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Scientific Basis for Swedish Occupational Standards XVIII

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ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE
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Arbetslivsinstitutet
National Institute for Working Life

National Institute for Working Life

The National Institute for Working Life is Sweden's center for research and development on labour market, working life and work environment. Diffusion of information, training and teaching, local development and international collaboration are other important issues for the Institute.

The R&D competence will be found in the following areas: Labour market and labour legislation, work organization and production technology, psychosocial working conditions, occupational medicine, allergy, effects on the nervous system, ergonomics, work environment technology and musculoskeletal disorders, chemical hazards and toxicology.

A total of about 470 people work at the Institute, around 370 with research and development. The Institute's staff includes 32 professors and in total 122 persons with a postdoctoral degree.

The National Institute for Working Life has a large international collaboration in R&D, including a number of projects within the EC Framework Programme for Research and Technology Development.

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Preface

The Criteria Group of the Swedish National Institute for Working Life (NIWL) has the task of gathering and evaluating data which can be used as a scientific basis for the proposal of occupational exposure limits given by the National Board of Occupational Safety and Health (NBOSH). In most cases a scientific basis is written on request from the NBOSH. The Criteria Group shall not propose a numerical occupational exposure limit value but, as far as possible, give a dose-response/dose-effect relationship and the critical effect of occupational exposure.

In searching of the literature several data bases are used, such as RTECS, Toxline, Medline, Cancerlit, Nioshtic and Riskline. Also information in existing criteria documents is used, e.g. documents from WHO, EU, US NIOSH, the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group. In some cases criteria documents are produced within the Criteria Group, often in collaboration with DECOS or US NIOSH.

Evaluations are made of all relevant published original papers found in the searches. In some cases information from handbooks and reports from e.g. US NIOSH and US EPA is used. A draft consensus report is written by the secretariate or by a scientist appointed by the secretariate. A qualified evaluation is made of the information in the references. In some cases the information can be omitted if some criteria are not fulfilled. In some cases such information is included in the report but with a comment why the data are not included in the evaluation. After discussion in the Criteria Group the drafts are approved and accepted as a consensus report from the group. They are sent to NBOSH.

This is the 18th volume which is published and it contains consensus reports approved by the Criteria Group during the period July 1996 to June 1997. Previously published consensus reports are listed in the Appendix (p 73).

Johan Högberg
Chairman

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The Criteria Group has the following membership (as of June, 1997)

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Contents

Consensus Report for Diethylene Glycol Ethyl Ether and Diethylene Glycol Ethyl Ether Acetate

December 11, 1996

Chemical and physical characteristics. Uses. (11, 16, 44)

Diethylene glycol ethyl ether (DEGEE)

CAS No:	111-90-0
Synonyms:	2-(2-ethoxyethoxy)ethanol, ethoxy diglycol, carbitol, diethylene glycol monoethyl ether, diglycol ethyl ether, beta-ethoxy-beta'-hydroxy diethyl ether, ethyl carbitol
Formula:	$CH_3CH_2–O–CH_2CH_2–O–CH_2CH_2–OH$
Molecular weight:	134.2
Density:	0.99 (20 °C)
Boiling point:	202 °C
Melting point:	- 76 °C
Vapor pressure:	19 Pa (0.14 mm Hg) (25 °C)
Relative evaporation rate:	0.02 (n-butyl acetate = 1)
Saturation concentration:	180 ppm (25 °C)
Conversion factors:	1 ppm = 5.58 mg/m^3 (20 °C)
	1 mg/m^3 = 0.179 ppm (20 °C)

Diethylene glycol ethyl ether acetate (DEGEEA)

CAS No:	112-15-2
Synonyms:	2-(2-ethoxyethoxy)ethyl acetate, ethyl diglycol acetate, diethylene glycol monoethyl ether acetate, carbitol acetate, ethyl carbitol acetate
Formula:	$CH_3CH_2–O–CH_2CH_2–O–CH_2CH_2–O–C=OCH_3$
Molecular weight:	176.2
Density:	1.01 (25 °C)
Boiling point:	217 °C
Melting point:	- 25 °C
Vapor pressure:	7 Pa (0.05 mm Hg) (20 °C)
Relative evaporation rate:	‹ 0.01 (n-butyl acetate = 1)
Conversion factors:	1 ppm = 7.32 mg/m^3 (20 °C)
	1 mg/m^3 = 0.137 ppm (20 °C)

At room temperature, diethylene glycol ethyl ether (DEGEE) and its acetate ester (DEGEEA) are colorless liquids with faint, sweet, pleasant odor and bitter taste. Their boiling points are relatively high and vapor pressures and evaporation rates low. Like most glycol ethers, both substances have very good solubility and mix completely with water and with both polar and non-polar solvents. The reported odor thresholds are 1.2 mg/m^3 (0.21 ppm) for DEGEE and 0.18 mg/m^3 (0.025 ppm) for the acetate ester (41). Another source (21) gives ‹ 0.21 ppm as the absolute odor threshold for DEGEE and 1.1 ppm as the recognition threshold.

In 1993 DEGEE was registered as an ingredient in 178 Swedish chemical products, and estimated annual use was just under 500 tons of pure substance. The major area of use was as solvent, but the substance was also used in paint, varnish, cleaners and binders. In Sweden DEGEE is not used in pharmaceuticals or non-prescription diet supplements, but does occur in cosmetics and skin care products (personal communication, Cecilia Ulleryd, Swedish Medical Products Agency, Nov. 15, 1996). In the United States, DEGEE was reported to occur in 80 cosmetic preparations in 1981 (1). The substance, under the name Transcutol®, is used in skin medications (33) and it has also been found in chemical air fresheners for consumer use (5).

The use of DEGEE in Sweden increased rapidly from 1985 to 1992, and in the following year as well (26, 27). DEGEE, along with mono-(EGBE) and diethylene glycol butyl ether (DEGBE), have been identified as the solvents most widely used in water-based paints and varnishes (22). Global use in 1993 was estimated to be 31,000 tons (13).

Air levels up to 4 mg/m^3 DEGEE have been measured around indoor painting with water-based paints (personal monitors, 20 monitoring occasions) (38). Air levels of 0.2 mg/m^3 have been reported after application of ”safe varnish” (schadstoffarmen Dispersionslacken) containing 0.2% to 0.3% DEGEE (31). DEGEE has frequently been identified in polluted groundwater in the United States (40).

In one study (28), 2-(2-ethoxyethoxy)acetic acid was identified in the urine of about 20 patients. The authors concluded that the substance was formed by biotransformation of DEGEE or its derivatives, but were unable to show any connection to specific pharmaceuticals or other environmental exposures.

DEGEEA occurred in 48 Swedish products in 1993; total use was 900 tons/year, mostly in paints and varnishes (27).

Uptake, biotransformation, excretion

Toxic effects, excretion of metabolites in urine, and comparisons with related glycol ethers all indicate that DEGEE and DEGEEA are efficiently absorbed via all paths of uptake. A man given a single oral dose of DEGEE (11.2 mmol) excreted 68% of the dose as 2-(2-ethoxyethoxy)acetic acid in urine within 12 hours (28). There is no other quantitative information on uptake.

Uptake of DEGEE by prepared human epidermis was 0.125 mg/cm^2/hour (10), slower than glycol ethers with shorter chains, such as diethylene glycol methyl ether (DEGME),

and faster than those with longer chains, such as DEGBE. DEGEE has been used to accelerate dermal absorption of medications (see e.g. Reference 33).

