, sperm, etc. (15, 18, 23, 37, 45, 71, 72).

In well-executed FDA studies (15, 71, 72) no significant effects on spermatogenesis, fertility and related endocrine functions were observed in rats exposed to 25, 100, 175 and 250 mg/l NaF in drinking water (approximately 1.5-12 mg F/kg body weight/day). The authors concluded that sodium fluoride did not affect reproduction if there was an adequate provision of nutrients. However, several other studies with research animals have shown effects on testes and spermatogenesis when sodium fluoride is administered perorally at high or relatively high doses (51, see also references in ref. 23 and 71). For example, abnormal sperm developed and spermatogenesis ceased with long term peroral administration of 10 mg NaF/kg body weight/day (4.5 mg F/kg body weight/day) to rabbits (44, 74). In a recently published study in rats, Zhang *et al.* (85) reported effects on spermatogenesis in offspring with administration of 25, 50 or 100 mg/l NaF via drinking water to the parental generation before mating, and during gestation and lactation, and to offspring 5 weeks following weaning. Small changes in the testes were observed at 25 mg/l as well as major changes (atrophy, reduced sperm count) at both the higher dose levels. Several markers indicated that fluoride-induced

inflammation and oxidative stress in the testes (85). However, the effect levels are uncertain as the doses were only given in terms of concentration in drinking water.

Effects on cognitive function and behaviour have been reported in a number of studies in rats and mice given NaF perorally. A study in rats fed by gavage for 3 months showed reduced performance in cognitive ability tests, signs of oxidative stress and a reduced number of neurones in the hippocampus. The dose level was 1 mg NaF/kg body weight/day (0.45 mg F/kg body weight/day) based on original weight (84). Two Chinese studies (49, 50) also reported effects on memory/learning and behaviour in mice and rats given NaF in drinking water for 1 and 6 months, respectively. A significant deterioration was observed in both studies at concentrations ≥5 mg/l. The effect levels are uncertain as the doses were given as concentrations in drinking water, whereas water intake and background intake were not given.

Renal damage was observed in the offspring of rats given sodium fluoride via drinking water at a dose level of 6 mg NaF/kg body weight/day (30 mg/l in drinking water) while lower body weight and degenerative changes in heart muscle and lungs were observed in offspring of rats given 10 mg NaF/kg body weight/day (50 mg/l in drinking water) (23). Other studies in which sodium fluoride was given to rats in drinking water reported effects on offspring in the form of increased skeletal variations at 25 mg NaF/kg body weight/day (a level at which the weight gain of mothers was lower) and reduced ossification in the hyoid bone at 28 mg NaF/kg body weight/day (23, 61).

An animal study showed an increase (not significant) in the incidence of osteosarcoma in male rats with prolonged exposure to 175 mg/l NaF in drinking water (total fluoride intake was ca 4.1 mg F/kg body weight/day) (61, 80). No increase in the incidence of osteosarcoma was reported in a later NTP study in male rats exposed to 250 mg/l NaF in drinking water (ca 4.5 mg F/kg body weight/day) for 2 years (63). In addition, no significant increase was observed in the incidence of osteosarcoma or other bone tumours in a long-term study in which rats (both sexes) were given feed to which had been added NaF equivalent up to 11.25 mg F/kg body weight/day (56).

Dose-dependent irritation was observed in an *in vitro* test on hens' eggs exposed to 0.05, 0.1, 0.2 and 1% aqueous solutions of hydrogen fluoride. The 0.1, 0.2 and 1% solutions were classified as strong eye irritants (34).

Conclusions

The critical effect of long-term occupational exposure to hydrogen fluoride is the effect on the bones. Calculations based on the intake of fluorides via food and drink indicate that exposure to between 6 and 14 mg F/day produces effects on bone. According to theoretical calculations the same amount of fluoride can be taken in by inhalation exposure at air concentrations of 0.8-2.0 mg F/m^3 during an 8-hour working day. With occupational exposure, background exposure should also be taken into account. This can be as much as 3 mg/day, hence there should be concern over the risk of skeletal effects at an air concentration of 0.4 mg F/m^3.

The critical effect of acute and short-term air exposure to hydrogen fluoride is the irritation of mucous membranes. Symptoms of irritation in the upper respiratory tract were reported in a chamber study at 0.7-2.4 mg/m^3. As with other irritant substances, a single exposure to high concentrations of hydrogen fluoride can lead to acute (so-called RADS) and long-term damage to the respiratory tract (breathlessness with exertion).

Hydrogen fluoride is readily absorbed through the skin. This can cause localised deep-seated tissue damage and systemic poisoning. Cases of fatal outcome have been reported.

Table 1. A selection of studies which describe the effects on humans of chamber exposure to hydrogen fluoride.

Exposure	Effects	Ref.
0.2-0.6 mg/m^3, 1 h	Mild symptoms of the upper respiratory tract in 4 out of 9 (p=0.06).	52
0.7-2.4 mg/m^3, 1 h	LOAEL* in the study. Mild symptoms of the upper respiratory tract in 6 out of 7 (p=0.10), significant increase in CD3-positive cells in the bronchial portion of the bronchoalveolar lavage fluid.	52, 53
0.7-1.6 mg/m^3 (av 1.1), 6 h 5 d/wk, 15 d	Exposure of 1 person. Mild tingling sensation in the face (skin, eyes), no skin flushing.	46, 61
1.4-4.2 mg/m^3 (av 2.1), 6 h, 5 d/wk, 25 d	Exposure of 1 person. Mild tingling sensation in the facial skin and eyes, mild nasal irritation, skin flushing.	46, 61
1.5-3.4 mg/m^3 (av 2.2), 6 h, 5 d/wk, 30 d	Exposure of 1 person. Mild tingling sensation in the facial skin and eyes, mild nasal irritation, skin flushing.	46, 61
1.7-4.7 mg/m^3 (av 2.7), 6 h, 5 d/wk, 10 d	Exposure of 1 person. Mild tingling sensation in the facial skin and eyes, mild nasal irritation, skin flushing and peeling.	46, 61
2.2-6.5 mg/m^3 (av 3.4), 6 h, 5 d/wk, 50 d	Exposure of 1 person. Mild tingling sensation in the facial skin and eyes, mild nasal irritation, skin flushing and peeling.	46, 61
2.5-6.3 mg/m^3 (av 3.8), 6 h, 5 d/wk, 25 d	Exposure of 1 person. Mild tingling sensation in the facial skin and eyes, mild nasal irritation, skin flushing and peeling.	46, 61
2.5-5.2 mg/m^3, 1 h	Symptoms of the upper respiratory tract in 7 out of 7 (mild symptoms in 4 and strong symptoms in 3) (p=0.02). Inflammatory response: significant increase in CD3-positive cells in the bronchial and bronchoalveolar portions of the bronchoalveolar lavage fluid, increase in myeloperoxidase and interleukin-6 in the bronchial portion of the bronchoalveolar lavage fluid.	52, 53
3.3-3.9 mg/m^3, 1 h	Symptoms of the upper respiratory tract in 7 out of 10 (mild symptoms in 6 and strong symptoms in 1). Inflammatory response (nasal lavage fluid): increase in neutrophil granulocytes and in the total number of cells, effect on TNF-α and eicosanoids.	54
3.3-3.9 mg/m^3, 1 h	Exposure of 10 individuals. No significant changes in FVC or FEV_1, no signs of acute inflammatory changes in the lungs.	55

h = hours, d = days, wk = weeks, av = average

* The Criteria Group has concluded that the most likely LOAEL in reference 52 is 0.7-2.4 mg/m^3.

Table 2. Effects on humans through dermal exposure to hydrogen fluoride.

Amount on the skin	Number of individuals	Blood concentrations	Effects	Ref.
Anhydrous hydrogen fluoride, 5% of body surface	1	-	Severe poisoning, skin damage	9
Anhydrous hydrogen fluoride, 2.5% of body surface	1	Serum fluoride concentration 3 mg/l	Death (poisoning, skin damage)	78
ca 5 g anhydrous hydrogen fluoride, 2.5% of body surface	1	Blood fluoride concentration 4 and 10 hours after the accident <3 mg/l	Severe poisoning, skin damage	10
70% hydrofluoric acid, on the face, chest, legs and arms	2	-	Both individuals died (poisoning, skin damage)	12
70% hydrofluoric acid, 22% of the body surface	1	Initial serum fluoride concentration 6 mg/l	Severe poisoning, skin damage	30
70% hydrofluoric acid, 9-10% of the body surface	1	Serum fluoride concentration postmortem 4.17 mg/l	Death (poisoning, skin damage)	57
70% hydrofluoric acid, 8% of the body surface	1	Serum fluoride concentration 4 hours after the accident 9.42 mg/l	Death (poisoning, skin damage)	62
150 ml of 70% hydrofluoric acid, 8% of the body surface	1	-	Death (poisoning, skin damage)	31
70% hydrofluoric acid, 3.5% of the body surface	1	-	Severe poisoning, skin damage	17
60% hydrofluoric acid, 2.5% of the body surface	1	Initial serum fluoride concentration 7.1 mg/l	Severe poisoning, skin damage	30
20% hydrofluoric acid, 3% of the body surface	1	-	Severe poisoning, Mild skin damage	83

The hands and forearms (total ca 2000 cm^2) together account for ca 10% of the total skin surface and one hand accounts for about 2% of the total skin surface (22).

Potential conflicts of interest

No potential conflicts of interest declared.

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Consensus Report for N,N-Dimethylformamide

December 10, 2014

This consensus report is mainly based on a SCOEL document from 2006 (33). Complementary data searches have been carried out in PubMed, up to and including March 2014. The report updates a previous consensus report published in Arbete och Hälsa 1983 (37).

Physical-chemical data and occurrence

CAS no.	68-12-2
Synonyms	DMF, N-formyldimethylamine, N,N-Dimethyl formic acid amide
Structural formula	$N(CH_3)_2CHO$
Molecular weight	73.09
Melting point	-60.5 ºC
Boiling point	153 ºC
Vapour pressure	0.35 kPa (20 ºC)
Density	0.944 g/cm^3
Log $K_{octanol/water}$	-1.01
Conversion factors	1 ppm = 3.03 mg/m^3; 1 mg/m^3 = 0.33 ppm

N,N-Dimethylformamide (DMF) is a colourless, flammable, polar and hygroscopic liquid with a pungent, fishy aroma. It is miscible with water and with many lipophilic solvents (33, 37). DMF is mainly used as a solvent in the synthesis of fine chemicals, in polyacrylonitrile fibre production, in polyurethane coating and in the electronics industry. DMF is also used in, for example, cleaning and in several forms of surface coating, such as lacquering. It can also be used as a solvent in plant protection agents (33).

Uptake, biotransformation, excretion

DMF is easily absorbed by the skin, respiratory tract and gastrointestinal tract (33). In one study 13 research subjects were exposed for 4 hours to DMF vapour via the lungs or skin. In the inhalation study the research subjects sat outside the exposure chamber from which they inhaled air. The average air concentration of DMF was 7.1 ppm. In the skin exposure study the subjects sat inside the chamber (90% of their skin exposed) and inhaled fresh air from outside. The DMF concentration in the chamber was 6.2 ppm. Uptake via the skin was calculated at between 22% and 71% (average 40%, n=13) of the total uptake by whole body exposure (skin and inhalation). The calculations were based on urinary excretion of the

metabolite N-methylformamide (NMF) (28). In a smaller study in which the research subjects were exposed to 17 ppm DMF vapour (50 mg/m^3, 4 hours) it was reported that dermal uptake was dependent on humidity and ambient temperature and comprised 13-36% of total uptake (theoretical calculations based on urinary excretion of the metabolite N-(hydroxymethyl)-N-methylformamide, HMMF) (27). The dermal uptake of DMF vapour is, therefore, substantial and on a par with other amphiphilic solvents such as N-methyl-2-pyrrolidone (NMP), dimethylacetamide and glycol ethers, and much greater than the dermal uptake of non-polar solvent fumes (30). As a liquid DMF has a very high dermal permeability. A trans-dermal penetration rate (flux) of 9.4 mg/cm^2/hour was recorded in an *in vivo* study (17). If ECETOC criteria for a skin notation (8) are used, i.e., exposure of 2000 cm^2 skin (equivalent to the hands and forearms) for 1 hour, the dose absorbed via skin is 18,800 mg, which substantially exceeds the dose taken up during inhalation exposure at the current Swedish occupational exposure limit of 10 ppm or 30 mg/m^3 (150 mg/day if one assumes an inhalation of 10 m^3 air for 8 hours and 50% uptake).

After absorption DMF is distributed uniformly throughout the body and is mainly metabolised in the liver and excreted rapidly as metabolites in the urine. DMF is mainly metabolised to N-(hydroxymethyl)-N-methylformamide (HMMF), which is the prime urinary metabolite. HMMF can be hydrolyzed to N-methylformamide (NMF). NMF can in turn form N-(hydroxymethyl)formamide (HMF) by N-methylhydroxylation and further hydrolysis to formamide (33). An alternative metabolic path for NMF is oxidation of the formyl group and conjugation with glutathione, which gives N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC; urinary metabolite). A reactive intermediate, which is assumed to cause DMF's hepatotoxic effects, is formed via this metabolic route (1, 33). The data indicate that DMF is metabolised to AMCC to a greater extent in humans than in research animals (26, 33). It was calculated that in 10 research subjects exposed to 60 mg/m^3 (20 ppm) DMF for 8 hours the dose absorbed via inhalation (dermal uptake was not taken into consideration) was 28-60 µmol DMF/kg body weight (2-4.4 mg/kg body weight). Urine analysis showed that 16.1-48.7% had been excreted as HMMF, 8.3-23.9% as formamide and 9.7-22.8% as AMCC (within 72 hours). With intra-abdominal injection of DMF (0.1-7 mmol/kg body weight) in research animals, 8.4-47.3% (increasing with dose) was excreted in the urine as HMMF, 7.9-37.5% (decreasing with dose) as formamide, and just 1.1-5.2% as AMCC (26).

In a study in humans (4 hours exposure) the biological half-life for NMF in urine was 4.75 ±1.63 hours with whole body dermal exposure (average exposure 6.2 ppm DMF) and 2.42 ±0.63 hours with inhalation exposure (average exposure 7.1 ppm DMF) (28). A half-life of 23 hours has been determined for AMCC (33).

There is a metabolic interaction between DMF and alcohol (9, 33). Ethanol and probably the metabolite acetaldehyde inhibit the metabolism of DMF and, conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. DMF can inhibit the enzymes alcohol dehydrogenase and aldehyde dehydrogenase, which leads to

an accumulation of acetaldehyde (alcohol intolerance). There is an inherited difference in sensitivity to alcohol between different populations which is dependent on genetic polymorphisms for the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. Ca 5% of Europeans and up to 90% of Asian ethnic groups have increased sensitivity to alcohol (33) because of this genetic factor.

DMF and its metabolites (HMMF, NMF) cross the placental barrier and appear in breast milk. Concentrations were similar in the foetus, in milk and in the mother's blood (31).

Biological exposure monitoring

The urinary metabolites NMF (the total of HMMF and NMF is determined) and AMCC can be used for biological exposure monitoring (1, 33). NMF can be used as an index for daily exposure and AMCC, which has a longer half-life, can be measured in urine samples at the end of the working week. Available data state that 5 ppm DMF in the air can be equivalent to 9-25 mg NMF/l urine (average ca 15 mg NMF/l). A value (after the shift) of ca 15 mg NMF/l urine can also be equivalent to an 8-hour time-weighted average of 5 ppm. Data on AMCC is more uncertain and a quantitative biological exposure limit can therefore not be based on this metabolite (33). ACGIH (1) has a semiquantitative exposure limit of 40 mg/l for AMCC in urine.

Toxic effects

Human data

The primary target organ for occupational exposure to DMF is the liver. Gastrointestinal (nausea, diarrhoea, vomiting, abdominal pain) as well as other symptoms, such as jaundice, weight loss and a lack of coordination have been reported. Effects on liver morphology and function, with an elevation of liver enzymes (ASAT, ALAT, ɣ-GT, alkaline phosphatases) in serum have also been observed. In addition, alcohol intolerance (due to inhibition of alcohol-metabolizing enzymes in the liver), manifested as facial flushing, dizziness, nausea, and a feeling of tightness in the chest, has also been observed in DMF-exposed workers. Alcohol intolerance has usually been observed after work and even when only small amounts of alcohol are consumed (33).

A Chinese study (13) examined different markers for DMF exposure and liver damage (ASAT, ALAT, ɣ-GT; parameters for liver fibrosis/liver cirrhosis) in 79 workers at a facility for the production of synthetic leather. The study did not include individuals who were carriers of hepatitis B virus and persons with a stated alcohol consumption of >50 g/day. The workers wore long-sleeved clothing and "impermeable gloves" but no form of respiratory protection. The individuals were divided into 3 groups based on a calculated 8-hour time-weighted average (TWA) for DMF in air (48 sampling stations) and the correlation was examined between air DMF concentration, measures of internal exposure, and liver function tests.