No systematic studies of the distribution of DEGEE or DEGEEA in the body have been published. The very low octanol-water coefficient (log P_{OW} = - 0.15) of DEGEE (34) implies that the substance is probably distributed in body fluids rather than accumulated in fatty tissue.

Esters of glycol ethers are efficiently hydrolyzed by the carboxylesterase in body tissues. In rat blood, for example, the acetate ester DEGBEA is broken down to DEGBE with a half time of less than 3 minutes (8). It can be assumed that DEGEEA is similarly transformed to DEGEE.

The primary metabolic pathway should be analogous to that of other glycol ethers: oxidation of the hydroxyl group in DEGEE via aldehyde to carboxylic acid, i.e. 2-(2-ethoxyethoxy)acetic acid (24). Similarly, the other major metabolic pathway would involve splitting of the central ether bond to ethylene glycol ethyl ether and subsequent oxidation to 2-ethoxyacetic acid (24). Support for the existence of these metabolic pathways is provided by the human study mentioned above (28) and indirectly by a study with pregnant mice that were given diethylene glycol dimethyl ether by gavage (7).

Dogs given DEGEE (3 to 5 g/kg) orally or subcutaneously excreted much higher amounts of glucuronic acids in urine, which indicates that conjugation is a major detoxification route (12).

Toxic effects

Animal data

DEGEE has moderate acute toxicity. The LD_{50} for oral doses of DEGEE is 5.4 to 7.9 g/kg for rats (2, 32), 7.9 g/kg for mice (2), 3.9 g/kg for guinea pigs (32), and 3.6 g/kg (50% in water) for rabbits (45). With intraperitoneal injection, the LD_{50} is 3.9 to 5.2 g/kg for mice (2, 29). With dermal application, the LD_{50} is 6.0 g/kg for rats and 8.4 g/kg for rabbits (18).

In a 90-day study, rats were given 0%, 0.5%, 1% or 5% DEGEE in food. Effects were observed only in the highest dose group: one death (1 male of 12 males and 12 females), reduced food intake, lower weight gain, swollen testes, hydropic degeneration of the liver, and kidney effects in the form of higher relative weight, hydropic degeneration, proteinuria (males only) and elevated aspartate aminotransferase (ASAT, GOT) activity in urine. The NOEL (No Observed Effect Level) was reported to be 1% DEGEE (17).

In another 90-day study, DEGEE was given in food to rats and mice (10 – 20 of each sex per dose group) and by gavage to pigs (3 of each sex per dose group). Effects noted in the highest dose groups (rats 5%, mice 5.4%, pigs 1000-1500 mg/kg/day) were deaths (no rats), reduced food intake, lower weight gain, reduced blood hemoglobin, oxaluria (rats and mice only), and effects on kidneys (lower relative weights, degeneration and atrophy of proximal renal tubuli, calcification of renal cortex) and liver (hydropic degeneration, periportal fatty degeneration, enlarged liver cells) (not rats). Effects on kidneys and liver were also observed in the next-highest dose groups (mice 1.8%, pigs 500 mg/kg/day). The NOEL was reported to be 0.5% (equivalent to about 250 mg/kg/day) for rats, 0.6% (850-

1000 mg/kg/day) for mice, and 167 mg/kg/day for pigs. No effects were seen on serum levels of urea or aminotransferases (ASAT and ALAT) in any dose group. The results indicate that pigs are most sensitive and rats least sensitive of the three species studied (14).

The same or similar effects were also observed in older studies in which DEGEE was given to rats and mice in food or drinking water (19, 30, 36).

In an eye irritation test with rabbits, made in accordance with OECD guidelines, DEGEE was classified as non-irritating to eyes (23). In an older study of eye irritation, also made with rabbits, DEGEE and its acetate were reported to be slightly irritating to eyes (2 on a 10-point scale), as were, for example, DEGME and its acetate (4). DEGEE has been used as a model substance in at least ten studies of in vitro alternatives to the eye irritation test (see for example Reference 15). In all these studies, the observed effects of DEGEE were slight.

No information was found on lethal levels for inhalation exposure. Considering the saturation concentration and the oral LD_{50} values, lethal air levels can hardly occur under normal conditions. Histological examination of rats and guinea pigs exposed for 8 hours to air saturated with DEGEEA at room temperature revealed lung and kidney damage (Union Carbide, unpublished data, 1939, cited in Reference16). In a teratogenicity study with rats, no maternal toxicity was observed after exposure to 100 ppm DEGEE 7 hours/day for 9 days, but the report contains no further details (37).

Human data

There are no reports on effects of occupational exposure.

There is one case report describing a man who drank about 300 ml of DEGEE. He developed severe symptoms of poisoning: CNS effects, breathing difficulty, thirst, acidosis and albuminuria (3).

An unpublished report (Kligman, 1972) cited by Opdyke (39) describes dermal application of 20% DEGEE in petroleum jelly, under occlusion, to 25 volunteers for 48 hours. The application resulted in no irritation or sensitization. In another sensitization study, pure DEGEE was applied under occlusion to the backs of 98 young men for 7 days, followed by a 3-day application 10 days later. No skin sensitization or edema was observed, but 7 of the men had prounounced skin reddening (6).

Mutagenicity, carcinogenicity

DEGEE was weakly mutagenic in bacterial tests, non-mutagenic to yeast, and non-mutagenic in a micronuclei test with bone marrow from mice (2). There are no mutagenicity studies of DEGEEA. With only a few exceptions, glycol ethers have been found to be non-mutagenic in several different mutagenicity tests (35).

No cancer studies of DEGEE or DEGEEA were found. In an older experiment that was not designed to study cancer, 10 rats were exposed to a bit over 2% DEGEE in food for two years. No observations of tumors were reported (36), though the thoroughness of the histopathological examination is not clear.

Addition of DEGEE (0.01 – 2 mM) caused a dose-dependent inhibition of cell proliferation in vitro in cultures of several types of cells, including human fibroblast, lymphoma and mastocytoma cells. The inhibition was not accompanied by cytotoxic effects (33).

Two months of treatment with DEGEE (2.5 or 5 g/l in drinking water) had no effect on the leukemia response in male rats. In this respect it differs from both ethylene glycol methyl ether, which eliminated all indications of leukemia after injection of leukemia cells, and ethylene glycol ethyl ether, which dramatically reduced them (9).

Reproduction toxicity

In a screening test, female mice were given DEGEE by gavage (5.5 g/kg/day) on days 7 to 14 of gestation. Despite pronounced maternal toxicity (7 of 50 died; 0 in controls), only slight effects were observed in young: reduced birth weight, but no reduction in survival or growth (43).

In a teratogenicity study, 19 female rats were exposed to 102 ppm DEGEE 7 hours/day on days 7 to 15 of gestation. The authors report that this was the highest possible exposure level, since higher levels resulted in aerosol formation. No effects were observed in young. The factors studied were food intake and growth of the mothers, litter size, numbers of implants, resorptions and living pups, their birth weights, and any deformities or anomalies in bones or tissues. The authors also mention that no maternal toxicity was observed, but do not report what variables were checked (37).

In another teratogenicity study, 13 rats were given dermal applications of DEGEE four times per day (6.6 g/kg/day) on days 7 to 16 of gestation. The mothers showed a slight effect in the form of lower weight gain, and there were skeletal aberrations in their young (missing, extra or fused ribs etc.), but no increase in the number of skeletal or visceral deformities (20).

In a pilot study made to determine the suitability of the fruit fly (*Drosophila melanogaster*) for teratogenicity screening, a tendency to a higher number of anomalies was observed after treatment with DEGEE. There were not enough flies studied to allow a proper statistical analysis, however (42).

In a multi-generation study (continuous breeding protocol), mice were given up to 2.5% DEGEE in drinking water (equivalent to about 4.4 g/kg/day). There were no observed effects on either their reproductive ability or that of their young. In the highest dose group, however, males had reduced sperm motility and females elevated liver weights; their young also had lower birth weights (46).

A small portion of DEGEE is very probably broken down to the toxic metabolite ethoxyacetic acid. This might explain the toxic effects on reproduction observed after high doses of DEGEE. The related substance ethylene glycol monoethyl ether, which is metabolized largely to ethoxyacetic acid, has toxic effects on reproduction at much lower doses (see e.g. Reference 25).

Dose-effect / dose-response relationships

Table 1. Dose-effect relationships observed in laboratory animals given DEGEE.

Species	Dose (g/kg/d)	Administration method	Effects	Ref.
Rat	5.4 - 7.9	single oral dose	LD_{50}	2, 32
	6.0	single dermal application	LD_{50}	18
	6.6	dermal, days 7-16 of gestation	Lower weight gain, skeletal variations in young, no increase in number of deformities	20
	2.7 - 5.5	5% in food, 90 days	Deaths, lower food intake and weight gain, reduced blood Hb, swolllen testes, effects on liver and kidneys, oxaluria	14, 17
	?	1% in food, 90 days	No observed effects	17
	0.26 - 0.57	0.5% in food, 90 days	No observed effects	14
Mouse	7.9	Single oral dose	LD_{50}	2
	7.0 - 12.9	5.4% in food, 90 days	Deaths, lower food intake and weight gain, reduced blood Hb, effects on liver and kidneys, oxaluria	14
	5.5	Oral, days 7-14 of gestation	7 of 50 females died, pups had lower birth weights	43
	4.4	2.5% in drinking water (continuous breeding protocol)	Reduced sperm motility (males), elevated liver weights (females), pups with lower birth weights, no effects on reproductive ability	46
	2.5 - 4.6	1.8% in food, 90 days	Effects on liver and kidneys	14
	0.8 - 1.1	0.6% in food, 90 days	No observed effects	14
Pig	1.5	Oral, daily for 90 days	Deaths (3 of 6), experiment aborted, severe anemia	14
	1.0	Oral, daily for 90 days	Lower food intake and weight gain, reduced blood Hb, effects on liver and kidneys	14
	0.5	Oral, daily for 90 days	Effects on liver and kidneys	14
	0.17	Oral, daily for 90 days	No observed effects	14

The only published inhalation study reports no observed effects after exposure to 100 ppm DEGEE 7 hours/day for 9 days. There are no other data on which to base a dose-effect or dose-response relationship for inhalation exposure. The dose-effect relationships for oral and dermal administration to mice, rats and pigs are summarized in Table 1.

Conclusions

There are no data on human exposures from which a critical effect of diethylene glycol ethyl ether (DEGEE) or its acetate ester (DEGEEA) can be determined. Judging from animal experiments, the critical effect is damage to kidneys and liver.

Effects on kidneys and liver are observed at relatively high doses (about half the lethal doses), and effects on testes and sperm at somewhat higher doses. There are also indications of effects on young, in the form of lower birth weights and skeletal variations.

There is no information on effects of occupational exposure to either substance, and there are virtually no toxicological data for DEGEEA. Analogies drawn from other glycol ethers make it reasonable to assume that DEGEEA is rapidly transformed to DEGEE in the body and that the two substances thus have the same toxicity.

DEGEE is absorbed via skin. It is reasonable to assume that both substances, like other glycol ethers, are efficiently absorbed via both skin and inhalation.

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Consensus Report for Ethene

December 11, 1996

Physical and chemical data. Occurrence

CAS No:	74-85-1
Systematic name:	ethylene
Synonyms:	acetene, elayl, olefiant gas
Formula:	$CH_2=CH_2$
Molecular weight:	28.05
Density:	0.98 (air = 1)
Boiling point:	- 104 °C
Vapor pressure:	4270 kPa (0 °C)
Melting point:	- 169 °C
Explosion threshold:	2.75 vol % in air (100 kPa; 20 °C)
Distribution coefficient:	log P_{OW} = 1.13 (octanol/water)
Conversion factors:	1 ppm = 1.15 mg/m^3
	1 mg/m^3 = 0.87 ppm

Ethene at room temperature is a colorless gas with a sweet odor and taste. The reported odor threshold is 290 ppm (333.5 mg/m^3) (1, 26). The gas dissolves readily in water, acetone, ethanol and benzene. Ethene is stable under normal pressure and temperature conditions, but may polymerize at higher pressure and temperature.

Ethene is used primarily in the production of polyethylene and ethylene oxide / ethylene glycol. It is also used as a raw material in the production of other chemical substances. Ethene is used to accelerate the ripening of fruit. (It is formed naturally by ripening fruit.)

There are virtually no data on occupational exposure to ethene in connection with production of the substance. It is usually produced in closed systems. In one study (17) it is estimated that during the years 1941 to 1947 the exposure level for ethene around production of ethylene oxide was about 600 mg/m^3. Measurements of occupational exposure to ethene in warehouses where the gas is used to control the ripening of bananas showed air concentrations ranging from 0.02 to 3.85 mg/m^3, with a mean value of 0.35 mg/m^3 (28). In a study of firemen, it was found that they were exposed to ethene in some phases of fighting fires (20).

Uptake, biotransformation, excretion

Six volunteers were exposed to 0, 5 or 50 ppm ethene (0, 5.75 or 57.5 mg/m^3) for two hours. Most (94.4%) of the inhaled ethene was immediately exhaled. Calculations based on clearance of uptake and metabolic clearance indicated that alveolar retention at steady state was 2% and the biological half time was 0.65 hours (12). From theoretical calculations of gas uptake in the lungs, it can be concluded that the low uptake of ethene is due to its low solubility in blood.

Ethene can be detected in exhaled air of unexposed persons. Women exhale more ethene at the time of ovulation. The biochemical origin of this endogenously produced ethene has not been explained, but four theories have been proposed: lipid peroxidation, enzyme-catalyzed oxidative breakdown of methionine, oxidation of hemoglobin, and metabolism in intestinal bacteria (18).

Two hemoglobin adducts, N-(2-hydroxyethyl)histidine (HOEtHis) and N-(2-hydroxyethyl)valine (HOEtVal), have been used as dose measures for formation of ethylene oxide from ethene.

Exposure to ethene at concentrations of 10 to 20 ppb (11.5 to 23 μg/m^3) has been associated with an increase of adducts (HOEtVal) amounting to 4 – 8 pmol/g Hb at steady state (29). Fruit store workers exposed to 0.02 to 3.35 ppm ethene (0.023 to 3.85 mg/m^3) had adduct (HOEtVal) levels of 22 to 65 pmol/g Hb; levels in unexposed controls were 12 to 27 pmol/g Hb (28). The adduct level due to endogenous ethylene alone is estimated to be about 12 pmol/g Hb (12).

It has been estimated from adduct data that about 2 to 3% of inhaled ethene is metabolized to ethylene oxide (14, 28). Exposure to 1 ppm ethene (1.15 mg/m^3) for 40 hours/week is calculated to increase the adduct level by 100 to 120 pmol/g Hb (9).