The low-exposure group had a TWA <2.55 mg/m^3 (<0.8 ppm), the medium exposure group a TWA between 9.04 and 19.5 mg/m^3 (ca 3-6.4 ppm) and the high-exposure group a TWA of about 36 mg/m^3 (ca 11.9 ppm). A significant dose-dependent increase in the group average value (geometric mean) for DMF-, NMF- and AMCC concentrations in urine was observed in the medium- and high-exposure groups when compared with the low-exposure group. The group average values for NMF were 1.80, 9.61, and 26.47 mg/g creatinine, respectively, with large variations within the groups. The group average values (and range) for AMCC were 4.25 (undetectable - 8.8), 25.4 (2.9-41.6), and 45.5 (7.4-145.7) mg/g creatinine, respectively. No significant difference was observed between the groups for parameters related to liver function. However, a non-significant dose-dependent increase was observed in the percentage of individuals with elevated ASAT and ALAT values (Table 1). When the workers were divided into groups on the basis of NMF and AMCC concentration in the urine, i.e., <15 or ≥15 mg/g creatinine for NMF and <40 or ≥40 mg/g creatinine for AMCC, a significant increase was recorded in the number of individuals with elevated values for liver enzymes and other markers for liver damage (ASAT, ALAT, ɣ-GT, hyaluronidase, total bile acids) with AMCC ≥40 mg/g creatinine. The authors concluded that urinary AMCC could be a good biomarker for evaluating (and avoiding) health risks with DMF exposure (13).

Several other studies have been carried out in Asian populations (Table 1). Wang *et al*. (38) divided workers at a plant manufacturing synthetic leather into three exposure categories (exposure index) based on estimated DMF exposure (10-minute air samples were taken; n=11). In the highest exposure group direct skin contact with DMF was more frequent than in the other groups and workers were exposed to higher air concentrations (25-60 ppm). Pain in the upper abdomen was more common (non-significant increase) in the highest-exposure group. A significant relationship was also reported between a higher prevalence of abnormal liver function (elevated value for ALAT) and an increase in exposure index. OR was 6.16 (95% CI 1.53-24.79, p-value 0.01) for the highest-exposure group (logistic regression analysis). OR was 1.23 (0.31-4.81) for the medium-exposure group. The group average value for ALAT also increased with increasing exposure index in workers with normal ALAT values (<35 IU/l). Lower alcohol consumption was also reported with increased exposure. Elevated creatinine phosphokinase (CPK) levels (increased with exposure index) were observed but it was unclear whether there was any association with exposure (38). The study did not include a non-exposed control group and effects in workers exposed to DMF concentrations <10 ppm could therefore not be evaluated (33).

Table 1. Effects of DMF exposure on Asian workers (modified from reference 33, with some subsequently published studies).

Number of individuals	Air conc. (ppm) average ±SD (range)	NMF in urine	Results	Ref.
17 workers	DMF: 0.4 toluene: 0.12 8-h TWA, personal monitor (+ noise: 72.8 dBA)	-		52
15 workers	DMF: 2.5 toluene: 3.3 8-h TWA, personal monitor (+ noise: 75.2 dBA)	-	Significantly higher systolic pressure (at rest) vs. low-exposure group (0.4 ppm), adjusted OR vs. low exposure group 7.9 (0.9-66.3) for high blood pressure.	
9 workers	up to 5.13 TWA for morning or afternoon day shift (5 different days), personal monitor	0.4-19.56 mg/d	No effects on liver enzymes (ALAT, ASAT, AP, ɣ-GT)[1], possible alcohol intolerance in some workers.	41
10 workers	2.5-10.4 (GM) TWA, personal monitor, morning and afternoon day shift	24.7 ±5.4 mg/g creat.	No effects on liver enzymes (ALAT, ASAT, AP)[1].	32
143 controls	-	-	Alcohol intolerance in 10/40 men.	2
207 workers (=whole group exposed to DMF only)	4.5 (AM), 1.8 (GM) 8-h TWA, personal monitor, 6-45 measurements/ workplace	-	No significant effects on liver enzymes, increased prevalence of, for example, symptoms of irritation and gastrointestinal symptoms (dose-related/to a large extent dose-related increase in, e.g., blurred vision, vomiting, abdominal pain, dizziness, eye irritation and nasal irritation). Alcohol intolerance:	
59 workers (subgroup 1)	0.2 (AM), 0.1 (GM)	-	Subgroup 1: alcohol intolerance in 2/11 men.	
23 workers (subgroup 1)	0.4 (AM), 0.3 (GM)	-	Individual exposure data: 0.1-1.9 ppm: alcohol intolerance in	
17 workers (subgroup 1)	0.7 (AM), 0.6 (GM)	-	1/7 men. Subgroup 2: alcohol intolerance in	
65 workers (subgroup 2)	3.9 (AM), 2.3 (GM)	-	9/22 men. individual exposure data:	
43 workers (subgroup 3)	9.1 (AM), 7.0 (GM)	-	2-4.9 ppm: alcohol intolerance in 5/7 men (sign. increase). 5-9.9 ppm: alcohol intolerance in 4/5 men (sign. increase). Subgroup 3: alcohol intolerance in 11/15 men (sign. increase). individual exposure data: ≤10 ppm: alcohol intolerance in 6/7 men (sign. increase).	

Table 1. Continued.

Number of individuals	Air conc. (ppm) average ±SD (range)	NMF in urine	Results	Ref.
8 controls (matched)	-	-		4
12 workers	11.4±3.9 in the breathing zone, the whole shift	17.9 ±8.9 mg/l	Significantly reduced sperm motility.	
13 controls	-	-		36[2]
13 workers	10.6 (median) (6.65-34.5) in the breathing zone, the whole shift	13.8 (median) (7.5-73.6) mg/l	Increase in mutations in mitochondrial DNA (white blood cells) compared with controls.	
33 workers	≤0.8, individually calculated 8-h TWA, stationary	1.80 (GM) (ND-6.19) mg/g creat.	Percentage with elevated[3] liver enzymes: ALAT (8%), ASAT (6%), ɣ-GT (8%).	13[2]
24 workers	3-6.4, individually calculated 8-h TWA, stationary	9.61 (GM) (3.43-54.1) mg/g creat.	Percentage with elevated[3] liver enzymes: ALAT (16%), ASAT (12%), ɣ-GT (20%).	
22 workers	11.9, individually calculated 8-h TWA, stationary	26.5 (GM) (11.3-117) mg/g creat.	Percentage with elevated[3] liver enzymes: ALAT (22%), ASAT (13%), ɣ-GT (17%).	
176 workers (=whole group)	11.6 ±13.8 (0.1-86.6) TWA stationary: 21 sites, 30-180 min; personal monitor: n=45, 90 min mornings and afternoons	-		21
74 workers	2.9 ±1.1 (0.1-5)	-	Prevalence of elevated[4] liver enzymes (ASAT, ALAT or ɣ-GT) 22%.	
37 workers	6.4 ±0.7 (5.9-8.2)	-	Prevalence of elevated[4] liver enzymes (ASAT, ALAT or ɣ-GT) 27%, adjusted OR vs low-exposure group 1.62 (0.61-4.28).	
65 workers	24.6 ±15.6 (11.2-86.6)	-	Prevalence of elevated[4] liver enzymes (ASAT, ALAT or ɣ-GT) 37%, adjusted OR vs low-exposure group 2.93 (1.27-6.8); almost significant ($p<0.1$) higher average values for ASAT, ɣ-GT vs low-exposure group; chronic liver disease.	

Table 1. Continued.

Number of individuals	Air conc. (ppm) average ±SD (range)	NMF in urine	Results	Ref.
76 workers	<10 personal monitor; 10-minute samples	-	ALAT (12 ±7 IU/l) and ASAT (15 ±4)[5]; 6.4% had alcohol consumption >24 g/d.	38
83 workers	10-40 personal monitor; 10-minute samples	-	ALAT (16 ±8 IU/l) and ASAT (16 ±4)[5]; increased percentage with elevated CPK; 3.7% had alcohol consumption >24 g/d.	
24 workers	25-60 personal monitor; 10-minute samples	-	ALAT (18 ±8 IU/l) and ASAT (18 ±5)[5]; significant increase in abnormal ALAT (>35 IU/l); increased percentage with elevated CPK; none had alcohol consumption >24 g/d.	

AM = arithmetic mean, GM = geometric mean, TWA = time-weighted average, creat. = creatinine, sign. = significant, conc = concentration, h = hour
[1]Repeated measurements over 3 years.
[2]The study is not included in reference 33.
[3]ASAT >40, ALAT >45, ɣ-GT >30
[4]ASAT >34, ALAT >36, ɣ-GT >26
[5]Subgroup with individuals who tested negative for hepatitis B surface antigen in serum, HBsAg(-).

Luo *et al*. (21) also reported increased incidence of abnormal (elevated) liver enzymes (Table 1). The study involved Taiwanese workers at a plant producing synthetic leather, circuit boards and epoxy resins. OR adjusted for hepatitis B virus, alcohol, BMI, gender, length of employment, epichlorohydrin and toluene, was 2.93 (95% CI 1.27-6.8) for a group of individuals exposed to >10 ppm DMF (average 24.6 ppm), when compared with a low-exposure group exposed to <5 ppm (average 2.9 ppm). There was a significant dose-response between DMF exposure and the prevalence of abnormal values for liver enzymes (p=0.006). Ultrasonography was carried out on 35 of the 47 individuals with abnormal values for liver enzymes to assess chronic liver disease. Significant relationships were observed between high cumulative DMF exposure, increased BMI, and hepatitis B virus carrier status. The study includes no information on dermal uptake (21). It also lacks a non-exposed control group, so that effects in the medium- and low-exposure groups cannot be evaluated (33). In a subsequent study in DMF-exposed workers (partly the same as in reference 21) the authors reported that individuals who lacked the GSTT1 gene appeared to be more sensitive, with respect to hepatotoxicity, than those with the GSTT1 gene, especially with high DMF exposure (22).

Cai *et al*. (2) showed no exposure-related effects on liver enzymes in Chinese workers at a plant producing polyurethane plastic and synthetic leather. The majority were exposed almost entirely to DMF alone, with insignificant exposure to other solvents. The average for the whole of this group was 4.5 ppm (range not specified). No information was given on dermal uptake. When the group was

divided into subgroups based on the type of workplace the average values were ≤0.7 ppm DMF for subgroup 1, 3.9 ppm for subgroup 2 and 9.1 ppm for subgroup 3 (Table 1). Serum analysis [albumin, ASAT/ALAT, ɣ-glutamyltranspeptidase (ɣ-GT)], alkaline phosphatase/leucine aminopeptidase, lactate dehydrogenase, total bilirubin, amylase, BUN, creatinine) and analysis of blood cell counts (Hb, number of red/white blood cells and thrombocytes) showed no significant difference in the prevalence of abnormal values or borderline abnormal values for the DMF-exposed group, compared with the control group. Abnormal values for ASAT/ALAT were observed in 2 out of 206 workers and 2 out of 142 controls. No abnormal values were recorded for ɣ-GT or alkaline phosphatase. The prevalence of symptoms was examined with the help of a questionnaire. Compared with the control group there was a significant increase in, for example, eye/nose/throat irritation, blurred vision, cough, dizziness, nausea, vomiting, tightness of the chest, shortness of breath and abdominal pain. When subgroups with different levels of DMF exposure were compared, a dose-related, or essentially, dose-related increase was observed in several of the symptoms. Symptoms of reduced alcohol tolerance were also reported. There was a significant increase in the incidence of complaints of reduced alcohol tolerance in men from the highest-exposure group (subgroup 3) and a non-significant increase in the incidence in men from the medium-exposure group (subgroup 2). On the basis of measurement data that was available for relatively few individuals, an increase in reduced alcohol tolerance was demonstrated in individuals with an average exposure of 2-4.9 ppm (and above), compared with the control group.

Two Japanese studies using biological monitoring reported normal values for liver enzymes (Table 1). In one study the average exposure via air was up to 5.13 ppm DMF, as shown in personal monitoring samples taken in the morning or afternoon, but according to the authors dermal uptake could also have occurred. It was stated that some workers showed reduced alcohol tolerance (unclear how many had been exposed to DMF) but that none had experienced ”typical episodes of DMF-dependent alcohol intolerance” (41). In the second study personal monitor sampling in the breathing zone showed DMF exposure via air of 10.4 ppm (with different production processes). Lower values were obtained with stationary sampling. For the whole group (n=10) the average value for AMCC in urine was 22.0 mg/g creatinine (32).

Several studies have also been carried out in European populations (Table 2). A German cohort study (39, 40) in workers at a plant producing synthetic fibres showed significantly higher values for ASAT and ɣ-GT in a DMF-exposed group (n=126), compared with a control group (n=54). The median value for alcohol consumption (all test individuals) was given as 50 g/day. Average exposure to DMF (8 hours) was 4.1 ppm and the average value for NMF in urine after the shift was 9.1 mg/g creatinine. Dermal uptake of DMF may have occurred. When the group was divided into 3 subgroups (control/low-exposure/high-exposure group) it was observed that the low-exposure group had a higher liver index (ASAT + ALAT + ɣ-GT) than the high-exposure group (significance not stated). The liver

index was also higher in the low-exposure group than in the control group (significance not stated). The low-exposure group consumed roughly the same amount of alcohol as the control group (had the same average level) and significantly more alcohol than the high-exposure group. Average exposure (mean value) was 1.4 ppm DMF in the low-exposure group and 2.5, 6.4 and 7.3 ppm, respectively, in the high-exposure group (mean values for three types of workplaces). A division into nine subgroups based on both DMF exposure (none, low, high) and alcohol consumption (none, <50 g/day, >50 g/day) showed that the liver index was affected by both DMF exposure and alcohol, but the increase was greater with increased alcohol consumption than with increased DMF exposure. The liver index was higher in low-exposure individuals with alcohol consumption than in non-exposed individuals with alcohol consumption, (significance not stated). However, no significant difference in liver index was observed between subgroups without alcohol consumption (none/low/high DMF exposure). 23 of the 70 in the high-exposure group consumed no alcohol and had no significant increase in liver index. Average exposure for the high-exposure group was up to 7.3 ppm (Table 2). The study also reported that alcohol intolerance was more common amongst DMF-exposed than amongst non-DMF-exposed individuals (anamnestic data). In the exposed group (whole group) 15% (0% in the control group) stated that they had drunk less since taking up employment at the plant. Facial flushing and problems after alcohol consumption were mentioned by ca 70% of the exposed group, compared with 3.8% of the control group. The facial flushing occurred to a similar extent in the low-exposure and high-exposure groups (39, 40).

In two Italian cohort studies (7, 11) in workers at plants producing synthetic leather an increase was observed in liver enzyme levels in serum at average air concentrations of about 7 ppm. However, dermal uptake occurred and may have been extensive. The study by Fiorito *et al*. (11) included 75 workers potentially exposed to DMF and 75 non-exposed controls. Only individuals who drank <50 g alcohol/day were included in the study. Many in the exposed group reported gastrointestinal symptoms, e.g., nausea and abdominal pain, and signs of alcohol intolerance. 40% had disulfiram-like (”antabuse-like”) symptoms when consuming alcohol and the majority of those exposed stated that they consumed <20 g alcohol/day. The number of individuals in the control group with various symptoms was not given in the study. The exposed group was shown to have significantly higher average values for liver enzymes. Abnormal transaminase values were reported in 23% (4% in the control group). Statistical calculations indicated a relationship between DMF exposure and higher values for liver enzymes, even after adjusting for confounding variables (age, alcohol consumption, serum cholesterol, BMI). 8-hour time-weighted averages for DMF at different times during the working day (total of 32 samples taken) were 6-7 ppm, but values up to 12-13 ppm were reported. Dermal uptake, for example through gloves, was also thought to occur. Biological monitoring (in urine) showed large variations in values after the shift (11). SCOEL (33) stated that the analysis method for NMF in urine was insensitive and could give values that were too low.

Table 2. Effects of DMF exposure on European workers (modified from reference 33).

Number of individuals	Air concentration (ppm), average ±SD (range)	NMF in urine average ±SD (range)	Results	Ref.
54 controls	-	-	Facial flushing after alcohol intake[1] (3.8%).	39, 40
126 workers (=whole group)	4.1 ±7.4 (<0.1-37.9), median 1.2 personal monitoring, 8-h TWA, n=118	14.9 ±18.7 (0.9-100) mg/l, 9.1 ±11.4 (0.4-62.3) mg/g creatinine, n=125	Synergistic effect with alcohol, significantly higher values for liver enzymes (ASAT, ɣ-GT), facial flushing after alcohol intake[1] (69.9%).	
51 workers	1.4 ±2.2 (<0.1-13.7), median 0.7	4.5 ±4.3 (0.6-19.9) mg/g creatinine	Low-exposure group: no significant effects on liver index in serum in workers who do not drink alcohol, effect on liver index in workers who drink alcohol, facial flushing after alcohol consumption[1] (70.9%).	
12 workers	2.5 ±3.1 (0.1-9.8), median 1.4	6.7 ±5.4 (0.8-17.2) mg/g creatinine	High-exposure group: no significant effects on liver index in workers who do not drink alcohol, reduced alcohol consumption; facial flushing after alcohol intake[1] (66.2%).	
25 workers	6.4 ±9.6 (0.8-36.9), median 2.3	11.6 ±13.1 (0.9-62.3) mg/g creatinine		
30 workers	7.3 ±10.2 (0.3-37.9), median 2.8	16.0 ±15.9 (0.4-54.0) mg/g creatinine		
54 controls (matched)	-	-		3
28 workers	6 (4-8.2) 8-h TWA (no information on sampling method)	22.3 mg/l	No significant effects on liver enzymes (ASAT, ALAT, ɣ-GT, AP).	
26 workers	1 (0.6-1.6) as above	7 mg/l	As above.	
28 controls (not matched)	-	-		19
22 workers	(0.3-15.4) stationary	20.5-63 mg/g creatinine (average values after shift; 5 d.)	No abnormal effects on serum biochemistry (including ASAT, ALAT, ɣ-GT, AP), signs of alcohol intolerance in some workers (after peak exposure).	

Table 2. Continued.

Number of individuals	Air concentration (ppm), average ±SD (range)	NMF in urine average ±SD (range)	Results	Ref.
75 controls (matched)	-	-		11
75 workers	7.1 (GM) ±0.7 (1.6-13) n=10; 6.2 (GM) ±0.6 (0.7-12) n=22; stationary 8-h TWA	13.6 (GM) ±3.3 mg/l, 13.4 (GM) ±3.2 mg/g creatinine (0-126)[2, 3]	Significantly higher average values for liver enzymes (ASAT, ALAT, ɣ-GT, AP); abnormal transaminase values[4] (23% exposed vs 4% controls); 50% had gastrointestinal symptoms; reduced alcohol consumption in many individuals, at least 40% mentioned alcohol intolerance reactions.	
100 controls (matched)	-	-		7
100 workers	7.3 (2.6-19), personal monitoring TWA	-	Headache, gastrointestinal/hepatic symptoms; eye and throat irritation[5]; significant increase in abnormal values for ɣ-GT (25% vs 10%); alcohol intolerance (39% vs 1%), reduced alcohol consumption.	

[1]Anamnestic history data.
[2]22 workers.
[3]The analysis method underestimates exposure when compared with reference 39.
[4]ASAT and ALAT: ≥40 IU/l.
[5]Probably partly dependent on other exposures.

The study by Cirla *et al*. (7) showed an average concentration of DMF in air of 7.3 ppm (range 2.6-19), and dermal uptake was probable. There was a greater prevalence of hand eczema in the DMF-exposed group than in the control group. It was also reported that, for example headache, nausea, some gastrointestinal symptoms, symptoms of irritation (though this was thought to be partly due to other exposures), were significantly more common in exposed workers. In addition, it was stated that indications of ”liver function deterioration” (three typical symptoms) were more common in exposed workers (8 exposed, 2 controls). However, ɣ-GT (abnormal values) was the only biochemical parameter with significantly increased prevalence in the exposed group. On the basis of information on alcohol intake the authors concluded that DMF (besides alcohol) affected the ɣ-GT value. 5 of the 25 exposed individuals with abnormal ɣ-GT drank no alcohol, 11 drank moderately (<1 l wine/day or the equivalent) and 9 drank more (≥1 l wine/day or the equivalent). The corresponding figures for

controls were 1, 3 and 6 out of 10, respectively. Alcohol intolerance reactions were observed almost exclusively in the exposed group (39% vs 1%) and 32 out of 100 had reduced or eliminated their alcohol intake.

No significant effects on liver enzymes were reported in a previous cohort study from Italy which is described briefly. The average exposure in the most exposed subgroup was given as 6 ppm DMF, and the NMF concentration in urine was given as 22.3 mg/l (3). A previous Belgian study (19) also failed to show any effects on liver enzymes in exposed workers. The workers wore gloves throughout the entire shift in order to prevent skin contact with DMF. However, some workers showed signs of alcohol intolerance towards the end of the day, after peak exposure. The average values for DMF in air at different sampling stations in the plant were 0.3-15.4 ppm.

The prevalence of high blood pressure was investigated in a study in workers at a facility for producing synthetic leather. A comparison between a subgroup (n=15) with an average exposure of 2.5 ppm DMF and 3.3 ppm toluene and a subgroup (n=17) with an average exposure of 0.4 ppm DMF and 0.12 ppm toluene showed that the more exposed subgroup had significantly higher systolic blood pressure at rest (131.7 vs. 118.8 mm Hg). However, the latter group had a significantly higher BMI than the low-exposure group. In a multivariate logistic regression analysis (after controlling for gender, age, BMI, smoking and alcohol consumption) the Odds Ratio for high blood pressure was 7.9 (0.9-66.3). Noise exposure in these groups was 75.2 dBa and 72.8 dBa, respectively. The extent of dermal exposure to DMF and toluene (no workers wore gloves) was uncertain (5).

Animal data

In a study mice and rats were exposed via inhalation to 0, 25, 100 and 400 ppm DMF, respectively, 6 hours/day, 5 days/week for up to 18 months and 2 years, respectively. Reduced weight/weight gain was observed in rats exposed to 100 ppm (only male rats) and 400 ppm. By contrast, mice had higher weight/weight gain at 100 ppm (only female mice) and 400 ppm, compared with control groups. Exposure-related histopathological changes were only seen in the liver. Liver toxicity (including significantly increased incidence of ”single cell necrosis” and centrilobular hepatocellular hypertrophy and a significant increase in liver weight) was reported in rats (both sexes) at 100 and 400 ppm. A significantly increased incidence of microscopic changes in the liver (including centrilobular hepatocellular hypertrophy and ”single cell necrosis”) was observed in mice at all exposure levels. However, at 25 ppm there were minimal changes and a significant increase in incidence, principally in male animals. A significant increase in relative liver weight was demonstrated in male mice at ≥100 ppm and in female mice at 400 ppm. No exposure-related effects were observed in the eyes or respiratory tract in rats or mice at any air concentration. Nor were any effects on haematological parameters reported in either rats or mice. The NOEL for rats was calculated as 25 ppm. No NOEL could be established for mice (24). Benchmark calculations (Benchmark response 5% extra risk) based on morphological observations in

mouse liver (centrilobular hepatocellular hypertrophy) gave a Benchmark dose of 14.7 ppm for both sexes combined and the lower confidence interval for this dose was 7.8 ppm (33).

In two other inhalation studies mice and rats were exposed to 50, 100, 200, 400 or 800 ppm DMF, 6 hours/day, 5 days/week for 13 weeks. The liver was the primary target organ. In one study (34) a significant increase was observed in relative liver weight in male and female rats at levels of ≥100 ppm and ≥200 ppm, respectively. There was no significant increase in relative liver weight in female mice but an increase was observed in male mice exposed to ≥50 ppm. Significantly lower body weight, compared with controls, was reported at doses ≥400 ppm (rats) and ≥50 ppm (male mice), respectively. A significant increase in the incidence of liver damage, including ”single cell necrosis” was observed in rats (both sexes) at levels ≥200 ppm and centrilobular hepatocellular hypertrophy was observed at exposures ≥400 ppm. A significant increase in the incidence of centrilobular hepatocellular hypertrophy was observed at all exposure levels in male mice and at 800 ppm in female mice. Focal hepatic necrosis was observed in the livers of mice, but the incidence was significantly increased only in female mice (at 100-400 ppm). The lower confidence interval for the Benchmark dose (Benchmark response 10% extra risk) was 1.1 ppm (male rats), 13.1 ppm (female rats) and 1.1 ppm (male mice) based on increased relative liver weight, and 68.5 ppm (male rats), 191 ppm (female rats), 17.5 ppm (male mice) and 372.5 ppm (female mice) based on hepatocellular hypertrophy (34). In the other study (23) a significant increase in relative liver weight was reported in both rats and mice at air concentrations ≥50 ppm (both sexes). Concentration-dependent reductions in body weight were also observed in rats at ≥400 ppm. In an extensive histopathological study (carried out in control animals and at an exposure of 800 ppm) exposure-related effects were only seen in the liver. Liver damage was examined in all groups. Liver damage was observed in rats at air concentrations ≥400 ppm, including minimal-to-moderate centrilobular hepatocellular necrosis. Minimal-to-mild centrilobular hepatocellular hypertrophy was reported in mice, at air concentrations ≥50 ppm in males and ≥100 ppm in females (23). A LOEC of 50 ppm, based on increased relative liver weight, was reported from the study (33).

DMF is stated to be an eye irritant in rabbits but not a skin irritant in rabbits and rats (33). DMF was not a sensitiser in the local lymph node assay (25).

Genotoxicity

DMF has been examined in a large number of genotoxicity tests *in vitro* and *in vivo*. IARC stated that the results in well-executed studies were consistently negative throughout, i.e., they indicated that DMF was not genotoxic (16). IARC also stated that reports of chromosome damage in workers exposed to DMF did not consider smoking as a possible cause (bias) or were not fully documented (16). A cytogenetic study (26 exposed, 26 controls) which did not appear in IARC (16) reported a significant increase in chromosomal aberrations, sister chromatid exchanges and UDS (unscheduled DNA synthesis), but it was uncertain whether

DMF exposure was a significant factor. There was said to be a high degree of simultaneous exposure to acrylonitrile (high concentrations) (33). In another study not assessed by IARC no significant relationship was observed between DMF exposure and SCE frequency. The result was based on data from 85 workers with low or high DMF exposure and no exposure or varying degrees of exposure to epichlorohydrin (6).

A Taiwanese study involving 13 DMF-exposed workers and 13 matched controls showed that mutations in mitochondrial DNA (in white blood cells) were more common in the exposed group. Mitochondrial DNA undergoes mutation more easily than genomic DNA and is a particularly sensitive marker for oxidetive stress and for, for example, ageing. Data further indicated that the mutations in mitochondrial DNA were more pronounced with higher DMF exposure. The median concentration of DMF in air was 10.6 ppm (range 6.65-34.5) and the median concentrations of NMF and AMCC in urine were 13.8 mg/l (range 7.5-73.6) and 40.7 mg/l (range 6.8-442), respectively. There was no information on possible dermal uptake. No individuals in the control group had detectable levels of DMF, NMF or AMCC (36).

Carcinogenicity

IARC reported that it was not possible to assess whether DMF was carcinogenic ("inadequate evidence") on the basis of epidemiological data (on, for example, testicular cancer) and that animal data suggest that the substance is not carcinogenic ("evidence suggesting lack of carcinogenicity") (16). An increase in tumours was observed in a study in which rats and mice were exposed via inhalation to 0, 25, 100 and 400 ppm DMF, 6 hours/day, 5 days/week, for 2 years and 18 months, respectively (24). IARC's overall assessment, which was based on this study and on human data, was that it was not possible to classify DMF with regard to carcinogenicity to humans (group 3) (16).

In later inhalation studies rats and mice of both sexes were exposed to 0, 200, 400 or 800 ppm DMF, respectively, 6 hours/day, 5 days/week for up to 2 years. A significant increase in the incidence of hepatocellular adenoma was observed in rats exposed to 400 ppm (male rats; however, the incidence in female rats was higher than in historical controls) and 800 ppm (both sexes). The incidence of hepatocellular carcinoma increased significantly at 800 ppm (both sexes). Preneoplastic hepatic changes (altered cell foci) increased significantly in both sexes at levels ≥400 ppm and in female rats also at 200 ppm. A significant increase was reported in cystic degeneration in the liver with exposures ≥200 ppm (male rats). Increased values for liver enzymes in serum were also observed along with a significant increase in relative liver weight in all DMF-exposed groups (rats). A dose-dependent reduction in growth was observed in both sexes and survival in female rats was significantly affected at 800 ppm (many died from liver necrosis). For mice there was a significant and dose-dependent increase in the incidence of hepatocellular adenoma and carcinoma at ≥200 ppm (both sexes). A significant increase in the incidence of hepatoblastoma was also reported (male mice: 200,

400 ppm). The incidence of preneoplastic changes in the liver also increased significantly (≥200 ppm, both sexes). Moreover, a significant increase in relative live weight was reported as well as an increase in liver enzymes in serum at all exposure levels (both sexes). Non-neoplastic, dose-dependent lesions were observed in the liver, particularly in male mice (≥200 ppm). There was also a dose-dependent reduction in growth, principally in male mice. Histopathological examination revealed no DMF-related neoplastic or non-neoplastic lesions in organs other than the liver, either in mice or rats (35). The study has been criticised with regard to the exposure. It was stated that aerosol formation and thereby dermal and/or peroral uptake may have occurred (18).

The same authors subsequently published a cancer study in male rats exposed by inhalation for 6 hours/day, 5 days/week (0, 200, 400 ppm), via drinking water (0, 800, 1600 mg/l) or by both inhalation and drinking water. A significant, dose-dependent increase in the incidence of hepatocellular adenoma was observed with inhalation exposure (≥200 ppm) and with exposure via drinking water (≥800 mg/l), and there was a significant increase in carcinomas with 1600 mg/l in drinking water. It was also observed that the incidence of hepatocellular tumours increased more than additively with the combined exposure and that malignancy also increased. A more than additive increase in cell proliferation (% PCNA-positive hepatocytes, cell proliferation marker) had also been observed in a previous study involving combined exposure and this was said to be a possible explanation for the increased carcinogenic effect with the combined exposure. The estimated daily intake with inhalation exposure to 200 and 400 ppm was 121 and 242 mg/kg body weight/day, respectively. The corresponding figures for exposure via drinking water (800, 1600 mg/l) were 44 and 82 mg/kg body weight/day, respectively (29).

Effects on Reproduction

Significantly reduced sperm motility was observed in 12 DMF-exposed workers at a synthetic leather plant, when compared with 8 matched controls. A dose-response relationship was reported with the urine concentration of the metabolite NMF, but not with the air concentration of DMF. The average level of DMF in air was 11.4 ppm and of NMF in urine 17.9 mg/l (4). The effects on sperm in the study were characterised with the help of special computer technology which, according to the authors, gives more reliable results than traditional microscopy. However, the exposure conditions are only briefly described. There is no information on possible skin exposure.

No exposure-related effects on the oestrous cycle were observed in either rats or mice after long-term inhalation exposure to 400 ppm DMF (6 hours/day, 5 days/week). And no changes regarded as exposure-related were seen in histopathological examination of sex organs (both male and female animals were examined) (24). Sperm were examined in a 13-week study in rats and mice exposed by inhalation to 50, 200 or 800 ppm (6 hours/day, 5 days/week). No effects on sperm were observed in mice and no effect on sperm motility in rats (on the other hand, an increased number of sperm was seen in rats at all exposure levels) (23). Nor

was any effect on sperm (number, motility, morphology) observed in a study in monkeys exposed by inhalation to 30, 100 or 500 ppm DMF, 6 hours/day, 5 days/week for 13 weeks (15).

In a multigenerational study 1000, 4000 or 7000 mg/l DMF in drinking water was given to mice (both sexes) which were exposed continually and which bred during weeks 2-15 of exposure. Reduced body weight was observed in the parent generation at the highest dose level (only in females). Significantly increased liver weights were seen at all exposure levels in both sexes. A significant increase in cauda epididymis weight (≥1000 mg/l) and significantly lower prostate gland weight (7000 mg/l) were also reported. A small decrease was observed in spermatid counts in the testes (significant at 1000 and 7000 mg/l), but there was no significant effect on sperm concentration/sperm motility or the proportion of abnormal sperm. Nor was any abnormal exposure-related histopathology (reproductive organs) observed. Over the course of the study fertility gradually decreased and there was a significant deterioration with respect to the final litter at levels ≥4000 mg/l (e.g., fewer pregnant females, fewer surviving young/litter, fewer litters, lower weight of newborn). Malformations also increased in exposed animals (proportion of litters with one/several abnormal young: 10.5%, 90%, 78%; 7.9% in controls). Reduced survival of young was also observed during the suckling period at ≥4000 mg/l. A substudy examined whether female and/or male animals were affected reproductively. Either female or male mice were exposed to 7000 mg/l DMF and paired with non-exposed animals. The data indicated that it was females that were affected by the exposure (lower birth weights, malformations). Another study examined fertility and reproductive parameters in generation two (the F_1 generation). In general, roughly the same effects were seen as in the parent generation, though in some cases at lower doses. For example, the weight of newborn young was already significantly lower with exposure to 1000 mg/l. The proportion of litters with one/several externally malformed young was 27.7% (significance uncertain), 60% and 75%, compared with 0% in controls. There was also a significant reduction in relative prostate weight at all exposure levels and lower absolute prostate weight at levels ≥4000 mg/l. Significantly reduced body weight was also observed in the F_1 generation in both sexes at doses ≥4000 mg/l. A significant increase in liver weight was reported at all dose levels (both sexes) (10).