Mice were exposed to 17 ppm (22.3 mg/m^3) ^{14}C-labeled ethene for one hour. Four hours later radioactivity was found primarily in kidneys and liver, with lesser amounts in testes and brain. A 48-hour urine sample contained S-(2-hydroxyethyl)cysteine, indicating that the ethene had been metabolized to ethylene oxide (8). Fischer-344 rats that were exposed to 10,000 ppm (11,500 mg/m^3) radioactively labeled ethene for 5 hours eliminated most of the radioactivity as exhaled ethene, while smaller amounts were excreted in urine and feces or exhaled as CO_2. Minor amounts of radioactivity were found in blood, liver, intestines and kidneys. The amounts of radioactivity in urine and CO_2 were higher in animals that had been pre-treated with Aroclor (a commercial PCB mixture), which indicates that ethene metabolism can be stimulated by substances that induce the mixed function oxidase system (15).

When Sprague-Dawley rats were exposed to between 0.1 and 80 ppm (0.12 and 92 mg/m^3) ethene, they eliminated 24% of available ethene by biotransformation and 76% by exhalation of unchanged ethene. The alveolar retention at steady state was 3.5% and the biological half time was 4.7 minutes (12). Metabolism was saturated at concentrations above 80 ppm (92 mg/m^3), with a maximum metabolism rate (V_{max}) of 0.24 mg/hour x kg body weight (11).

When Sprague-Dawley rats were exposed for 21 hours to ethene levels exceeding 1000 ppm (1150 mg/m^3) the amount of ethene absorbed per unit of time was constant (2). When Fischer-344 rats were exposed to 600 ppm (690 mg/m^3) ethene, the blood level of ethylene oxide rose rapidly during the first five to ten minutes and then dropped to a level that remained constant during the remainder of the 60-minute exposure. The level of cytochrome P-450 in liver declined steadily during the experiment (22). This was taken to indicate that during metabolism of ethene the phenobarbital-induced form of cytochrome P-450 is destroyed by transformation of the cytochrome heme to an abnormal porphyrin (23).

Sprague-Dawley rats were exposed to 300 ppm (345 mg/m^3) ethene 12 hours/day for three consecutive days: the concentration of ethene was low in all examined organs 12 hours after the last exposure. However, the levels of hemoglobin adducts and of 7-alkylguanine in lymphocytes and liver were elevated, indicating the formation of ethylene oxide (10).

Hemoglobin adduct (HOEtVal) levels of about 100 pmol/g Hb have been measured in several strains of rats, mice and hamsters after exposure to ethene (18). Calculations based on animal data indicate that uptake of 1 mg ethene per kg body weight corresponds to a tissue dose of ethylene oxide amounting to 0.03 mg x hour/kg body weight. This value agrees with the one calculated for human uptake (32).

Toxic effects

Ethene is not irritating to eyes or skin (4). People exposed to a concentration of 37.5% in air for 15 minutes experienced some memory disturbance, and 50% in air results in loss of consciousness due to oxygen deprivation (4).

Mice repeatedly exposed to concentrations resulting in loss of consciousness showed no histopathological changes in kidneys, adrenal glands, heart or lungs (24). The concentration was described as ”atmosphere in which the partial pressure of oxygen was 20 per cent and ethylene 90 per cent.”

Fischer-344 rats exposed to 10,000 ppm (11,500 mg/m^3) ethene for 5 hours showed no toxic effects (15). Nor were toxic effects observed in Sprague-Dawley rats with ethene exposures up to 10,000 ppm (11,500 mg/m^3) 6 hours/day, 5 days/week in a 90-day study (25), or in Fischer-344 rats with exposures up to 3000 ppm (3450 mg/m^3) in a two-year study (16). This absence of toxicity may be due to saturation of ethene metabolism (18).

Rats pre-treated with Aroclor and 24 hours later exposed to ethene concentrations of 10,000, 30,000 or 57,000 ppm (11,500, 34,500 or 65,550 mg/m^3) for 4 hours had dose-dependent effects on liver, indicated by elevated serum levels of sorbitol dehydrogenase and alanin-α-ketoglutarate transaminase and by the histological observation of centrilobular necrosis (5, 6, 15).

Mutagenicity, carcinogenicity, teratogenicity

Ethene caused no mutations in tests with *Salmonella typhimurium* (TA 100), either with or without metabolic activation (34). Ethene induced no micronuclei in the bone marrow of

rats and mice exposed to up to 3000 ppm (3450 mg/m^3) 6 hours/day, 5 days/week for four weeks (33).

The DNA adduct 7-(2-hydroxyethyl)guanine (7-HOEtGua) was found in levels of 2 to 6 nmol/g DNA in lymphocytes from untreated Sprague-Dawley rats (13) and in DNA from several different tissues from Fischer-344 rats and B6C3F1 mice (35). After mice were exposed for eight hours to 11 ppm (12.9 mg/m^3) radioactively labeled ethene, 7-alkylation of guanine could be demonstrated in DNA from liver, spleen and testes: 0.17 nmol/g DNA was measured in liver; 0.098 in spleen and 0.068 nmol/g DNA in testes, which was less that 10% above the background level (27).

Groups of Fischer-344 rats (120 of each sex) were exposed to 0, 300, 1000 or 3000 ppm (0, 345, 1150 or 3450 mg/m^3) ethene 6 hours/day, 5 days/week for up to 24 months. Rats were sacrificed and examined after 6, 12, 18 and 24 months. There was no difference in survival between exposed rats and controls. Histological comparisons of the high-dose group and the controls revealed no indications of any exposure-related toxicity and no elevated incidence of tumors (16).

Groups of Sprague-Dawley rats (both sexes) were exposed to 0 or 10,000 ppm ethene (0 or 11,500 mg/m^3) 8 hours/day, 5 days/week for three weeks. One week later the animals were given polychlorinated biphenyls (unspecified), 10 mg/kg body weight, by gavage twice a week for 8 weeks. The animals were then sacrificed and examined for ”ATPase-deficient foci.” There was no difference between the ethene-exposed animals and controls. (When ethylene oxide was used as a positive control, there was a pronounced increase of foci.) (7)

According to the IARC (18), it is not possible to determine whether ethene is carcinogenic to either man or experimental animals (”inadequate evidence”) and ethene has therefore been placed in Group 3: ”unclassifiable as to its carcinogenicity to humans.” As for the metabolite ethylene oxide, in the judgement of the IARC (19) there is ”limited evidence” that it is carcinogenic to humans and ”sufficient evidence” that it is carcinogenic to experimental animals, and in the overall assessment ethylene oxide is therefore placed in Group 1: ”carcinogenic to humans.”

In a theoretical presentation (29, 30, 31) it is postulated that ethene might cause cancer via activation to ethylene oxide which then binds to DNA, and that the consequent risk of cancer in Sweden due to ethene in city air would be equivalent to 30 cases per year (at an average exposure of 1.8 mg/m^3).

One study reports 6 miscarriages among 15 pregnant women who were working in a petrochemical industry. This rate was higher than that for 1,549 women who were living in the surrounding area. The main product was ethene (350,000 tons/year), but the women were also exposed to other substances including ethylene oxide, vinyl chloride and phthalates. No exposure data are given, but measured ethene concentrations in air outside the plant were on average 10 to 15 ppb (2).

Dose-response / dose-effect relationships

There are no data that can be used as a basis for calculating a dose-effect or dose-response relationship for human exposure to ethene. Occupational exposures of 0.023 to 3.5 mg/m^3 have resulted in elevated formation of hemoglobin adducts (28). Data from animal studies are summarized in Table 1.