A study in which mice (182, 548 mg DMF/kg body weight/day) and rats (166, 503, 1510 mg DMF/kg body weight/day) were fed by gavage on days 6-15 of gestation, reported an increase in, for example, malformations (both species) at doses ≥500 mg/kg body weight/day (14). In mice which received 548 mg/kg body weight/day 7% of the foetuses were malformed (0.5-0.9% in controls); the malformations included cleft palate and exencephaly; no effects were observed in the mothers. Smaller foetuses and increases in retardations and variations were also seen at this dose level. At 182 mg/kg body weight/day some animals were shown (in the absence of maternal toxicity) to have malformations (1.6%, not signifycant), including cleft palate, significantly shorter foetuses and an increase in

retardations and variations. In rat mothers dose-dependent effects were observed in the form of reduced body weight gain at the two highest doses, and there was a significant, dose-dependent reduction in placental weight at all doses. A well as malformations, the two high-dose groups showed a dose-dependent effect in the form of smaller foetuses and an increase in resorptions. At the dose level 166 mg/kg body weight/day there was a small non-significant increase in early resorptions. LOELs (borderline prenatal toxicity) of 182 and 166 mg/kg body weight/day were reported in mice and rats, respectively (14). A study in rats fed by gavage on days 6-20 of gestation (50, 100, 200, 300 mg DMF/kg body weight/day) reported maternal toxicity (significantly reduced weight gain and food intake) and significantly lower foetal weight at doses ≥100 mg/kg body weight/day plus a significantly increased incidence of two skeletal variations at doses ≥200 mg/kg body weight/day. No significant increase in malformations was observed in any dose group. The NOAEL for maternal toxicity and developmental toxicity was 50 mg/kg body weight/day (31).

An inhalation study in rabbits (50, 150, 450 ppm, 6 hours/day on days 7-19 of gestation) reported significantly lower foetal weight and a significant increase in malformations and variations at 450 ppm. No significant changes were reported at 150 ppm but the authors concluded that there was a marginal effect (increase in some skeletal variations). Maternal toxicity was observed at 450 ppm (lower body weight) and to some extent at 150 ppm (reduced weight gain). The NO(A)EL for mothers and foetuses was given as 50 ppm. The authors stated that exposure to 150 ppm was equivalent to ca 45 mg DMF/kg body weight/day (14). An inhalation study in rats (287 ppm, 6 hours/day, at various stages of gestation) recorded an increase in early resorptions and implantation associated pregnancy loss, smaller foetuses (length, weight) and an increase in variations/retardations (but no increase in malformations). There was reduced weight gain in mothers and lower placental weight (14). In another inhalation study rats were exposed to 30 or 300 ppm DMF (6 hours/day on days 6-15 of gestation). At 300 ppm there was a reduction in weight gain in mothers and foetal weight was somewhat lower (significant), but there was no increase in malformations. 30 ppm was given as the NOAEL for both maternal toxicity and development toxicity (20).

With dermal exposure in rabbits (skin application, semi-occlusive; 100, 200, 400 mg DMF/kg body weight/day, 6 hours/day, days 6-18 of gestation) Hellwig *et al.* (14) reported a teratogenic effect (including skeletal malformations) in the high dose group. A somewhat lower (significant) body weight gain was observed in mothers in this group. The NOAEL was estimated at 200 mg/kg body weight/day (14). The same authors exposed rats (via the skin) to 94, 472 or 944 mg DMF/kg body weight/day, 3 hours/day, on days 6-10 and 13-15 of gestation. A largely dose-dependent increase in foetuses with variations and retardations was observed. There was also a dose-dependent increased number of live foetuses with ”malformations” per litter (2.46%, 3.05%, 5.46% vs 0 in controls; significant at the highest dose) which according to the authors could indicate a weak teratogenic effect and a (linear) dose-response relationship. (However, the most common type

of "malformation" observed, wavy ribs, is not always regarded as a malformation). At the highest dose foetuses were somewhat shorter (significant). There was no evident maternal toxicity but body weight gain was initially somewhat lower (significant) in mothers in the high dose group. A significant reduction in placental weight was observed in all exposed groups (non-dose-related) (14). In another study in rats with dermal exposure (DMF applied in a compress) on days 6-15 (0.25, 1 or 2 ml/kg body weight/day) or on days 1-20 (2 ml/kg body weight/day) during gestation, significant effects were observed, including a reduction in the pregnancy rate, increased post-implantation losses, a reduced number of foetuses per litter, lower foetal weight, delayed ossification and maternal toxicity (lower body weight/lower body weight gain) at the dose level 2 ml DMF/kg body weight/day. The LOEL was given as 1 ml/kg body weight/day (950 mg/kg body weight/day) (a somewhat lower foetal weight, increased incidence of delayed ossification; somewhat lower body weight gain in mothers) (12, 33).

Dose-effect-/dose-response relationships

Effects on the liver have been reported in DMF-exposed workers (Tables 1, 2). Alcohol intolerance (due to inhibition of certain ethanol-metabolising hepatic enzymes) has been observed in some studies at air concentrations as low as 1.4 ppm. Other types of effects on the liver, such as elevated levels of liver enzymes (markers of liver damage) in the blood, have been reported in some studies at the same or slightly higher air concentrations, whereas in other studies such effects have not been reported at these air concentrations (see below). It is difficult on the basis of epidemiological data to give an air concentration at which the effects start to occur because there are synergistic effects with alcohol and there may be dermal uptake. The measurement of urinary metabolites (NMF, AMCC) could be a better way to assess exposure.

A German study reported signs of alcohol intolerance (facial flushing) in 71% of a low-exposure group with an average exposure of 1.4 ppm DMF (range <0.1-13.7 ppm) and in 3.8% of a non-exposed control group (39, 40). Dermal uptake of DMF may have contributed. The low-exposure group also had a higher liver index (ASAT + ALAT + ɣ-GT) than the control group (significance not specified). A further division into subgroups showed that the liver index was affected most by increased alcohol consumption. The liver index was higher in the low-exposure group with alcohol consumption than in the non-exposed group with alcohol consumption (significance not specified). However, there was no significant difference between the groups without alcohol consumption but with varying degrees of DMF-exposure (none/low/high). 23 of the 70 individuals in the high-exposure group consumed no alcohol and did not have a significantly increased liver index. Average exposure for the high-exposure group was up to 7.3 ppm (Table 2). When the entire group of DMF-exposed workers was compared with the control group, significantly higher values for ASAT and ɣ-GT were observed. The average exposure was 4.1 ppm DMF (39, 40).

A Chinese study also reported an increased incidence of complaints of alcohol intolerance in DMF-exposed men (2). There was also a significant increase for individuals with an average exposure of 2.4-9 ppm, but the result was based on personal data from relatively few individuals. No exposure-related effects on liver enzymes were observed in groups of workers with an average exposure of up to 9.1 ppm DMF. However, when compared with the control group, there was an increased prevalence of symptoms (including symptoms of irritation, dizziness, nausea, vomiting, tightness of the chest, and breathlessness). Several of the symptoms were said to increase in line with DMF exposure. The average concentration of DMF in air for the entire group was 4.5 ppm. There was no information on dermal uptake (2).

Two Japanese studies reported normal values for liver enzymes with an average exposure via air of up to 5.1 ppm (also dermal absorption) and 10.4 ppm DMF, respectively (32, 41). The study with average exposure up to 5.1 ppm reported that some workers were less tolerant to alcohol but had not experienced ”typical episodes of DMF-related alcohol intolerance”. It was also unclear how many of them had been exposed to DMF (41).

Two Italian studies (7, 11) showed increases in liver enzymes in serum and in alcohol intolerance reactions at average air concentrations of around 6-7 ppm (group average). However, dermal uptake had occurred and may have been extensive. Another Italian study (3) reported no significant effects on liver enzymes. The average exposure in the most exposed subgroup was given as 6 ppm DMF (range 4-8.2 ppm). An earlier Belgian study (19) also showed no effects on liver enzymes but alcohol intolerance was observed in some workers (after peak exposure). The average values for DMF in air at different sampling stations were 0.3-15.4 ppm.

No significant effects were reported on measured parameters for liver function, e.g., elevated values for liver enzymes, in a Chinese study with average DMF air concentrations (8-hour time-weighted average) of up to 12 ppm. However, a dose-dependent percentage increase (non-significant) was observed in individuals with elevated values for ASAT and ALAT. When workers were instead divided into groups on the basis of NMF and AMCC concentration in the urine, i.e., <15 or ≥15 mg/g creatinine (NMF) and <40 or ≥40 mg/g creatinine (AMCC), respectively, a significant increase was reported in the number of individuals with elevated values for liver enzymes and other markers for liver damage at AMCC ≥40 mg/creatinine (13).

Luo *et al*. (21) reported an increased risk of elevated liver enzyme levels in a group of individuals with time-weighted averages of DMF >10 ppm (group average: 24.6 ppm), compared with a low-exposure group (<5 ppm DMF; average 2.9 ppm). The study did not include a non-exposed control group. In a later study the authors reported that individuals who lacked the GSTT1 gene appeared to be more sensitive with respect to liver toxicity than those who had the GSTT1 gene (22).

Chang *et al*. (4) reported a significant reduction in sperm motility in 12 DMF-exposed workers, compared with 8 matched controls. Average levels of DMF in air and NMF in urine were 11.4 ppm and 17.9 mg/l, respectively. A dose-response relationship was seen with the urine NMF concentration but not with the air DMF concentration. The study does not mention the extent of any dermal uptake (4). Shieh *et al.* (36) showed an increased occurrence of mutations in mitochondrial DNA in white blood cells in a study of 13 DMF-exposed workers. The mutations reported were more pronounced at higher DMF exposure. The median concentration of DMF in air was 10.6 ppm (range 6.65-34.5) and the median concentrations of NMF and AMCC in urine were 13.8 mg/l and 40.7 mg/l, respectively. The study does not give the extent of dermal exposure. According to the authors mutations in mitochondrial DNA are regarded as markers for oxidative stress, and in the literature oxidative stress has been suggested as a mechanism for DMF-induced toxicity. The study by Shieh *et al*. (36) is seen as a follow-up to the reproductive toxicity study (4) as it shows DMF's mitochondrial toxicity and because mitochondrial toxicity is a feasible explanation for the results in the reproductive toxicity study (effects on sperm). The mitochondrial study strengthens the credibility of the reproductive toxicity study.

Animal studies

Inhalation studies with repeated exposure to DMF are summarised in Table 3.

Effects on the liver

Effects on the liver have been observed with repeated inhalation exposure to DMF at air concentrations of ≥25 ppm in mice and ≥50 ppm in rats (23, 24, 34, 35). Benchmark calculations (5% extra risk) based on morphological observations in mouse liver (centrilobular hepatocellular hypertrophy; both sexes combined) from the study by Malley *et al*. (24) gave a Benchmark dose of 14.7 ppm and the lower confidence interval for this dose was 7.8 ppm (33). Use of data from another study (34) in the Benchmark calculation gave a lower confidence interval (10% extra risk) of 1.1 ppm (male rats), 13.1 ppm (female rats) and 1.1 ppm (male mice) based on increased relative liver weight, and 68.5 ppm (male rats), 191 ppm (female rats), 17.5 ppm (male mice) and 372.5 ppm (female mice) based on hepatocellular hypertrophy.

Preneoplastic changes in the liver have been reported to increase with long term exposure to DMF, in mice at air concentrations ≥200 ppm (both sexes) and in rats at air concentrations ≥200 ppm (females) and ≥400 ppm (males). Increased incidence of liver tumours (adenoma, carcinoma) was observed in mice at air concentrations ≥200 ppm (both sexes). A significant increase in the incidence of hepatoblastoma was also reported (male mice: 200, 400 ppm). An increased incidence of hepatocellular adenoma was reported in male and female rats at air concentrations of ≥400 ppm and 800 ppm, respectively. An increased incidence of hepatocellular carcinoma was observed at 800 ppm (35). In another cancer study

Table 3. Effects on research animals in inhalation studies with repeated exposure to DMF.

Exposure	Animal species	Effects	Ref.
25 ppm 6 h/d, 5 d/wk, 2 years	rats	NOEL for chronic toxicity (including hepatotoxicity[1]).	24
25 ppm 6 h/d, 5 d/wk, 18 mo	mice	Minor effects on the liver (hypertrophy, single cell necrosis).	24
30 ppm 6 h/d, days 6-15 of gestation	rats	NOAEL for maternal toxicity and developmental toxicity.	20
50 ppm 6 h/d, 5 d/wk, 13 wk	rats	Effects on the liver (increased weight).	23
50 ppm 6 h/d, 5 d/wk, 13 wk	mice	Effects on the liver (increased weight; mild hypertrophy in male animals).	23
50 ppm 6 h/d, 5 d/wk, 13 wk	mice	Effects on the liver (increased weight, hypertrophy) and reduced body weight in male animals.	34
50 ppm 6 h/d, days 7-19 of gestation	rabbits	NOAEL for maternal toxicity and developmental toxicity.	14
100 ppm 6 h/d, 5 d/wk, 2 years	rats	Effects on the liver (increased weight, increased SDH activity, hypertrophy, single cell necrosis in female animals), lower body weight/weight gain in male animals.	24
100 ppm 6 h/d, 5 d/wk, 18 mo	mice	Effects on the liver (hypertrophy, single cell necrosis, increased weight in male animals), increased body weight gain in female animals.	24
150 ppm 6 h/d, days 7-19 of gestation[2]	rabbits	Some effects on body weight in mothers, increased frequency of skeletal variations in foetuses (not significant).	14
200 ppm 6 h/d, 5 d/wk, 2 years[3]	rats	Liver tumours (adenoma).	29
200 ppm 6 h/d, 5 d/wk, 2 years	rats	Effects on the liver (including increased weight, increase in enzymes, e.g., ASAT/ALAT, preneoplastic changes), reduced growth.	35
200 ppm 6 h/d, 5 d/wk, 2 years	mice	Liver tumours (significant increase in adenomas and carcinomas and, in male animals, also in blastomas), other effects on the liver (increased weight, increase in enzymes, e.g., ASAT/ALAT, increase in non-neoplastic and preneoplastic changes, principally in male animals).	35

Table 3. Continued.

Exposure	Animal species	Effects	Ref.
287 ppm 6 h/d, during parts of gestation	rats	Reduced weight gain in mothers, increase in resorptions/implantation losses, increase in retardations/variations, fewer foetuses.	14
300 ppm 6 h/day, days 6-15 of gestation	rats	Reduced weight gain in mothers, slightly lower foetal weight.	20
400 ppm 6 h/d, 5 d/wk, 2 years	rats	Effects on the liver (increased weight, increased SDH activity, hypertrophy, single cell necrosis), lower body weight/body weight gain.	24
400 ppm 6 h/d, 5 d/wk, 2 years	rats	Liver tumours (significant increase in adenomas in male animals), other effects on the liver (including increased weight, increase in enzymes, e.g., ASAT/ALAT, preneoplastic changes), reduced growth.	35
400 ppm 6 h/d, 5 d/wk, 18 mo	mice	Effects on the liver (increased weight, hypertrophy, single cell necrosis), increased body weight/body weight gain.	24
400 ppm 6 h/d, 5 d/wk, 2 years	mice	Liver tumours (significant increase in adenomas and carcinomas and, in male animals, also in blastomas), other effects on the liver (increased weight, increase in enzymes, e.g., ASAT/ALAT, increase in non-neoplastic and preneoplastic changes, principally in male animals), significantly lower body weight in male animals.	35
450 ppm 6 h/d, days 7-19 of gestation	rabbits	Effect on body weight in mothers, increase in malformations and variations, lower foetal weight.	14
500 ppm 6 h/d, 5 d/wk, 13 wk	monkeys	NOAEL for general toxicity (including liver toxicity) and for effects on sperm.	15
800 ppm 6 h/d, 5 d/wk, 2 years	rats	Liver tumours (significant increase in adenomas and carcinomas), other effects on the liver (including increased weight, increase in enzymes, e.g., ASAT/ALAT, preneoplastic changes), reduced growth.	35
800 ppm 6 h/d, 5 d/wk, 2 years	mice	Liver tumours (significant increase in adenomas and carcinomas), other effects on the liver (increased weight, increase in enzymes, e.g., ASAT/ALAT, increase in non-neoplastic and preneoplastic changes, principally in male animals), significantly lower body weight.	35

h = hours, d = days, wk = week/weeks, mo = months, SDH = sorbitol dehydrogenase

[1]A small (significant) increase in sorbitol dehydrogenase (SDH) activity was seen by the authors as insufficient reason to give this value as a LOEL.

[2]Said to be equivalent to 45 mg/kg body weight/day.

[3]Estimated daily intake 121 mg/kg body weight/day.

in male rats a significant increase was observed in the incidence of hepatocellular adenoma at air concentrations ≥200 ppm. An increase was also reported in the incidences of hepatocellular adenoma and carcinoma with exposure to ≥800 mg/l and 1600 mg/l, respectively, in drinking water. The daily intake with inhalation exposure to 200 and 400 ppm was estimated at 121 and 242 mg/kg body weight/day, respectively. The corresponding figures for exposure via drinking water (800, 1600 mg/l) were 44 and 82 mg/kg body weight/day, respectively (29).

Liver tumours were observed in two long-term studies in mice and rats (29, 35), but not in a third study in which, however, exposure was to some extent lower (24). Available data suggest that the carcinogenic effect is related to the liver toxicity observed in short-term studies in animals (23, 34) and is probably related to the liver toxicity that is also seen in humans (7, 11, 13, 21, 38). The LOEL for liver toxicity in animals has been given as 25 ppm (24) and a Benchmark dose (10%) as 1.1 ppm (34). Extrapolation from animal studies to humans is unreliable because of quantitative differences in metabolism between humans and animals related to the formation of AMCC (26, 33) and a complex interaction with ethanol observed in human studies (7, 11, 40). However, the lack of clear genotoxic data suggests that cancer develops only after long-term exposure and above a non-defined exposure threshold.

Effects on Reproduction

A teratogenic effect was shown in a study in rabbits exposed via inhalation to 450 ppm. Marginal effects on foetuses (non-significant increase in certain variations) were observed at 150 ppm. According to the authors this dose is equivalent to ca 45 mg DMF/kg body weight/day. This study gave a NO(A)EL of 50 ppm for maternal and developmental toxicity in rabbits (14). Maternal toxicity (reduced body weight gain, lower placental weight), foetotoxicity and embryolethality (but not an increase in malformations) were observed in rats exposed by inhalation to 287 ppm (14). Another study in rats (20) reported reduced weight gain in mothers and some reduction in foetal weight (no increase in malformations) at 300 ppm. 30 ppm was given as the NOAEL for both maternal toxicity and developmental toxicity (20).

With dermal application a teratogenic effect and slight maternal toxicity was reported in rabbits given 400 mg DMF/kg body weight/day. The NOAEL was estimated at 200 mg/kg body weight/day (14). In rats a largely dose-dependent increase was observed in the number of foetuses with variations and retardations with dermal exposure to 94, 472 and 944 mg/kg body weight/day. A dose-dependent increase was also observed in foetuses with "malformations", though the significance was unclear at both the lower doses. Reduced placental weight was observed at all dose levels (not dose-related). Maternal toxicity, expressed as a reduction in body weight gain, was observed at the highest dose. In a further study in rats (dermal exposure) a LOEL of 1 ml/kg body weight/day (950 mg/kg body weight/day) was given for the reproductive effects (delayed ossification, some reduction in foetal weight). Some maternal effect was observed (12, 33).

Significant reproductive and developmental toxicity (including an increase in malformations and reduced fertility) was reported in a multigenerational study in mice where 4000 mg/l DMF was given in drinking water (stated to be roughly equivalent to 820 mg/kg body weight/day). At 1000 mg/l DMF in drinking water (stated to be roughly equivalent to195 mg/kg body weight/day) the weight of newborn was lower and there was an increased incidence of malformations (significance uncertain). There was a significant increase in liver weight at all dose levels (1000, 4000, 7000 mg/l) in both female mice (mothers) and male mice. No NOAEL was obtained in the study (10). In another study doses ≥500 mg/kg body weight/day (by gavage) caused an increased incidence of malformations in mice, without maternal toxicity, and in rats with some degree of maternal toxicity; a dose-dependent reduction in placental weight was observed in rat mothers at all doses (166, 503, 1510 mg/kg body weight/day) as well as reduced body weight gain at the two highest doses. The LOEL (borderline prenatal toxicity) was given as 182 (mice; no maternal toxicity) and 166 mg/kg body weight/day (rats) (14). A study in which rats were fed 50-300 mg/kg body weight/day by gavage reported an increased incidence of two skeletal variations at doses ≥200 mg/kg body weight/day and lower foetal weight at doses ≥100 mg/kg body weight/day. No significant increase in malformations was observed in any dose group. The NOAEL for maternal toxicity and developmental toxicity was 50 mg/kg body weight/day (31).

Conclusions

The critical effect of occupational exposure to DMF is the inhibition of enzymes in the liver that metabolise alcohol (which results in alcohol intolerance) and other substances. Two studies report signs of alcohol intolerance at 1.4-4.9 ppm DMF. Adverse liver effects, expressed as increased levels of liver enzymes in blood, can occur at the same or slightly higher air concentrations. DMF is also easily absorbed through the skin and it is difficult to give an air concentration at which these effects occur as epidemiological studies lack data on amounts of dermal uptake.

Milder effects on the liver have been observed in mice with repeated exposure to 25 ppm DMF. Liver tumours have been observed in research animals with much higher levels of DMF exposure and are thought to result from more advanced liver damage.

One study showed an effect on sperm (reduced sperm motility) at an average concentration of 11.4 ppm. This was a small study and further studies are needed before any firm conclusions can be drawn as to whether DMF affects sperm motility at these levels. In research animals other reproductive toxic effects have been observed at substantially higher air concentrations.

DMF is easily absorbed through the skin, both as a vapour and as a liquid. Urinary metabolite concentrations (NMF, AMCC) may, therefore, be a better measure of exposure than air DMF concentration. Dermal uptake through contact with DMF in liquid form can substantially exceed uptake via inhalation and may lead to serious liver damage.

Potential conflicts of interest

Gunnar Johanson (member) has declared that he was involved in SCOEL's evaluation of DMF in 2006.

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Consensus Report for Dichloromethane (Methylene chloride)

December 10, 2014

This report is based partly on a report from National Toxicology Program (59) and on a report from ATSDR (8). Data searches were carried out in PubMed up to and including August 2014.

Physical-chemical data

CAS no.	75-09-2
Synonyms:	Methylene chloride, methane dichloride, DCM
Empirical formula	CH_2Cl_2
Molecular weight:	84.93 g/mol
Boiling point:	40 °C at 760 mm Hg
Melting point:	-97 °C
Vapour pressure:	46.1 kPa
Density:	1.3 kg/dm^3 at 25 °C
Solubility in water:	20 g/l at 20 °C
Conversion factor:	1 mg/m^3 = 0.284 ppm, 1 ppm = 3.52 mg/m^3
Partition coefficients:	fat:air, 65.8; muscle:air, 9.9; blood:air, 9.1 (35).
	Log $K_{oil/water}$: 1.25

Occurrence and use

Dichloromethane (DCM) is a solvent which at room temperature is a colourless liquid with a sweetish smell. The substance is stable at room temperature but can form explosive compounds in environments with high oxygen contents. DCM is miscible with alcohol, ether, dimethylformamide and carbon tetrachloride (60).

DCM is mainly used as a solvent in paint and grease removal and cleaning, in the manufacture of pharmaceuticals, in various chemical processes and as a propellant in aerosols. DCM was previously used as an extraction agent in the production of some food products and coffee and, in some countries, as a pesticide. In 2009 DCM was being produced by 26 companies throughout the world (60). In 1993 DCM was banned in consumer products in Sweden and in 1996 its industrial used was banned, though there were exceptions for which special permission was required (33). A ban on the use of DCM, or mixtures containing DCM, in products for paint and lacquer removal was also introduced in the EU in 2012. The ban mainly concerns consumer products. The industrial or occupational use of DCM in paint removal is permitted but safe handling is required, with effective ventilation and protective equipment. It is also required that operators have

sufficient information, instructions and training for handling the equipment (25). In 2007 127 tonne DCM (raw material) was imported into Sweden, of which ca 40 tonne was used as a laboratory chemical and ca 70 tonne as a solvent in the pharmaceuticals industry. Ca 15 tonne were exported as raw material. No DCM was produced in Sweden in 2007 but chemical products containing 11 tonne DCM (5 tonne in paint removal agents and 4 tonne in degreasing and cleaning agents) were imported. Of the 42 products that contained the substance, 3 were available to consumers (Kemikalieinspektionen 2014: http://apps.kemi.se/flodessok/floden/_flodenbild/floden.cfm?id=1012). Sales of DCM in Sweden decreased from 1172 ton in 1993 to 129 tonne in 2011 (Kemikalieinspektionen 2014: http://www.kemi.se/sv/Innehall/Statistik/Kortstatistik/Kortstatistik-over-amnen-och-amnesgrupper/Klorerade-losningsmedel/). A supervisory campaign in Stockholm in 2003 showed that 11 companies were still using DCM but that most had reduced their usage since 1996 (78).

Air measurements in the work environment

An exposure study in Taiwan examined the levels of DCM in individuals who worked in paint removal and painting aircraft. Measurements of exposure in paint removal showed average DCM levels of 20-42 ppm (standard deviation 11-32 ppm) over a total work period of 28 hours (85). On two occasions (spring and autumn) exposure measurements revealed levels of 26 and 120 ppm DCM (8 hours, TWA) for American car mechanics who carried out paint removal work. For 3 different work tasks short-term exposure (9-18 min) involved levels of 72, 93 and 120 ppm (24).

Uptake biotransformation excretion

The most important exposure route for DCM is inhalation. DCM can also be taken up through the skin and via the gastrointestinal tract. With inhalation, 31-75% is absorbed (1), 25-34% of which is excreted as carbon monoxide (65). Following inhalation of air containing 50 to 200 ppm DCM, 70-75% of the DCM taken up was excreted unchanged in exhaled air (8, 19). Absorption via the lungs can be affected by physical work and by body fat (8). Excretion of DCM occurs primarily through exhalation but also via urine (8).

An absorption study in 1964 examined dermal uptake in workers at Dow Chemicals, USA. Four volunteer workers immersed their thumbs in ca 90 ml DCM for 30 minutes. Exhaled air from both non-exposed control individuals and the study subjects was analysed. After dermal exposure the solvent was allowed to evaporate. DCM was absorbed by the skin several times more rapidly than four other chlorinated solvents that were examined in the study (carbon tetrachloride, trichloroethylene, tetrachloroethylene and 1,1,1-trichloroethane). The research subjects felt intense pain in their exposed thumb within two minutes of the start of exposure, after which this feeling gradually decreased and the thumb became numb. Skin reddening appeared after exposure but both redness and numbness

disappeared within one hour after the end of exposure. Exhaled air contained 11 mg DCM/m^3 at the end of exposure and 2 hours later the concentration had fallen to 2.4 mg/m^3 (74).

With exposure, DCM is distributed throughout the body, mainly in fatty tissue and the liver (8). At lower exposures (200-500 ppm) DCM undergoes biotransformation, mainly via the CYP450 system, above all by CYP2E1, and carbon monoxide (CO) is formed (5, 8, 53). At higher concentrations the CYP450 system becomes saturated and DCM is therefore mainly metabolised by the enzyme GSTT1 to formaldehyde and S-(chloromethyl)glutathione (5). Both these metabolites are seen as important in tumour development. Formaldehyde can give rise to DNA protein adducts (crosslinks) and the glutathione metabolite that is formed is reactive and can form large (”bulky”) DNA-adducts (5). The dose-dependent switch from CYP- to GST-mediated metabolism represents a biologically feasible model to explain the non-linear risk of cancer of the liver in experimental animals subjected to DCM exposure (6). In humans DCM has also been associated with liver cancer, but above all with bile duct cancer (cholangiocarcinoma). Two studies on expression of the enzyme GSTT1 in humans have shown that the bile duct epithelium contains higher levels of GSTT1 than do hepatocytes (66, 71), but there is no expression of CYP4502E1 (66). The risk of cancer may possibly be affected in individuals with GSTT1 polymorphisms (36, 73), where a high expression may increase the risk (23).

Biological exposure monitoring

DCM in exhaled air is a common exposure marker that has been detected up to 24 hours after high exposure (8). About 70-75% of the DCM that is taken up is excreted unchanged via exhaled air following inhalation of 50 to 200 ppm (8, 20). As excretion via the lungs occurs rapidly during the first hour, the measurement of DCM in exhaled air is only relevant 6-8 hours after exposure (20). DCM can also be detected in blood but disappears quickly, so this method is also of limited usefulness. Inhaled DCM in plasma has a half-life of 40 minutes (21).

DCM can also be measured in urine. Air exposure levels correlate well with urine concentrations (65). When DCM was measured, using gas chromatography, in urine samples from 95 workers (50 men and 45 women) the concentration of DCM in most urine samples was between 0.01 and 0.3 mg/l. The concentration of DCM in air was between 0 and 100 ppm in most samples (65). Concentrations of 5.2 ppm were measured in a workplace in Israel and urine samples from 7 workers had DCM concentrations of 0.02-0.06 mg/l (31).

As CO is formed in CYP metabolism, carbon monoxide bound to haemoglobin, carboxyhaemoglobin (COHb), has been proposed as a biomarker for DCM exposure, but smokers and others exposed to CO also have elevated COHb (77). After a working day, workers exposed to 7-90 ppm DCM (8 hours TWA) had average COHb concentrations of 1.7-4.0% (non-smokers) and 5.0-6.4% (smokers). Volunteer research subjects exposed to 200 ppm DCM for four hours had COHb levels of about 5%. Immediately after exposure to 50, 100, 150 and 200 ppm DCM,

volunteer non-smokers had blood COHb levels of 1.9, 3.4, 5.3 and 6.8%, respectively (20). In workers at a cellulose triacetate plant at Lanakan in Belgium a linear dose-response relationship was observed between DCM exposure (1-159 ppm) and COHb concentration in blood (4). In a study with volunteer research subjects (non-smokers) Soden *et al*. showed that exposure to 100 ppm DCM (7.5 hours) resulted in COHb concentrations of 3.4-5.7%, exposure to 200-250 ppm in 6.8-9.6%, and exposure to 500 ppm in 11.4% COHb (72). The COHb concentration was 0-2% in non-exposed nonsmokers and 2-6% in non-exposed smokers (72).

The Finnish Institute of Occupational Health (Arbetshälsoinstitutet) recommends measuring COHb in blood directly after the end of exposure to DCM, when the ”biomonitoring action limit” is set at 4% (http://www.ttl.fi/en/work_environment/biomonitoring/pages/default.aspx, 2014-04-08). In the EU, SCOEL has recommended that DCM is measured in blood or urine, since the measurement of COHb gives "normal values" for smokers. SCOEL proposes thresholds of 1 mg/litre in blood and 0.3 mg/litre in urine when carrying out measurements directly after a shift (67). ACGIH also recommends measuring DCM in urine directly after a shift and gives a BEI (Biological Exposure Index) of 0.3 mg/litre (1). The Health and Safety Executive (HSE) in the UK recommends a method for monitoring DCM exposure as exhaled CO (http://www.hsl.gov.uk/media/66149/carbon%20monoxide_layout%201.pdf, 2014-05-19). A CO concentration of ca 30 ppm in exhaled air is equivalent to an air concentration of DCM which gives COHb levels below 5%. HSE recommends that exhalation samples are taken at the end of the work shift. However, smoking and other forms of CO exposure may contribute to elevated COHb levels.

Toxic effects

Human data

Acute toxicity with DCM exposure mainly involves the central nervous system. DCM is converted to CO in the body and can give rise to COHb levels of up to 30%. COHb can have acute toxic effects and, primarily in earlier literature, COHb has sometimes been ascribed the role of a mediator of DCM effects in, e.g., the CNS. Table 1 has been compiled in order to facilitate a comparison of the effects described for DCM exposure with the effects described for inhalation of air with elevated CO levels.

COHb levels with DCM exposure were studied in 11 healthy male volunteers aged 23-43. In experiment 1, one volunteer was exposed to 213 ppm DCM for 1 hour. The COHb level rose from an initial 0.4% to 2.4% 3 hours after the end of exposure. No symptoms were reported. In experiment 2, three volunteers were exposed to 986 ppm for 2 hours. One person complained of a headache after 1 hour of exposure. An effect on VER (Visual evoked response) was observed for all three. The COHb level was 10% after 1 hour of exposure (average), and 17 hours after the end of exposure the COHb level was still elevated (average 3.9%).

Table 1. Comparative data: COHb in blood and the effect of raised CO levels in inhaled air.

COHb (%)	Effect
<10	See the table text below
10	Shortness of breath with vigorous exercise
13	Effect on the CNS development of children
20	Shortness of breath with moderate exercise, occasional headache
25	Stillbirths
30	Headache, dizziness, irritation.
40-50	Headache, confusion, unconsciousness upon exertion
60-70	Unconsciousness, respiratory failure, convulsions, death
80	Rapidly fatal

The table shows the guideline values taken from NEG 2012 (77). For COHb below 10% it is stated that 3-7% COHb results in reduced stamina and in cardiovascular effects. Cardiovascular effects (altered ECG p-wave) have been demonstrated at 2.4% COHb and 7.1% COHb. Decreased lung ventilation but no ECG effects were observed at 3.4-4.3% COHb. At 5.1% COHb there was a decrease of 10% in the duration of the post-exposure exercise but no cardiovascular effects (77). At 2.4 or 4.7% COHb, CO-exposed individuals with stable exertional angina experienced angina and ST changes more quickly than when not exposed to CO (3). The foetus is more sensitive than adults and effects on the foetus have been reported (77).

In a third experiment, 3 individuals were exposed to 514 ppm for 1 hour and then to 869 ppm for a further 1 hour. 15 minutes after exposure to the higher dose one of the individuals experienced headache. VER was affected in all three individuals. Clinical-chemical and haematological tests were normal and no symptoms of irritation were reported at any of the exposure levels (75).

Several case studies have reported deaths associated with very high exposure to DCM (8, 16, 51, 80). An American report from 2012 described 12 DCM-related deaths associated with the repair and lacquering of bath tubs between the years 2000 and 2011. The products used contained 60-100% DCM (16). Another study reported two cases of fatal poisoning following acute exposure to 168,000 ppm DCM while burying drums containing solvents. The work was carried out in a well 2 metres underground without any ventilation. The DCM concentrations in the blood of the workers were 572 and 601 mg/l, respectively, and their blood COHb levels were 30% (8, 52). The cause of death associated with very high exposure may depend on effects on the central nervous system, including unconsciousness and respiratory depression (8).