Table 1. Effects of ethene inhalation on experimental animals.

mg/m^3	Duration	Species	Effects	Ref.
12.9	8 hours	Mouse	7-alkylation of guanine in DNA	27
92	6 hours	Rat	Saturation of ethene metabolism	11
3450	28 days	Mouse	No increase in micronuclei	33
3450	2 years	Rat	No toxic effects	16
11,500	5 hours	Rat	No toxic effects	15
11,500	90 days	Rat	No toxic effects	25
11,500	24 hours	Rat (pre-treated with Aroclor)	Liver effects	5, 6

Conclusions

Judging from available data on toxicity to humans, the critical effect of exposure to ethene is its effect on the central nervous system. (Ethene has been used as an anesthetic.) From animal data it can be observed that, if the animals have been enzyme-induced, effects on the liver may be the critical ones.

It has been debated whether exposure to ethene can give rise to toxic effects and/or cancer caused by the metabolite ethylene oxide. In its 1981 report, the Criteria Group stated that the critical effects of exposure to ethylene oxide were the mutagenic, cytogenetic and carcinogenic effects, and that cytogenetic effects of ethylene oxide were seen at occupational exposures of about 2 mg/m^3 (21).

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Consensus Report for Cyanoacrylates

March 5, 1997

This report is based mostly on a criteria document from the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (46) and covers primarily methyl 2-cyanoacrylate and ethyl 2-cyanoacrylate.

Chemical and physical data. Uses.

Methyl 2-cyanoacrylate (46)

CAS No:	137-05-3
Synonyms/trade names:	mecrylate, 2-propenoic acid, 2-cyano methyl ester, methyl 2-cyano-2-propenoate, 2-cyanoacrylic acid methyl ester, methyl α-cyanoacrylate
Formula:	$C_5H_5NO_2$
Molecular weight:	111.10
Vapor pressure:	0.33 kPa at 48 °C (11) ‹ 0.27 kPa at 25 °C (14) 0.026 kPa at 10 °C (73)
Conversion factors:	1 ppm = 4.53 mg/m^3 1 mg/m^3 = 0.22 ppm

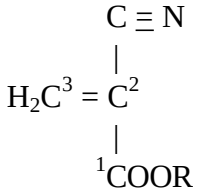
Methyl 2-cyanoacrylate at room temperature is a thin, colorless liquid with a sharp odor. The odor threshold is between 1 and 5 ppm. The substance is soluble or partially soluble in methyl ethyl ketone, toluene, N,N-dimethylformamide, acetone and nitromethane.

Ethyl 2-cyanoacrylate (46)

CAS No:	7085-85-0
Synonyms/trade names:	ethyl cyanoacrylate, ethyl 2-cyano-2-propenoate, 2-propenoic acid 2-cyano ethyl ester
Formula:	$C_6H_7NO_2$
Molecular weight:	125.12
Vapor pressure:	‹ 0.27 kPa at 25 °C (14)
Conversion factors:	1 ppm = 5.12 mg/m^3 1 mg/m^3 = 0.20 ppm

Ethyl 2-cyanoacrylate at room temperature is a clear, colorless liquid with an irritating odor.

Cyanoacrylates have the following general chemical structure:



alkyl 2-cyanoacrylate monomer

where R = - CH_3 gives methyl 2-cyanoacrylate, R = - CH_2- CH_3 gives ethyl 2-cyanoacrylate, etc.

Adhesives based on alkyl 2-cyanoacrylate were introduced on the market in the late 1950s. The bonding ability of cyanoacrylates is believed to be the result of an anion polymerization that is exothermic and rapid – within minutes or seconds, even at room temperature. Heat, extreme pressure, or addition of solvents or special catalysts are not necessary, since the polymerization is initiated by weak bases such as water and alcohols, or nucleophilic groups of proteins such as amines or hydroxyl groups, which are on the surfaces to be joined. Because of their ability to form strong bonds with a large number of materials – rubber, metals, glass, wood, plastic, leather, cork, nylon, ceramics, porcelain etc. – they were soon widely used in a variety of industries. The methyl and ethyl derivatives were particularly popular, and were later marketed for household use (14, 18). For practical reasons it is often desirable to alter their physical characteristics, and glue formulations intended for commercial use may therefore contain a number of different additives (14).

Some cyanoacrylates, particularly the n-butyl and isobutyl derivatives, have also been tested and used as surgical adhesives. Their advantages are that they are biologically degradable and that they can polymerize on damp surfaces, which makes it possible to join skin and mucous membranes (13). Cyanoacrylates are also used for developing latent fingerprints (25).

About 500 kg of methyl and 6000 kg of ethyl 2 cyanoacrylate were imported to Sweden in 1993, for both household and industrial use. The medical use of cyanoacrylates in Sweden is limited to small amounts of n-butyl 2-cyanoacrylate for closing minor skin lesions.

Uptake, biotransformation, excretion

There are no data on human uptake, biotransformation, or excretion.

It has been shown in animal studies that cyanoacrylates can be absorbed via the digestive tract and by skin after local application or subcutaneous implantation (4, 10, 30, 50, 51, 55, 60, 72). No information on uptake by inhalation was found in the literature.

Uptake was studied by applying 3-^{14}C-labeled methyl, n-butyl, and n-heptyl 2-cyanoacrylate to intact skin of rats (Sprague-Dawley). The methyl homologue was eliminated most rapidly: 4.2% of the total applied radioactivity was excreted in urine within five days, compared to about 0.2% for each of the other two homologues. Application on skin after peeling it with a dermatome yielded values three to four times this high (50). In

studies of the breakdown of methyl 2-cyanoacrylate-3-^{14}C implanted under the skin of male rats (Walter Reed) it was found that 6.6% of the applied dose remained at the implantation site after 154 days and that excretion was 46.1% in urine and 5.5% in feces. No radioactivity was detected in liver, kidneys, spleen, brain, muscle or fat (10). Comparable results were obtained with n-butyl 2-cyanoacrylate-3-^{14}C in a similar study of male rats (Sprague-Dawley) (55). However, after 154 days 91.7% of the substance remained at the site of implantation, and total radioactivity excreted in urine was 2.3% and in feces 0.71%.

Guinea pigs (Hartley) absorbed methyl 2-cyanoacrylate-2-^{14}C rapidly from a full-thickness skin incision that was closed with the adhesive (60). Most of the radioactivity was eliminated in urine, with small amounts in feces, exhaled air (as CO_2) and the scab on the sore. After 4 and 18 days some radioactivity was detected in liver, kidneys, spleen, heart, brain and blood, but after 64 days the radioactivity had subsided to base levels. After 107 days the cyanoacrylate had been absorbed almost completely from the site of the incision.

To trace the breakdown pathways, methyl 2-cyanoacrylate-2-^{14}C, -3-^{14}C and -^{14}CN labeled monomers were implanted under the skin of mixed-breed dogs and metabolites in urine were studied (72). According to the authors, the results indicate that cyanoacrylate is broken down with the formation of formaldehyde and through ester hydrolysis.

Uptake of ^{14}C-labeled methyl and n-butyl cyanoacrylates from the digestive tracts of Sprague-Dawley rats was demonstrated by measuring radioactivity in urine (51). Uptake could be demonstrated when the cyanoacrylates were applied directly to intact mucous membranes in the mouth and also when polymerized methyl and n-butyl cyanoacrylate were applied as powder directly in the stomach. Both methods of administration yielded higher values for the methyl homologue than for the butyl homologue.

In one study it was shown that about 5% of the cyan groups in methyl 2-cyanoacrylate implanted under the skin of rats or dogs is metabolized to thiocyanate and excreted in urine (31). These results, however, could not be duplicated in another study (30).

Toxic effects

General toxicology (animal data)

Inhalation: The LC_{50} was estimated to be 101 ppm for rats that were exposed to methyl 2-cyanoacrylate for 6 hours (1). Repeated inhalation of 31.3 ppm methyl 2-cyanoacrylate, 6 hours/day, 5 days/week for a total of 12 exposures, caused only a slight retardation in weight gain. There was no nasal or tracheal damage and no visible evidence of systemic toxicity. Nor could changes be noted in rats exposed to 3.1 ppm on the same schedule (1).

Dermal administration: The estimated LD_{50} for methyl 2-cyanoacrylate applied to the skin of guinea pigs is › 10 ml/kg body weight (1).

In another study, n-butyl 2-cyanoacrylate was implanted under the skin of beagles (400 mg/kg) and liver function was monitored for 6 months. No negative effects on liver function were observed, nor were any pathological effects observed on other vital organs at autopsy (24).

Oral administration: The LD_{50} for rats given oral doses of methyl 2-cyanoacrylate was estimated in one study to be 1.6 to 3.2 g/kg body weight (1).

In another study, attempts to estimate the LD_{50} for methyl or butyl cyanoacrylate were not successful. After polymerization, the cyanoacrylates were ground to a powder which was suspended in water and given orally to rats. The powder in amounts of 1.4 and 2.1 g was tolerated, but larger amounts made the animals vomit. Rats injected with liquid cyanoacrylate in amounts ranging from 0.1 to 1 ml showed no indications of poisoning (22).

Oral administration of poly(methyl 2-cyanoacrylate) to Sprague-Dawley rats and beagles, in doses of 50, 100 or 200 mg/kg body weight/day for 90 days, yielded no clinical, macroscopic or histological indications of systemic poisoning (54). Animals of both sexes were studied.

Unweaned Sprague-Dawley rats of both sexes were fed with polymerized n-butyl 2-cyanoacrylate which had been ground to powder, up to 6.4 g/day for 10 days. The rats showed normal weight gain during a subsequent 90-day observation period. No lethal dose level was reached, and examination revealed no macroscopic or histopathological changes caused by the substance (52).

Other means of administration: The acute toxicity of Aron Alpha (98% ethyl cyanoacrylate; 2% methacrylate and hydroquinone together) was tested on Wistar rats by intraperitoneal injection (49). The animals were observed for a week. The LD_{50} was determined to be 6.76 ml/kg.

Nanoparticles (diameter ≈ 0.4 μm; 9.2 ml/mg suspension) of poly(n-butyl 2-cyanoacrylate) and poly(isobutyl 2-cyanoacrylate) were injected into the caudal vein of NMRI mice. The LD_{50} was determined to be 198 mg/kg for the first substance and 230 mg/kg for the second (27). The injection medium alone, however, was somewhat toxic (LD_{50} = 33.4 ml/kg).

General toxicology (human data)

The only information found in the literature was one case report describing a patient with peripheral neuropathy (20). The authors attributed the patient's symptoms to exposure to cyanoacrylate vapor. The patient had a 20-year history of frequent exposure to other wood and plastic glues at work, however.

Local tissue toxicity

Alkyl 2-cyanoacrylates have great potential as tissue adhesives in surgery and dentistry because they polymerize on and adhere to living tissue and are biologically degradable. All cyanoacrylates, however, are locally toxic to some extent. The degree of toxicity depends on the amount and type of cyanoacrylate applied and the tissue it is applied to. The local irritation and toxicity caused by these compounds at the site of application and in surrounding tissue have been studied and described in detail, in both man and experimental

animals. The initial histopathological findings after application of cyanoacrylates are indications of acute inflammation, which later becomes chronic (46).

The mechanism for the local toxicity shown by cyanoacrylates is not known. It seems that the tissue effects of cyanoacrylate adhesives might be due to the heat produced during polymerization (23, 44, 74) and to liberation of toxic breakdown products including formaldehyde, cyanoacetate (32, 36, 39, 70, 72) and alcohols formed by hydrolysis of the ester bond (37, 72). The more severe local toxicity observed for alkyl cyanoacrylates with short chains (the methyl and ethyl derivatives) is assumed to be due to the fact that they break down more rapidly than those with longer chains, which would lead to a locally higher concentration of toxic breakdown products (37, 39). It has also been suggested that the monomer itself has a direct toxic effect (3, 16, 61).

Irritation and sensitization

Irritation: There is a published study from 1968 (45) that describes symptoms of irritation in 14 volunteers exposed to methyl 2-cyanoacrylate vapor in concentrations of 1 to 60 ppm. The odor threshold was between 1 and 5 ppm for most of the subjects. Irritation of throat and nose usually occurred at about 2 to 3 ppm, and smarting, irritated eyes at about 4 ppm (see also Table 1). In another study, it was found that 10 to 50% of attentive persons can detect the odor of 2 ppm methyl 2-cyanoacrylate (2).

Working conditions in a factory where beads and stones were mounted with methyl 2-cyanoacrylate glue were studied for 5 years (38). Employees showed symptoms of irritation, including contact dermatitis and inflammatory changes in nose, throat and conjunctiva. Exposure to cyanoacrylate vapor was measured in an experimental work situation, and was found to be 2 mg/m^3 (0.4 ppm). An air purification system was installed and semiautomated work methods were introduced, and there were no symptoms of irritation during a subsequent observation period of 2 years.

A group of workers at an electronics factory who were exposed to a glue containing ethyl 2-cyanoacrylate developed irritative dermatitis on their faces (9). The outbreak occurred when humidity at the workplace was fairly low. When the humidity was raised above 55% no further outbreaks occurred. The authors conclude that the alkyl cyanoacrylate monomers in vapor polymerize to an inert material with help of the water in the air. The conclusion is in agreement with another study which reports that a woman who suffered from asthma induced by exposure to cyanoacrylates at work felt some relief on the days a humidifier was turned on (41).

Methyl 2-cyanoacrylate causes mild irritation on direct contact with skin (1,71). If large amounts of cyanoacrylates come into contact with skin, the heat liberated by polymerization can cause burns (18, 74).

Skin sensitization (type IV allergy): In a study of guinea pigs (Hartley) using a sensitization method described by Polak et al (58), neither methyl nor butyl 2-cyanoacrylate gave rise to contact sensitization (56).

It was long believed that cyanoacrylates could not cause skin sensitization because of their extremely rapid polymerization and the binding induced by water and other

nucleophilic groups in the epidermis. During the past decade, however, 13 case reports have been published in which cyanoacrylates are suspected to have caused skin sensitization (5, 8, 17, 19, 26, 57, 64, 65, 68).

In 9 of these cases ethyl 2-cyanoacrylate was reported to be the cause, and in the other cases the cyanoacrylate was not specified. It has been proposed, however, that the observed allergic reactions might have been caused by other acrylates, which are found in small amounts as contaminants even in the purest cyanoacrylate preparations (26). Considering the widespread use of cyanoacrylates in industries and households, sensitization seems to be rare, which would indicate that cyanoacrylates are not particularly strong skin sensitizers. Sensitization to cyanoacrylates may be more common than previously believed, however, since they have been neglected as possible sensitizers and are not included with other acrylates in skin sensitization tests. A further reason may be the difficulty of diagnosing a contact allergy by using a patch test (8).

Respiratory sensitization (type I allergy) and asthma: There are two assessments of the health risks to workers occupationally exposed to ethyl cyanoacrylates.