One case report describes a 64-year-old man who became unconscious in a tank containing only small amounts of DCM (38). The man had probably inhaled DCM fumes for ca 1 hour. The COHb level in his blood was 7.5% but fell to 0.4% within 4 days. The man's condition worsened within a month of the accident and he scored 19 out of 30 points in a neuropsychological test, which indicated mild dementia (38). The man also experienced a limited field of vision in both eyes after

a month and a mild cataract was observed. His vision gradually deteriorated in the 3 years after the accident.

Acute exposure to DCM caused cardiac arrest in two workers exposed to high levels of DCM (no information on concentration is given). Two individuals who helped in the rescue work complained of dizziness and nausea. The COHb level in one of the workers who later died rose for 9 hours after the exposure, despite oxygen treatment. The authors conclude that the fatalities were probably not due to the high levels of COHb but to solvent-induced narcosis. They also point out that rescue and emergency service personnel without protective equipment may themselves suffer acute effects if the DCM concentration is high (47).

A case report from 2005 describes a man who suffered unilateral facial paralysis associated with DCM exposure. Eleven Israeli soldiers worked for 3 hours removing paint stains from the floor using paint remover containing DCM in a closed room without ventilation or protective equipment. All complained of headache, dizziness and throat irritation. On the following day one of the soldiers woke with facial paralysis but he had recovered completely after 3 weeks. The authors estimate an exposure of between 1000 and 5000 ppm (34).

During the period 1961-80, 118 incidents of acute effects of solvents (DCM, xylene, toluene, styrene) in the UK were reported to Her Majesty's Inspectorate. It was estimated that 33 of these incidents were caused by DCM. The individuals involved had worked in, for example, painting, the production of chemicals, paints or adhesives, paint removal and cleaning. In 13 cases exposure had resulted in unconsciousness. Other commonly reported symptoms were dizziness (11/33 cases) and headaches (9/33 cases). Other symptoms reported were confusion (2 individuals), respiratory symptoms such as coughing, breathlessness and tightness of the chest (4 individuals), and gastric symptoms (13 individuals) (9).

One woman who was exposed to DCM experienced a sudden bilateral hearing loss several days after exposure. The woman initially had a COHb level of 6.9% which fell to 5.1% on day 2. After 25 days of oxygen treatment the hearing-associated symptoms disappeared (13). The article gives no information on exposure levels.

A case report describes a 66-year-old man who died from cardiac infarction after using a paint remover containing 80% DCM while painting, which was a hobby. The man had worked in a closed room in the cellar without ventilation. On two previous occasions the man had been taken to hospital with acute chest pains, on the second occasion with an acute cardiac infarction, after having worked with the paint remover, but at the time no connection had been made between the illness and his hobby activity (76).

After 4 hours of exposure to 200 ppm and 300 ppm DCM volunteer research subjects reported effects on their vision and hearing, and psychomotor changes were also observed. The subjects had COHb blood levels of 5%. One case of dementia has been reported following exposure to 500-1000 ppm for 3 years (8).

The long-term effects of DCM on the central nervous system were studied in a group of 46 workers at an acetate film plant. The workers were exposed to a mix-

ture of DCM and methanol (9:1) and the air concentration of DCM was between 75 and 100 ppm. The men worked in three different shifts, up to 3 days in a row. Twelve men with the same shift work but not exposed to solvent were also included in the study as a reference group. Six of the exposed men reported symptoms [pain in the arms, chest pain when sitting or lying down, or chest pain with physical activity and stress (”walking or hurrying”)] which could be related to heart disease (none amongst those not exposed). The workers also reported CNS symptoms: frequent headaches, dizziness, balance problems, memory disorders, and numbness and tingling in the hands and feet. Twenty men (43%) in the exposed group reported CNS symptoms, compared with 1 individual in the control group (8%). Twenty-nine men who were exposed for at least 10 years reported CNS symptoms more frequently than those exposed for a shorter time (at least one symptom reported). 29 of the exposed workers (and 29 new controls) took part in a follow-up. The exposed workers showed worse results in a motor test (dotting rapidly on either side of two parallel lines 10.5 cm apart) but in other neurological tests the exposed group achieved better results than the reference group. The authors conclude that the study does not show any differences in the long-term effects of DCM (18).

The effect on mood of DCM exposure during a shift was studied in 44 workers from the same plant as above. The workers were exposed to 28-173 ppm DCM (a mixture of DCM and methanol 9:1) and 36 control individuals were included in the study. The workers rated themselves on a scale of tiredness, from wide awake to very sleepy. One time test measured the ability to substitute digits with symbols. A visual reaction test was also included. DCM- and COHb-levels in blood were measured before and after the shift, as also were DCM air concentrations. The results showed significant correlations between the DCM concentration in blood and mood changes, physical fatigue, sleepiness, and a reduced feeling of "good health". One of the test results (the digit symbol substitution) showed deterioration (17). The workers had previously been chronically exposed to DCM but these effects were related to exposure over a single shift. A statistically significant difference between exposed workers and controls was observed for the morning shift (06.00-14.00). Exposure measurements were recorded daily in the study.

Irritant effects in the eyes and respiratory tract were reported in 12 Swedish graffiti removers (7, 8). The graffiti removers had filled in a questionnaire that had been sent to them earlier and on the day when exposure measurements were taken they were interviewed about symptoms of irritation, etc. Blood and urine samples were taken after the end of work. The solvent mixture used contained DCM, N-methyl-2-pyrrolidone, glycol ethers and trimethylbenzene, and air concentrations were measured over one day with personal monitors. The air concentrations of N-methyl-2-pyrrolidone, glycol ethers and trimethylbenzene were low or undetectable. For DCM the 8-hour average values varied between 18 and 1200 mg/m^3 [5-340 ppm, average 260 mg/m^3 (74 ppm)]. The work was often carried out in cramped, poorly ventilated spaces where exposure levels could become very high and

the measured short-term values (15 minutes) varied between 6 and 5315 mg/m^3 [2-1510 ppm, average 1117 mg/m^3 (320 ppm)], with the highest short-term value being measured for work in a lift. Respiratory protection was not used. The hands were frequently exposed to cleaning fluid and protective gloves, if any were worn, were made of leather. Both the questionnaire and the interview showed a signify-cant increase in symptoms of irritation (eye irritation, nasal congestion and nasal catarrh) when compared with the values from previously gathered data on the prevalence of symptoms of irritation in randomly selected individuals living in the same area as those who were exposed. No changes were seen in the concentrations of creatinine, aspartate transaminase, alanine transaminase, and gamma-glutamyl-transpeptidase in blood samples (markers of liver toxicity), nor of alpha-1-micro-globulin, beta-2-microglobulin or N-acetyl-beta-glucosaminidase (markers of renal toxicity) in urine samples, which could be related to exposure. Nor were there any acute effects on the central nervous system. The authors concluded that the symptoms of irritation were caused by solvents used by the graffiti removers, including DCM (7, 8).

A group of 25 retired aircraft mechanics who had worked on average for 12 years and had been exposed to solvents for at least 6 years between 1970 and 1986, were compared with a non-exposed reference group. The workers' tasks included paint removal, repair, renovation and repainting. DCM exposure ranged from low concentrations up to 800 ppm, average ca 100 ppm (the average was higher, 225 ppm, for those working in paint removal). No significant differences between the groups were observed in various neurological tests (including olfac-tion, vision, grip strength, visual and verbal memory). The exposed group achie-ved higher results for verbal memory but lower results in tests of concentration (though the difference was not significant) (46). Although the article uses the word "solvents" it does not specify any other solvent exposure. The reference group comprised retired business and union representatives with a low probability of solvent exposure. Individuals in the reference group had not worked for more than 2 years on other jobs within the company. No exposure data was found for individuals in the reference group but, on the basis of interviews and assessments of work tasks, it was concluded that the extent of solvent use was small.

An increase in red blood cells, haemoglobin and haematocrit was reported in women exposed to high concentrations of DCM (average 475 ppm) at a plant manufacturing cellulose triacetate. These effects were not observed in men. More than 60% of the exposed workers (men and women involved in the study) had been exposed for less than 5 years; only 3% had been exposed for less than one year (63). The workers had been allocated to groups corresponding to average exposures of 140 ppm (low exposure), 280 ppm (medium exposure) and 475 ppm (high exposure). A difference between men and women was only seen in the high exposure group (475 mm).

A number of studies in workers exposed to levels of 26-1700 ppm DCM failed to show any electrocardiographic effects or increased mortality from heart disease (8). No relationship was observed between exposure and heart disease, SMR

(standardised mortality ratio) = 0.9 (95% CI 0.65-1.2), in a cohort of workers in cellulose fibre production exposed to DCM (140-475 ppm). Comparisons were made with the general population. The authors point out that a ”healthy worker effect” could explain the low value (45). A cohort study involved 1473 male workers employed during the period 1946-1988 in the production of cellulose triacetate film. The cohort was monitored up to and including 2006 and the relationship between cumulative exposure to DCM and mortality from ischaemic heart disease was analysed using Cox regression. This analysis included 1034 exposed and 312 non-exposed workers. Average exposure for those exposed was 19 ppm. The relative risk of cumulative exposure at 1000 ppm-years was calculated as 1.47 (95% CI 0.91-2.39) for death from ischaemic heart disease (83).

Animal data

The effect of DCM has been examined in many animal studies; an illustrative selection is given below. For summaries of various animal studies refer to ATDSR (8).

Studies in animals have shown that high concentrations of DCM can lead to unconsciousness and death (8). Acute exposure (4-8 hours) to DCM at 16,000-19,000 ppm was lethal for rats and mice. Also, long term exposure to DCM 1000-16,000 ppm was lethal for various animal species, including rats, mice, guinea pigs, rabbits and dogs (8).

After the end of the exposure period rats exposed to DCM for 19 days (3250-16,000 ppm) had lower weights than control animals and animals with lower exposure (1625 ppm). Weight loss was also observed in rats exposed to 8400 ppm DCM for 13 weeks. Rats exposed to 4000 ppm DCM for 2 years exhibited restless behaviour and showed itching around the eyes and nose during the exposure period (59). Mice exposed to DCM for 19 days (16,000 ppm) showed hyperactivity which was considered to be related to chemical exposure. Hyperactivity was also seen in mice exposed to 4000 ppm DCM for 2 years (dose-response), and was most noticeable in females. During the final year of exposure to 4000 ppm the females showed lethargic behaviour (59).

In rats which inhaled DCM (70 ppm) there was a reduction in metabolism and dopamine levels in certain parts of the brain, and a dose-dependent change in noradrenaline levels was observed at 70-1000 ppm (26). The animals had been exposed for 6 hours/day for 3 days. Gerbils exposed to DCM (350 ppm for 3 months, plus 4 months without exposure) had increased concentrations of GFA protein and the protein S-100 in the frontal and sensorimotor cortices (64). These increases may be a sign of astrogliosis and an indication of brain damage. After three months of exposure to 210 and 350 ppm, DNA concentrations in the hippocampus and cerebellum were significantly reduced when compared with control animals, which is a sign of cell death in these areas of the brain (64). Further mechanistic studies of CNS effects, at high exposure levels, are described in the review of Bale *et al*. 2011 (10).

High concentrations of DCM cause lung damage and pulmonary inflammation in rats, mice and guinea pigs. Mice exposed to 200,000 ppm DCM suffered cardiac arrhythmias. Corneal thickening has been reported in rabbits after acute exposure to 490 ppm (8). DCM exposure resulting in COHb levels of 4-7% has been shown to affect nerve conduction velocity in the peripheral nervous system (87).

Fatty liver and an increase in liver enzymes in plasma have been observed in animals exposed to DCM. Fatty liver disease was observed in guinea pigs exposed to 5000 ppm DCM for 6 months. Similar effects were observed in monkeys, mice and dogs following exposure to 5000 ppm for 4 weeks. Liver enzymes were increased in plasma in rats exposed to 250 ppm DCM for 10 days. Repeated exposure to 200-500 ppm DCM for 2 years caused hepatocellular vacuolization in the liver of rats, but no effects were observed with exposure to 50 ppm (8). NTP's two-year study in rats showed effects on the liver such as haemosiderosis, hepatocellular necrosis, bile duct fibrosis and inflammation (59).

Dogs exposed to 1000 ppm DCM for 4 weeks and rats exposed to 5000 ppm for 14 weeks developed renal tubular vacuolisation. Tubular degenerative and regenerative changes were observed in rats after continuous exposure to 25 and 100 ppm for 100 days. Dogs and monkeys subjected to the same exposure showed no tubular degenerative or regenerative changes (8) (no further details are available). After 2 years of exposure renal changes were observed in rats exposed to 2000 ppm (59).

Genotoxicity

In vitro

A study examined cytotoxicity (MI, mitotic index), cell proliferation (CPK, ”cell proliferation kinetic value”) and genotoxicity (SCE, sister chromatid exchange) in peripheral blood cells (mononuclear) exposed to DCM *in vitro*. The blood cells were taken from 20 healthy men and the material was divided into three groups: group I comprised cells from individuals with low GSTT1 activity (n=4); group II, cells from individuals with medium activity (n=10); and group III, cells from individuals with high activity (n=6) (<0.1, 0.33 ±0.03 and 7.37 ±1.35 nmol formaldehyde/min/mg protein, respectively). A multivariate analysis showed that the results for all three measured parameters (MI, CPK, SCE) were related to the specific GSTT1 activity (MI and CPK negatively and SCE positively correlated) and that the differences were significant from 60 ppm upwards (62). The authors used a headspace technology to measure concentrations of DCM but it unclear whether the values given refer to the gas phase or to the concentration in the incubations and it is difficult to draw any quantitative conclusions from the study.

Human data

The frequencies of HPRT mutations, chromosomal changes, micronuclei and SCE were examined in lymphocytes from 46 workers exposed to both styrene and DCM, as well as in lymphocytes from 23 controls. The average exposure (TWA)

to DCM was 108 mg/m^3 (0-742 mg/m^3), which is equivalent to 31 ppm [exposure to styrene was 17 ppm, which is an effect level for genotoxicity (55)]. The cytogenetic parameters were significantly increased in all samples from the workers. However, the authors did not draw any conclusions on mutagenicity because of insufficient control data (82).

Animal data

DCM has shown positive results in a number of different genotoxicity tests. Studies have shown that mice are more sensitive to DNA damage in DCM exposure than are rats (29).

Single strand DNA breaks were detected in liver and in lung homogenate from mice exposed to 4000-8000 and 2000-6000 ppm DCM (29). On the other hand, no liver DNA damage (single-strand breaks) was observed in rats exposed to 4000 ppm DCM for 6 hours (28). There were reduced numbers of single-stand breaks in hepatocytes from mice and rats exposed to DCM which were incubated with buthionine sulphoximine (which reduces glutathione levels). The result indicates that DCM induction of DNA damage involves conjugation with glutathione. According to the authors this probably occurs via the metabolite S-chloromethyl-glutathione, as the level of the metabolite formaldehyde was too low (28).

Because of the large number of cases of bile duct cancer among printing workers exposed to dichloropropane (DCP) and DCM (see the section Carcinogenicity), the genotoxic effects of both these substances were studied singly and in combination (79). Mice of strain B6C3F1 were exposed to 400, 800 or 1600 ppm DCM, or to 150, 300 or 600 ppm DCP, or to the combination DCM + DCP, 400 + 150 ppm or 800 + 300, ppm via inhalation, 6 hours per day, 5 days per week, for 6 weeks. Genetically modified mice (gpt Delta C57BL/6J) were also exposed to DCP (300 ppm), DCM (800 ppm) or DCP + DCM (300 + 800 ppm) to study mutagenic effects in the liver. Significantly increased levels of DNA damage were detected in the liver using the Comet Assay following DCP exposure (300 and 600 ppm) but no significant effect was observed after DCM exposure only. The combination DCP and DCM produced still higher levels of DNA damage which indicates that DCM can potentiate DNA damage caused by DCP. Neither DCP nor DCM caused mutations or chromosomal changes in haematopoetic cells. In experiments with genetically modified mice an increase was observed in mutation frequency in the liver only after combined exposure to DCM + DCP. Mutations of a different type than in control animals indicates that a solvent-related mechanism lay behind the mutagenicity in the exposed animals (79). The research examined the effects on the whole liver and not on the bile duct separately which reduces the relevance of the study to the risk assessment of DCM with respect to bile duct cancer. A non-significant increase in point mutations was also observed in animals exposed to the highest concentration of DCM; these mutations were not seen in control animals.

Carcinogenicity

Human data

In 2014 IARC upgraded DCM from group 2B (possibly carcinogenic to humans) to group 2A (probably carcinogenic to humans) (12). The new classification was mainly based on newer studies which showed cancer in the bile duct, on studies which showed an increased risk of non-Hodgkin's lymphoma in humans, and on sufficient evidence of cancer in animals. Table 2 summarises epidemiological studies of cancer risk in individuals occupationally exposed to DCM.

Table 2. Epidemiological studies of cancer risk associated with exposure to DCM in occupationally exposed individuals.