The first was made at a factory producing auto parts, which employed about 90 workers (33). In the area where parts were glued with cyanoacrylate, the concentration of airborne ethyl cyanoacrylate was measured 4 times: twice at breathing height, about 30 cm from the nose of the worker using the glue; and twice in the vicinity of the application, about 60 cm from the worker's nose. The ethyl cyanoacrylate concentrations, determined according to a method described by McGee et al (45), were 4.4, 4.6, 4.6 and 4.6 mg/m^3 (≈ 1 ppm). Sixteen workers exposed to ethyl cyanoacrylate on some occasion were given a questionnaire. Those who worked with cyanoacrylates reported slightly more upper respiratory symptoms than workers in the same factory who were exposed to lead. Some of the workers (the exact number is not given) described symptoms indicating a possible asthmatic reaction, which often appeared in the evenings or nights after they had been working with cyanoacrylate. The authors concluded that exposure to ethyl cyanoacrylate causes acute irritation of mucous membranes and possibly sensitization of lungs.

The other study was made at a factory with about 80 employees, in which industrial, household and automotive products were manufactured (40). Ethyl cyanoacrylate was the primary exposure, but there was also some suspicion of exposure to methyl ethyl ketone. Ten measurements were made of ethyl cyanoacrylate vapors at breathing height over the workbenches in the hall where the glue was used. Concentrations, determined by the method described in McGee et al (45), ranged from not detectable (‹ 0.1 mg/m^3) up to 1.6 mg/m^3 (0.3 ppm). A questionnaire was filled out by 73 workers, 21 of whom reported that they worked with cyanoacrylate for at least 1 day per week. Symptoms such as wheezing, tightness in the chest and /or shortness of breath were reported by 26 workers. Health examinations were given to 23 of those who reported symptoms and 20 who did not report symptoms. Eight of those examined were diagnosed as having work-related asthma, meeting the criteria used for diagnosis of asthma. The authors considered it impossible to determine whether the ethyl cyanoacrylate was the cause of the work-related asthma, but recommended that exposure be reduced.

Twenty-six case reports of cyanoacrylate-induced asthma have been published, all but one of which were attributed to occupational exposure (15, 28, 29, 41, 47, 62, 63, 67). The cyanoacrylate was reported in one case to be methyl 2-cyanoacrylate, and in 8 cases to be ethyl 2-cyanoacrylate: in the other cases the type was not specified. The duration of exposure before the appearance of symptoms ranged from 1 week to 14 years. In only one case (62) which was diagnosed as cyanoacrylate-induced asthma, it was reported that exposure levels for ethyl cyanoacrylate vapors never exceeded 0.2 ppm (1.0 mg/m^3) at breathing level at and around the workbench. One case of urticaria triggered by an unspecified acrylate has recently been reported (28).

The basic mechanism behind cyanoacrylate-induced asthma/respiratory disease is not known, but an immunological etiology has been proposed. Prick tests given to patients have failed to support this hypothesis, however, and there is no evidence of a specific IgE-mediated reaction. An irritative mechanism can therefore not be excluded (63).

Mutagenicity, carcinogenicity, reproduction toxicity

Methyl 2-cyanoacrylate and adhesives containing methyl 2-cyanoacrylate have been shown to be mutagenic in Ames' tests with *Salmonella typhimurium* (TA 100), both with and without microsomal activation (3, 61). Methyl 2-cyanoacrylate vapor was also shown be mutagenic to TA 100 in a modified Ames' test for volatile compounds (3, 61). No mutagenic effects were observed in tests with ethyl, allyl, isobutyl, or n-butyl derivatives or with pre-polymerized methyl 2-cyanoacrylate. Methyl 2-cyanoacrylate also had a mutagenic effect in another Salmonella test (the strain was not specified), whereas 2-ethylhexyl 2-cyano-3,3-diphenyl acrylate yielded negative results (75). In one study (42) n-butyl 2-cyanoacrylate was found to have a weak, dose- and monooxygenase-dependent mutagenic effect in one of six Salmonella strains (TA 1537) in an Ames' test, but it was not shown whether the mutagenicity was due to the cyanoacrylate, a blue dye or other additives.

Several long-term cancer studies of cyanoacrylates have been made with mice (43), rats (7, 21, 22, 43, 53, 54, 59, 66), rabbits (69), dogs (12, 34, 43, 53, 54) and monkeys (34, 35). In all cases, single doses of cyanoacrylates have been injected, sprayed or dropped in or on various organs such as liver or skin. In four of the studies, all of which were with rats, evidence was found of neoplastic changes caused by methyl 2-cyanoacrylate injected subcutaneously (53, 54), n-butyl 2-cyanoacrylate implanted under skin and peritoneum (59), isobutyl 2-cyanoacrylate implanted on the ventral side of the liver (7) and of an unspecified alkyl 2-cyanoacrylate injected subcutaneously (21). It has been questioned whether these findings are relevant to human exposures, and some researchers (6, 7, 13, 22, 69) believe that the observed carcinogenic qualities of cyanoacrylates represent an Oppenheimer effect (48), i.e. a carcinogenesis caused by foreign bodies, which can be induced by many different polymers (polyvinyl chloride etc.) and which is not specific for the chemical characteristics of the polymer. No information regarding carcinogenic effects of cyanoacrylates on humans was found in the literature.

Only one study of the reproduction and/or fetotoxic effects of cyanoacrylates was found (43). The report describes the absence of effects on the second generation of rats, which were observed for 6 and 12 months, when the livers of their parents had been sprayed with butyl or isobutyl 2-cyanoacrylate.

Dose-effect / dose-response relationships

The acute irritative effect of methyl cyanoacrylate vapor on eyes and mucous membranes was studied under experimental conditions by McGee et al (45). The relationships between the vapor concentration in air and the symptoms reported by the subjects are summarized in Table 1.

Another study (38) reports symptoms of irritation in workers in a factory where exposure to cyanoacrylate vapor, as estimated in an experimental work situation, was 2 mg/m^3 (0.4 ppm).

Available data are altogether too sparse to allow determination of other dose-effect or dose-response relationships (for skin sensitization, asthma/respiratory disease etc.), since most of the reports contain no quantitative data on exposure. One report describes a woman who, after 4 or 5 months of work with glue containing ethyl cyanoacrylate, developed itching and pain in the nose, dry cough, chronic rhinitis and a feeling of tightness across the chest. Air samples taken at breathing height over her work station showed that the concentration of cyanoacrylate vapor did not exceed 0.2 ppm (62). Two studies report symptoms of mucous membrane irritation and asthma in workers exposed to ethyl cyanoacrylate. Measurements of ethyl cyanoacrylate vapor in locales where the glue was used indicated concentrations ranging from not detectable to 1.6 mg/m^3 (0.3 ppm) in one case (40) and to 4.6 mg/m^3 (≈ 1 ppm) in the other (33).

Table 1. Dose-response relationships for acute effects of exposure to cyanoacrylate vapor, as reported by 14 volunteers exposed to cyanoacrylate vapor concentrations ranging from 1 to 60 ppm. (Data from Reference 45)

Exposure * (ppm)	Symptoms
1 – 5	Odor threshold
2 – 20	Irritation of nose and throat
4 – 15	Irritation and burning in eyes
› 20	Runny nose, watery eyes
50 – 60	Pronounced irritation of eyes and nose, indications of painful eye irritation; a few hours after the exposure 2 of the subjects developed vision disturbances that lasted 2 hours

* There was considerable individual variation, and the given exposure levels are rough approximations of the threshold values that apply to most of the subjects.

Conclusions

The critical effects of both short-term and long-term exposure to cyanoacrylates are irritation of skin and mucous membranes and induction of asthma / respiratory disease. Only a few reports give air concentrations, and it is therefore difficult to determine the level at which symptoms appear.

Judging from human data, cyanoacrylates can be suspected of being contact allergens. However, there are few case reports of allergic contact eczema.

Cyanoacrylates have been shown to be carcinogenic in studies with rats, but the relevance of these findings to human exposures has been questioned.