Exposure/number	Occupation/industry/ type of study	Results	Ref.
80-540 ppm (for an average of 4 years) 62 men, 1991-2006	Offset printing plant, Osaka, Japan	11 men diagnosed with bile duct cancer, SMR = 2900 (95% CI 1100-6400). Comparison with the Japanese population. Ten of these men were exposed to DCM, and all 11 to DCP. Average age at diagnosis 36 years; average age at death 37 years (6 workers). Total of 17 cases (2013) of bile duct cancer out of a total of 70 exposed.	40, 42, 43, 86
140, 280, 475 ppm (average exposure for the 3 main work tasks); a total of 1271 workers participated	Cellulose fibre production	Tumours of the liver and bile duct, SMR = 5.8 (95% CI 1.8-14).	44
140, 280, 475 ppm (average exposure for the 3 main work tasks); a total of 1271 workers participated	Cellulose fibre production	Tumours of the buccal cavity, SMR = 1.5 (95% CI 0.18-5.4) (2 cases). Tumours of the liver and bile duct, SMR = 3.0 (95% CI 0.81-7.6) (4 cases, of which 3 cases were bile duct cancer). Melanoma, SMR = 1.9 (95% CI 0.24-7.0) (2 cases).	45
Nordic occupational cancer database, 74,949 printing workers	Printing workers in the Nordic countries	Liver cancer SIR = 1.4 (95% CI 1.1-1.6). Intrahepatic bile duct cancer SIR = 2.3 (95% CI 1.5-3.6).	88
DCM exposure	Meta-analysis DCM exposure	Cancer of the pancreas, meta-relative risk = 1.4 (95% 0.8-2.5).	61
19 ppm (average) for 9 years (average). 1473 workers participated in the study.	Production of cellulose triacetate	Small increase in cancer of the brain (8 observed, compared with 4.4 predicted).	83

Table 2. Continued.

Exposure/number	Occupation/industry/ type of study	Results	Ref.
Exposed to chlorinated solvents	Case control study	Glioma/meningioma, odds ratio = 0.5 (95% CI 0.3-0.9).	56
300 cases, 320 controls	Case control study, workers in the chemical and petrochemical industries	Brain tumours (astrocytoma, glioblastoma, glioma with astrocytic cells, odds ratio 2.4 (95% CI 1.0-5.9). For those employed for more than 21 years the odds ratio was 6.1 (95% CI 1.1-44).	30
DCM exposure	Meta-analysis	Multiple myeloma, odds ratio 2.0 (95% CI 1.3-3.2).	49
Previous work with DCM	Case control study	Multiple myeloma, 2.0 (95% CI 1.2-3.2).	27
Previous work with DCM	Case control study	Lymphoma, 0-≤26.3 ppm x years, odds ratio = 0.4 (95% CI 0.2-1.0); >26.3-≤175 ppm x years, odds ratio = 0.8 (95% CI 0.3-1.9); >175 ppm x years, odds ratio = 2.2 (95% CI 0.4-12).	68
Previous work with DCM	Case control study	Non-Hodgkin's lymphoma, odds ratio 1.5 (95% CI 1.0-2, 3).	86

SMR = Standardised mortality ratio

A meta-analysis from 2013 showed a significant increase in the risk of multiple myeloma with an odds ratio of 2.0 (95% CI 1.3-3.2) with exposure to DCM (based on three studies). No significant increase in risk was seen for other types of cancer: non-Hodgkin's lymphoma 1.3 (95% CI 0.86-1.7), based on 6 studies; leukaemia OR=1.2 (95% CI 0.54-2.7), based on 3 studies; breast cancer OR=1.0 (95% CI 0.48-2.2), based on three studies; cancer of the brain and CNS OR=1.1 (95% CI 0.78-16), based on five studies; of the airways and lungs OR=0.82 (95% CI 0.62-1.1), based on five studies; of the liver and bile duct OR=1.7 (95% CI 0.30-9.6), based on two studies; of the rectum OR=1.1 (95% CI 0.71-1.8), based on three studies; of the pancreas OR=0.97 (95% CI 0.93-1.1), based on four studies; and of the prostate OR=0.76 (95% CI 0.51-1.1), based on three studies. When it was suspected that diagnoses of non-Hodgkin's lymphoma and multiple myeloma had been wrongly classified, this data was pooled which resulted in an odds ratio of 1.4 (95% CI 1.0-1.8). A total of 5 different cohort studies and 13 different case-control studies were included in the meta-analysis (49). Eight of these studies are described separately in this document: (11, 27, 30, 45, 56, 68, 83, 86). Assessment of exposure for 10 of the studies was based on a job exposure matrix, while 8 studies used self-reported exposures, occupational history and cumulative exposure (49). The authors point out that false classification with regard to exposure is generally a limiting factor in epidemiological studies. Only five studies where adjusted for smoking. There were probably mixed exposures involving several solvents.

A case-control study, including 601 cases of non-Hodgkin's lymphoma (NHL) and 717 control individuals, was carried out amongst women in Connecticut to examine the relationship to exposure to solvents. A job-exposure matrix was used to assess occupational exposure. An increased risk of NHL was associated with previous solvent exposure (odds ratio 1.4, 95% CI 1.1-1.8). Exposure to DCM gave an odds ratio of 1.5 (95% CI 1.0-2.3). However, no significant dose-response trend was observed in the analysis of exposure intensity (86).

The relationship between cancer and exposure to DCM was studied in a cohort of workers in cellulose fibre production in 1990 (44). The study involved 1271 workers who had been employed for at least 3 months between 1954 and 1976 at the company in Rock Hill, South Carolina, USA. Data on DCM exposure was lacking for large parts of the study period but the exposure was assumed to be substantially higher than for, e.g., manufacturers of photographic film (an average of 26 ppm TWA over 22 years). An occupational hygiene study from 1977 had shown DCM levels (8 hour TWA) of up to 1700 ppm DCM. Average exposures for the three main work tasks were 140, 280 and 475 ppm. Exposure was mainly to DCM but there was also concomitant exposure to methanol (DCM:methanol 9:1, methanol up to 140 ppm) and acetone (up to 1600 ppm). Detailed occupational information was obtained for 356 workers who were employed at the time of the study and for 119 workers who had ended their employment after 1979. The status of the cohort was given for the period January 1954 to September 1986 and was compared with the national cause of death statistics. Mortality was also compared with that of the general local population (York County). 53% of the cohort's workers had been employed for at least 10 years. 122 deaths were identified amongst 29,960 person years and death certificates were found for 118 individuals. For most causes of death SMR was near to 1.0 but significant increases were seen for cancer of the liver and bile duct: SMR 5.8 (95% CI 1.8-14). There were four observed cases, compared with the 0.35 expected. A more detailed analysis showed that three workers who had died from liver or bile duct cancer had been exposed to DCM for 28, 20 and less than 1 year, respectively, but there was a lack of information on the fourth worker. Two of the three workers who died from bile duct cancer were women, aged 47 and 60. A follow-up study was carried out in 1993. The type of cancer with the highest SMR (standardised mortality ratio) was cancer of the buccal cavity SMR=1.5 (95% CI 0.18-5.4), based on 2 cases; cancer of the liver and bile duct SMR=3.0 (95% CI 0.81-7.6), based on 4 cases (of which 3 cases were bile duct cancer); and melanoma SMR=1.9 (95% CI 0.24-7.0), based on 2 cases. The workers were compared with the general population (45). Both studies by Lanes *et al*. (44, 45) have low power. The cohort was originally assembled to look at cardiovascular disease and the findings of tumours in the liver and bile duct were incidental, which is also discussed in Lanes *et al*. 1993, as no new cases were observed in the follow-up. Another weakness in the studies is the fact that those employees who were not identified as having died were assumed to be alive at the end of the study, which means that cases could have been missed. In addition, risk estimates were not

recorded separately for men and women and the majority of the employees were women.

A cohort of British workers at a plant which manufactured film base from cellulose triacetate was studied in order to examine the relationship between DCM exposure and mortality from cancer and heart disease (83). 1785 workers (men) who were employed between 1946 and 1988 were monitored up to 2006. 1473 workers were exposed to DCM at 19 ppm (8 hour TWA) for an average of 9 years. 559 deaths occurred during the follow-up period. Mortality amongst DCM-exposed workers was generally lower than in the general population (both locally and nationally), SMR 0.79 (95% CI 0.72-0.86). A small increase was observed in cancer of the brain and/or central nerve system (8 observed, compared with 4.4 expected), but no dose-response relationship was seen for DCM exposure. No cases of cancer of the liver or bile duct were observed.

A hospital-based case control study from 2012 examined the relationship between a number of chlorinated solvents and the risk of glioma and meningioma (brain tumours). No increased risk of brain tumours was observed for DCM exposure: odds ratio 0.5 for those who had probably been exposed (95% CI 0.3-0.9). The exposure assessment was based on interviews involving detailed questions about job history and chemical usage (56). A meta-analysis from 2001 studied DCM exposure and a relationship with pancreatic cancer. An MRR (meta-relative risk) of 1.4 (95% CI 0.8-2.5) was observed for DCM but a dose-response analysis showed no trend (61). Exposure to DCM and an increased non-significant risk of multiple myeloma was observed in a case-control study from 2011. The exposure assessment was based on interviews as well as occupational history, exposure to solvents and job exposure matrices. The risk became significant, odds ratio 2.0 (95% CI 1.2-3.2), when the workers with jobs assessed as low-exposure were reclassified as non-exposed (low-exposure merged with non-exposure) (27).

A case-control study examined the relationship between brain tumours and previous occupational activity in the chemical and petrochemical industries. An analysis was carried out of death certificates for 741 men who died from brain tumours or tumours of the central nervous system from January 1978 to June 1980 in southern Louisiana and between January 1979 and December 1981 in northern New Jersey and Philadelphia. The same number of death certificates were obtained for randomly selected controls (men who died from other forms of cancer, cerebrovascular disease, epilepsy, and homicide, including suicide). Information on previous occupations, work tasks, workplace, type of industry and production, and dates of employment were obtained from relatives. Of the 438 cases who had full interviews, 300 were diagnosed with brain tumours in the form of astrocytoma, glioblastoma and/or glioma. 320 controls were included in the study. On the basis of occupational history, job exposure matrices were formulated which characterised various exposures to 6 different chlorinated hydrocarbons and organic solvents, including DCM (30). An increased risk of brain tumours was observed for exposure to organic solvents, including DCM (odds ratio 2.4 95% CI 1.0-5.9). The risk increased significantly with exposure (dose-response

relationship) to DCM; odds ratio = 6.1 (95% CI 1.1-44) and more than 21 years of employment. With cumulative exposure a statistically significant trend was observed for workers who were likely to have had the highest exposure, but the increase in risk was not linear. Those judged to have the highest DCM exposure were painters, workers in paint and lacquer production, boat building and repair, and workers in the electronics industry (30).

A non-significant increase in risk was observed for lymphoma (Hodgkin's lymphoma, B-cell non-Hodgkin's lymphoma, T-cell non-Hodgkin's lymphoma and other types of lymphoma) in individuals who had previously worked with DCM. This was reported in a German case-control study from 2007 (68): >0-≤26.3 ppm x years, odds ratio = 0.4 (95% CI 0.2-1.0); >26.3-≤175 ppm x years, odds ratio = 0.8 (0.3-1.9); >175 ppm x years, odds ratio = 2.2 (0.4-11.6) (68).

Barry *et al*. showed that the genetic variation in the enzyme CYP2E1 can influence the cancer risk in solvent exposure. Data was taken from a case control study of women in Connecticut, USA, who had been diagnosed with non-Hodgkin's lymphoma (NHL). 518 women with NHL took part in interviews and gave blood samples or samples from the oral mucosa (buccal cells) which were compared with samples from 597 matched control individuals. The interviews were based on a survey of occupational history, job titles, and periods of employment. Self-reported occupations were coded in accordance with standardised occupational and industry classification and were linked to a job exposure matrix. The odds ratio for NHL was calculated for DCM-exposed women with TT polymorphism (rs2070673) CYP2E1 as 4.4 (95% CI 2.0-9.6). DCM-exposed women with another genotype (TA or AA) had an odds ratio of 0.80 (95% CI 0.36-1.8) (11). Another experimental study of immortalised lymphocytes showed that cells with the genotype rs2070673TT had significantly higher CYP2E1 expression and enzyme activity when compared with the other genotypes that were studied (91).

Amongst 62 men who worked at an offset printing plant in Osaka, Japan, 11 developed tumours of the bile duct, cholangiocarcinoma (bile duct cancer), (5 intrahepatic and 6 extrahepatic). The workers had been exposed to a calculated level of 100-670 ppm 1,2-dichloropropane (DCP) (exposed during the period 1985-2006) and 80-540 ppm DCM (exposed 1985-1998). Exposure to DCP and DCM took place during the cleaning of rubber cylinders. Kerosene was also used. This paint removal task was carried out about 300-800 times over 16 hours (2 shifts). The work was carried out in basements with poor ventilation. The workers used gloves but no breathing masks. The Japanese authority JNIOSH subsequently carried out experiments to reconstruct the work environment in this printing plant and to measure and estimate the exposure concentrations for DCP and DCM. Eleven women had also worked in the printing plant but were excluded from the study as none of them had developed bile duct cancer. Age at the time of diagnosis was between 25 and 45 and age at the time of death for the 6 deceased workers was between 27 and 46. All 11 patients had been exposed to DCP for 7-17 years (average 10 years) and had been diagnosed with bile duct cancer 7-20 years (average 14 years) after the first exposure. Ten of the cases had also been exposed

to DCM for 1-13 years (average 7 years). SMR (standardised mortality ratio) for bile duct cancer was calculated as 2900 (95% CI 1100-6400, 6 cases, compared with the 0.00204 expected) for all workers combined; SMR = 5000 (95% CI 1600-12,000, 5 cases, compared with the 0.0010 expected) for workers who had merely been located on the premises of the printing facility. None of the patients with bile duct cancer had high alcohol consumption and all tested negative for Hepatitis B and C (43), see Table 2. The study was initiated when a former employee made contact with the authors and told them that several of her work colleagues had developed bile duct cancer (personal communication from Shinji Kumagai, 2014-03-25). Six new cases of bile duct cancer were discovered amongst the company's employees between 2012 and 2013, and there are now 17 cases amongst the 70 individuals at this workplace (42). A follow-up study reported that all 17 patients had been exposed to DCP, 11 to DCM and 8 to 1,1,1-trichloroethane (40). Ten of the cases were still working at the printing facility when diagnosed, while 7 were previous employees. Of these 7 workers 2 had been employed at other printing plants which did not use DCM, DCP or 1,1,1-trichloroethane. Thirteen of the cases were smokers. The total number of previous and existing workers was given as 111 (40). A press release from the Japanese *Ministry of Health, Labour and Welfare* gives high concentrations of 1,2-DCP as the cause of these cases of bile duct cancer, whereas the time of exposure to DCM was considered too short.

A further 9 cases of bile duct cancer (at other printing plants in Japan) have been reported. These workers were significantly older at the time of diagnosis than those mentioned above; the average age was 44 years at diagnosis (31-57 years). Other results parameters in laboratory tests (AST, ALT, gamma-GTP) and pathological findings (e.g., the proportions of bile duct cancer cases that were intrahepatic and extrahepatic) did not vary between the studies. Five workers had been exposed to DCM and 1,2-DCP, two workers to DCM, 1,2-DCP and 1,1,1-trichloroethane, and two workers to DCM and 1,1,1-trichloroethane. The duration of exposure varied from 3 years and 10 months to 19 years. None of the workers consumed large amounts of alcohol but six of them were smokers (39).

Exposures to DCM and DCP were estimated for individuals who had worked at three smaller Japanese printing plants and who had been diagnosed with bile duct cancer. Exposure to DCM was low (<1-4 ppm) at one of the plants. At the other two printing plants the DCM concentration was higher: for paint removal 0-560 ppm (TWA 9 hours 0-150 ppm) and 91-290 ppm (TWA 11.5 hours 60-240 ppm), respectively. Other concomitant exposures included 1,2-DCP and kerosene (89).

A histological study of the tumours from the Japanese cases revealed constitutional expression of GST-T1 in bile duct epithelium, but no expression of CYP4502E1. Various tumour precursors were also found in the bile duct; these express DNA damage markers and mutations. The comment is made that the biliary tree is supplied with arterial blood, which means that inhaled DCP or DCM can be metabolised by the bile duct epithelium without first passing the hepatocytes. A further comment is that the gall bladders in at least some of the

cases expressed CYP4502E1, which could explain why these cases did not develop gall bladder cancer (66).

A case report from 2014 describes a man who was exposed for 11 years to a mixture of 50% DCM and 50% 1,1,1-trichloroethane at another offset printing plant and who was diagnosed with bile duct cancer at the age of 44. The exposure to DCM was calculated as 240-6100 ppm (41).

IARC (Vol. 65) classifies occupational exposure in printing work as group 2B (possibly carcinogenic to humans). According to IARC's assessment there is some epidemiological evidence that printing work causes cancer of the lungs, upper respiratory tract (oropharynx), urinary bladder and kidneys, or leukaemia (32). Other studies have shown an increased risk of mortality from liver cancer, oesophageal cancer, stomach cancer and cancer of the cheeks and throat (14, 48, 50). As work in the printing industry may involve various types of chemical exposure, as well as mixed exposures, it can be difficult to determine the association between a specific exposure and an increased cancer risk. In view of the cluster of bile duct cancer cases in the Japanese printing industry described above, a summary is presented in the section below of two further studies which show an increased risk of liver cancer and bile duct cancer associated with printing work, but in which the relationship to DCM exposure is unclear.

A study by Nordiska Yrkescancerdatabasen (Nordic Occupational Cancer Database) was based on censuses from 1960, 1970, 1980 and 1990. In individuals aged 30-64 an increase in cancer incidence was observed for workers in the printing industry, SIR (standardised incidence ratio) for liver cancer 1.4 (95% CI 1.1-1.6), based on 142 cases; for intrahepatic bile duct cancer, SIR 2.3 (95% CI 1.5-3.6), based on 21 cases (88). The SIR for liver cancer was particularly elevated for printers and lithographers. The SIR for intrahepatic cancer was increased in typographers and printers. No increased incidence was observed for tumours of the gallbladder and extrahepatic bile duct. The study was based only on male workers; a similar pattern in incidence ratio was observed for women, but there were only a limited number of cases. Exposure to DCM and DCP is discussed by the authors in the Japanese study by Kumagai *et al*. 2013 (43). The Nordic workers were exposed to benzene (before 1964), petrol (before 1960), DCM, lead (before 1985), 1,1,1-tricloroethane and toluene. There is no exposure data for DCP in the Nordic job exposure database (NOCCA JEM). It was noted in the study that the high incidence ratio for intrahepatic bile duct cancer in typographers was to a large extent related to an increased number of cases in Sweden (SIR for Sweden 2.3, based on 8 cases) (88). Bile duct cancer may therefore possibly be associated with DCM exposure. According to the Product Register (KemI) only very small amounts of DCP have been used in Sweden, which is why any association with DCP exposure is more uncertain.

The risk of liver cancer associated with occupational exposure to organic solvents was examined in a case-control study in Danish workers. The study involved 973 cases, 599 of whom were individuals with hepatocellular carcinoma, 329 with bile duct cancer and 45 with a mixed diagnosis (liver cancer). 15,348

control individuals participated in the study. The men showed an increased risk (odds ratio) in occupations such as car repair, the paper and graphics industries (including offset printing) and the glass and metal industries. The women showed a marked increase in the risk of liver cancer for work in the paper and graphics sectors, particularly for offset printing where the observed risk was increased 10-fold, OR = 13 (95% CI 5.5-31). There was no data on alcohol habits. The authors did not record the type of liver cancer in the results; all liver cancer cases were pooled. The authors only discuss exposure to trichloroethylene and tetrachloroethylene as possible underlying causes of the increased risk of liver cancer amongst workers in the printing industry (22).

Animal data

A number of cancer studies with DCM have been carried out in animals (15, 57, 59, 69, 70). Inhalation studies in rats showed an increase in mammary fibroadenoma in females exposed to 1000, 2000 and 4000 ppm DCM (59); a small increase in the same type of tumour was also observed in males. NTP classified DCM as ”clear evidence” for female rats and ”some evidence” for male rats (59). An increased number of benign mammary tumours were observed in females exposed to 500 ppm in another study (57). Rats exposed via drinking water showed liver changes (at 50, 125 and 250 mg/kg body weight), with an increased number of liver tumours in females (50 and 250 mg/kg), but the increase was comparable with those found in historical controls (69). An effect on the liver was seen in mice exposed to DCM via drinking water, with preneoplastic liver changes observed in males (70). In NTP's 2-year study in mice which inhaled DCM, a dose-dependent increase was observed in liver and lung adenocarcinoma/carcinoma in both males and females. For both groups DCM was classified as ”clear evidence of carcinogenicity" (59).

In a study from 2014, 50 F344/DuCrj male and female rats and 50 Crj:BDF1 male and female mice were exposed to 0, 1000, 2000 and 4000 ppm DCM for 2 years via inhalation. Male rats developed subcutaneous fibroma, mammary fibroadenoma and mesothelioma (in the peritoneum); female rats had an increased number of mammary adenomas. DCM-exposed mice developed hepatocellular adenoma and carcinoma as well as bronchiolar-alveolar adenoma and carcinoma of the lungs (2). The results of cancer studies in animals are summarised in Table 3.

NTP's cancer test results were used in the 1980s in a PBPK analysis. This explains non-linear dose-response data with regard to cancer: at low doses DCM is metabolised via the P450 system, whereas at high doses DCM is metabolised by GST enzymes and reactive, carcinogenic intermediates are formed in this system. With support from kinetic data on the corresponding human enzymes, the authors conclude that the risk for humans of being affected by cancer at low levels of exposure (below 100-500 ppm) is about one-tenth the risk predicted by a linear extrapolation from cancer data from mice (6). The authors do not discuss the

Table 3. Cancer studies in animals exposed to DCM.

Exposure	Animal species (number, gender)	Effects	Ref.
0, 50, 200, 500 ppm, inhalation	Rats, Sprague-Dawley (males and females)	No malignant tumours of any type were observed. Histopathological changes in the liver and mammary gland. Benign mammary tumours in females in the high dose group (500 ppm). The NOAEL was set at 200 ppm.	57
0, 500, 1500, 3500 ppm, inhalation	Rats and hamsters	Female rats exposed to 3500 ppm showed increased mortality. Female hamsters exposed to 1500 and 3500 ppm showed reduced mortality. Increased COHb, more in hamsters than in rats. Female rats exposed to high doses had more benign tumours in the mammary glands (dose-response). At 1500 and 3500 ppm, an increased number of sarcomas was seen in male rats, in or around the salivary glands.	15
0, 5, 50, 125, 250 mg/kg body weight/ day, via drinking water	Rats, F344 (500 males and 500 females)	Liver tumours in female rats (50 and 250 mg/kg/day) but comparable with historical controls. Increased number of preneoplastic liver foci and fatty changes at all doses except the lowest. The NOEL level was set at 5 mg/kg/day (in both females and males).	69
0, 1000, 2000, 4000 ppm, inhalation	Rats, F344/DuCrj (50 males and 50 females)	Mammary tumours, peritoneal tumours and subcutaneous tumours in males, mammary tumours in females.	2
0, 60, 125, 185, 250 mg/kg body weight/day, via drinking water	Mice, B6C3F1	The high dose caused an increase in blood leukocytes. Changes in the liver in both females and males, preneoplastic changes in male mice. Neoplastic changes were at the level observed in historical control animals. The NOEL was set at 185 mg/kg/day.	70
0, 1000, 2000, 4000 ppm, inhalation	Mice, Crj:BDF1 (50 males and 50 females)	Tumours of the liver and lungs (both males and females).	2
0, 2000, 4000 ppm, inhalation	Mice, B6C3F1 (50 males and 50 females)	Hepatic adenoma, males: 10/50, 14/49, 14/49 Hepatic carcinoma, males: 13/50, 15/49, 26/49 Alveolar/bronchiolar pulmonary adenoma, males: 3/50, 19/50, 24/50 Alveolar/bronchiolar pulmonary carcinoma, males: 2/50, 10/50, 28/50 Hepatic adenoma, females: 2/50, 6/48, 22/48 Hepatic carcinoma, females: 1/50, 11/48, 32/48 Alveolar/bronchiolar pulmonary adenoma, females: 2/50, 23/48, 28/48 Alveolar/bronchiolar pulmonary carcinoma, females: 1/50, 13/48, 29/48	59
0, 1000, 2000, 4000 ppm, inhalation	Rats, F344/N (50 males and 50 females)	Mammary adenoma, males: 0/50, 0/50, 0/50, 1/50 Mammary fibroadenoma, males: 0/50, 0/50, 2/50, 4/50 Mammary adenoma, females: 0/50, 0/50, 0/50, 1/50 Mammary fibroadenoma, females: 5/50, 11/50, 13/50, 22/50	59

possibility that concomitant exposures to substances which inhibit P450 could affect the kinetics of DCM metabolism. Later studies have shown high expression of GST in bile duct epithelium and in the cell nuclei of the epithelium in humans (66, 71), but no expression of CYP4502E1 (66), which could increase the risk in humans.

Effects on Reproduction

Human data

Eight of 34 male workers exposed to 3-154 ppm DCM via inhalation and dermal exposure (and styrene 1.5-10 ppm) were infertile and complained of genital pain. Two of these workers also had testicular atrophy. All four who gave sperm samples had substantially reduced sperm levels. The workers had been exposed to DCM for ca 2 years (37). The levels of COHb in blood for the eight infertile workers were 1.2-11% for non-smokers (6 individuals) and 7.3-17% for smokers (2 individuals) (8). The high COHb levels measured presumably reflect the massive dermal exposure.

In a register-based study of female workers at 8 pharmaceutical companies in Finland a higher proportion of spontaneous abortions was observed than in the general population. A case-control study included 44 workers who had had a miscarriage and 130 workers who had had normal births. Information on occupational exposure was obtained from questionnaires filled in by doctors or nurses at the companies. Chemical exposure was more common amongst the cases than in control individuals. The study showed an odds ratio of 2.3 (95% CI 1.0-5.7) for miscarriage amongst those exposed to DCM. According to the authors the significance was ”borderline”. The study was based on only a few cases (44 individuals) and there was no data on smoking and alcohol consumption (8, 81).

Animal data

Effects on offspring after exposure to 100, 500 and 1500 ppm DCM were examined in a two-generation inhalation study in rats (58). Thirty male and female rats (F_0) were exposed for 14 weeks, 6 hours/day, 5 days/week, before mating. In F_0 animals no effects were observed on fertility, gestation, survival, litter size or weight of offspring. Nor was any effect observed in the weaned F_1 animals. After weaning, 30 F_1 male and female rats were selected randomly from each dose group; these groups were exposed for 17 weeks to 0, 100, 500 or 1500 ppm DCM before mating. Again, no effect was observed in either F_1- or F_2-animals (which were monitored up to the age of 28 days).

NTP's two-year study in rats and mice showed an increased frequency of testicular atrophy in male mice (54). When groups of 50 mice were exposed to 0, 2000 and 4000 ppm DCM, testicular atrophy was observed in 0/50, 4/50 and 31/50 mice, respectively. These effects were not seen in rats (54).

Dose-effect-/Dose-response-relationship

A number of case reports describe acute deaths associated with high DCM exposure (8, 16, 51, 80).

Exposure to 28-173 ppm DCM mainly resulted in CNS effects such as deterioration in mood, fatigue, and poorer results in a symbol test (17). The workers had previously been chronically exposed to DCM but these effects were related to exposure over a single shift. The conditions of exposure were inadequately recorded in the study. CNS effects at low exposure levels have also been reported in animal studies. Thus, altered neurotransmitter metabolism was demonstrated at 70 ppm (26) and indications of brain damage at 210-350 ppm (64).

DCM is metabolised to CO which, like inhaled CO, can bind to haemoglobin, forming COHb. This can adversely affect oxygen transport, resulting in, amongst other things, CNS symptoms such as headaches. At 100 ppm DCM, COHb levels can rise to 3.4-5.7% (72). This compares with SCOEL's biological threshold value for inhaled CO of 4% COHb (67).

Irritant effects on the eyes and nose have been described for occupational exposure (graffiti removal) to solvents. The authors claim that DCM is a possible cause (7, 8). It is unclear whether the relationship between exposure and the experience of irritation was dependent on exposure peaks. It is also unclear whether the experience of irritation was associated with those days when DCM was used. It is, therefore, difficult to determine any effect level in the study. When exposed in an exposure chamber, healthy male volunteer research subjects reported no symptoms of irritation with exposure to 986 ppm for 2 hours (75).

A number of studies show carcinogenic effects for DCM in animals. Several cohort- and case-control studies have shown a relationship between increased risk of different types of cancer and DCM exposure in humans. An increased risk of multiple myeloma was observed in a case-control study (27) and in a meta-analysis from 2013 (49).

Two studies report on 17 workers who were exposed to DCP (for an average of 10 years), 11 of whom were exposed concomitantly to DCM (for an average of 7 years) and developed bile duct cancer (40, 42). In 2014 further cases involving similar exposure were reported from other printing plants (39, 90). In the Japanese reports DCP was regarded as a clear cause of the substantial increase in the development of this uncommon form of cancer. Some cases had not been exposed to DCM, or had only experienced slight DCM exposure, but had been exposed to other solvents (not associated with bile duct cancer). Still other cases had been exposed to DCM and another solvent, but not DCP (39, 41).

Studies from the 1980s reported that it was mostly at high doses of DCM (>500 ppm) where reactive metabolites were formed, such as formaldehyde and glutathione metabolites. This process is mediated by GST enzymes, whereas low doses are metabolised via CYP450 which does not give rise to reactive intermediates or mutations. It was assumed that this affected the dose-response relationship for DCM-induced cancer so that the response was disproportionately low with low exposure levels, or had a "threshold". However, many substances are

metabolised by the CYP450 system and this can be susceptible to various forms of inhibition (e.g., by carbon monoxide). DCP has been shown to reduce the level of P450 and to increase GST activity in experimental animals after 4 weeks of exposure (84), and such an effect can increase DCM metabolism via GST, thereby increasing the formation of reactive DCM intermediary metabolites. This, together with a high content of GST in the bile duct epithelium and in cell nuclei in the bile duct epithelium, may have contributed to the development of bile duct cancer in the Japanese cases. The study of Sato *et al*. 2014 confirms the expression of GST in bile duct epithelium and supports the concept by demonstrating a lack of CYP450 expression and by emphasising the blood supply to the biliary tree (66). The Criteria group, therefore, considers that DCP was a carcinogenic factor in the Japanese cases but that DCM cannot be discounted as a carcinogenic co-factor in the majority of cases.

One consideration which could expand the perceived role played by DCM and which was not discussed in the Japanese studies, is the possibility that DCM may have been present in consumer products and that DCM exposure may have occurred outside the workplace. In addition, IARC's register study (88) concludes that many cases of bile duct cancer amongst printing workers were found in Sweden where DCM, but probably not DCP, was used extensively. Overall, the Criteria group considers that DCP clearly appears to be a carcinogen and that the synergistic effects between DCP and DCM can be thought to have played a role in the Japanese cases, but also that there is strong support for regarding DCM as carcinogenic. It is possible that synergistic effects with DCP or other chemicals are required for this property to be manifested.

Conclusions

The critical effect of DCM in occupational exposure is effects on the CNS. One study describes CNS effects in humans at 28-173 ppm DCM but the exposure conditions were inadequately recorded. Effects on the CNS in experimental animals (altered neurotransmitter metabolism and indications of brain damage) have been reported at 70 and 210-350 ppm, respectively.

DCM, like inhaled CO, gives rise to COHb formation. COHb can result in oxygen deficiency and cause CNS effects, amongst other things. SCOEL gives a biological threshold for inhaled CO of 4% COHb; 100 ppm DCM can result in ca 4% COHb.

DCM is a reproductive toxin with respect to sperm production and testicular atrophy. This was reported in a study involving high occupational dermal exposure combined with air exposure.

DCM is genotoxic and probably carcinogenic to humans. However, the epidemiological studies are difficult to interpret as DCM occurs alongside other substances, particularly 1,2-dichloropropane (DCP).

DCM is effectively absorbed both via the respiratory system and the skin (in liquid form) and dermal uptake can be substantial.

Acute deaths have occurred with occupational exposure.

Potential conflicts of interest

Maria Albin (member) has declared that, in a letter to Arbetsmiljöverket (The Swedish Work Environment Authority) dated 21/06/2013, she commented that new studies had linked dichloromethane and 1,2-dichloropropane to an uncommon form of cancer (cholangiocarcinoma) in offset printing workers in Japan and that the authority should consider issuing a warning to users. The members Bengt Järvholm and Håkan Westberg also signed the letter.

Gunnar Johanson (member) has declared that he was involved in SCOEL's evaluation of dichloromethane and the consensus decision on recommended occupational exposure limits for the EU.

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Summary

Montelius J (ed). Swedish Criteria Group for Occupational Standards. *Scientific Basis for Swedish Occupational Standards.* XXXIV. Arbete och Hälsa 2017;51(3):1-133. 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 November, 2013 through December 2014.

Key Words: Aluminium, Aluminium compounds, Consensus report, Dichloromethane, N,N-Dimethylformamide, Hydrogen fluoride, Methylene chloride, Occupational exposure limit (OEL), Risk assessment, Scientific basis, Toxicology.

Sammanfattning

Montelius J (ed). Kriteriegruppen för hygieniska gränsvärden. *Vetenskapligt underlag för hygieniska gränsvärden.* XXXIV. Arbete och Hälsa 2017;51(3):1-133. 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 november 2013 – december 2014.

Nyckelord: Aluminium, Aluminiumföreningar, Diklormetan, N,N-Dimetylformamid, Hygieniskt gränsvärde, Metylenklorid, Riskvärdering, Toxikologi, Vetenskapligt underlag, Vätefluorid.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2015;49(1):1-130.

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

Desflurane	May 27, 1998	1998;25	XIX
Diacetone alcohol	December 14, 1988	1989;32	X
Dichlorobenzenes	February 11, 1998	1998;25	XIX
1,2-Dibromo-3-chloropropane	May 30, 1979	1981;21	I
Dichlorodifluoromethane	June 2, 1982	1982;24	III
1,2-Dichloroethane	February 29, 1980	1981;21	I
Dichloromethane	February 29, 1980	1981;21	I
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
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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