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Consensus Report for Potassium Aluminum Fluoride

June 4, 1997

Potassium aluminum fluoride ($K_xAl_yF_z$) is a flux used in soldering aluminum at a few companies in Sweden. The flux contains a small amount of potassium aluminum tetrafluoride ($KAlF_4$), which at room temperature is a solid powder (1).

This report is based on two articles (1, 2), both of which report that exposure consisted exclusively of potassium aluminum tetrafluoride ($KAlF_4$), although the primary exposure was actually to potassium aluminum fluoride ($K_xAl_yF_z$).

Physical and chemical data.

CAS No:	60304-36-1
Systematic name:	Potassium aluminum fluoride
Trade name:	Nocolok 100 flux
Formula:	$K_xAl_yF_z$
Melting point:	560 – 577 °C
Density:	2.8 g/cm^3
Solubility in water:	4.5 g/l (20 °C)

Uptake, biotransformation, excretion

There is no available information on uptake, biotransformation or excretion.

Toxic effects

One company has been using potassium aluminum fluoride ($K_xAl_yF_z$) as a soldering flux for about ten years. The items to be soldered were treated with a solution of $K_xAl_yF_z$ in water. When this solution dries it leaves the surface covered with a fine powder of $K_xAl_yF_z$ that functions as a flux. After the items were assembled they were soldered in an oven. Ten persons at this company were exposed to $K_xAl_yF_z$ at the same time. Over a ten-year period 22 exposed workers visited the regional occupational health clinic because of respiratory problems. The latency time before the problems appeared ranged from 1 to 60 months (median 6 months). Nearly all of the workers (21 of 22) were bothered by coughing or tightness in the chest. Nine reported nasal irritation. Five had irritated eyes, and four had a skin rash. Five of the 22 had a family history of atopia. The respiratory problems diminished or disappeared after termination of exposure (2).

Sixteen of the 22 workers were tested for bronchial hyperreactivity. Methacholine tests showed pronounced hyperreactivity in two of those tested. During the test the VTG (Volume of Trapped Gas) increased abnormally in 8 of the 16 workers tested. VTG is a method of studying conditions in the small respiratory passages. Three persons had a serum content of IgE that exceeded the reference value (› 100 kU/l) (2). IgE antibodies specific for aluminum or aluminum compounds could not be identified. Prick tests were negative (personal communication, Ulf Hjortsberg, University Hospital, Malmö, Sweden, February 1997).

Measurements made during the years 1985 – 1988 showed levels of total respirable particles around 1.1 mg/m^3 (median concentration; range 0.6 – 2.4 mg/m^3), of which about 0.3 mg/m^3 was fluoride (median; range 0.1 – 0.9 mg/m^3). After installation of a central exhaust system in 1988 total respirable dust dropped to 0.7 mg/m^3 (range 0.4 – 1.3 mg/m^3) and total respirable fluoride dropped to 0.1 mg/m^3 (range 0.03 – 0.3 mg/m^3).

Mutagenicity, carcinogenicity, teratogenicity

There are no data on mutagenicity, carcinogenicity, or teratogenicity of $KAlF_4$ for either humans or animals.

Dose-effect / dose-response relationships

Coughing and/or a feeling of tightness across the chest were common symptoms among workers exposed to $K_xAl_yF_z$ in connection with soldering of aluminum. Exposure to $K_xAl_yF_z$ appears to increase bronchial hyperreactivity (2). It seems likely that the hyperreactivity is an irritative rather than an allergic reaction. The median concentration of respirable particles was 1.1 mg/m^3 during the years 1985 –1988 and 0.7 mg/m^3 after 1988. The median concentration of respirable fluoride particles was 0.3 mg/m^3 during the years 1985 – 1988 and 0.1 mg/m^3 after 1988 (2). No reduction of symptoms could be established with certainty at the lower concentration (personal communication, Ulf Hjortsberg, University Hospital, Malmö, Sweden, February 1997).

It is impossible to establish a NOAEL (No Observable Adverse Effect Level).

Conclusions

Information on the risks of exposure to $K_xAl_yF_z$ is based solely on one case report from one company. The critical effect of occupational exposure to $K_xAl_yF_z$ is respiratory problems. It is not possible to designate a single substance as being responsible for these effects.

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Consensus Report for Inorganic Manganese

June 4, 1997

This report is based on previously published Consensus Reports (19, 30, 31), on some international surveys of the literature (2, 53), and on original works published from 1990 to August, 1995.

Chemical and physical data. Uses

Manganese is used to form alloys with several other metals. Occupational exposure to manganese dust may occur during production of e.g. steel, glass, and welding electrodes, and during welding – especially welding of alloys. Some dry-cell batteries contain manganese dioxide, and various manganese salts are used as catalysts, fluxes, oxidants and reducing agents. Some pesticides, fertilizers, bleaches and disinfectants also contain manganese salts. Manganese occurs with oxidation numbers of +II to +VII

Manganese is an essential trace element in all living organisms.

Table 1. Chemical and physical data for manganese, manganese oxides and manganese chloride.

Substance	Formula	CAS No.	Molecular weight	Soluble in water
Manganese	Mn	7439-96-5	54.94	no
Manganese chloride	$MnCl_2$	7773-01-5	125.84	yes
Manganese dioxide	MnO_2	1313-13-9	86.94	no
Manganese tetroxide	Mn_3O_4	1317-35-7	228.79	no

Uptake, distribution, excretion

No information on skin uptake of inorganic manganese compounds was found in the literature. Uptake of manganese via the lungs was demonstrated in a study in which volunteers inhaled an aerosol containing $MnCl_2$ and MnO_2. The amount of manganese taken up via the lungs was not reported, but it was reported that 40 to 70% (average 60%) of inhaled manganese was recovered in feces during the four days following the exposure (33). No differences in uptake or excretion between the two substances could be shown.

A daily dietary intake of about 2 to 3 mg manganese is considered adequate by WHO (53), and a person's normal daily intake in food has been estimated to be between 2 and 7 mg (33). The degree of absorption is affected by both the amount taken in and the amount in tissues (39). People and experimental animals absorb only 3 or 4 percent of the amount of manganese in food (13, 33). It has been observed in anemic subjects that iron deficiency increases absorption of manganese from the digestive tract (33). In animal experiments, it has been shown that simultaneous ingestion of ethanol and manganese increases both the uptake and the toxicity of the manganese (45).

Occupational exposure is mostly due to inhalation of dust containing manganese. There are no data that clarify interaction between uptake via lungs and uptake via the digestive tract. The regulation of uptake that occurs via the digestive tract might be circumvented, allowing considerably greater amounts of manganese to be absorbed by the body.

The adult human body contains an estimated 12 to 20 mg manganese (13), with the highest concentrations in liver, large intestine and kidneys (about 1 μg Mn/g wet weight) (43). Manganese passes the placental barrier, and levels in the fetus and the mother are therefore about the same (43). In blood, manganese is transported mostly bound to proteins (20).

It has been shown in animal experiments (23) that manganese is excreted mostly (95 –99%) by active transport via the gall bladder: 99% of an intravenous dose was excreted in feces within five days. Increased intake of manganese increases the rate of excretion (39). Persons not occupationally exposed excrete only about 6% (with large individual variation) in urine (42).

Reports of the biological half time vary considerably (19). Whole-body half time after inhalation of $^{54}MnO_2$ was reported to be about a month for healthy, unexposed subjects, and about two weeks for miners exposed to manganese (34).

Toxic effects

Animal data

Most animal studies are of two compounds: manganese dioxide (MnO_2) and manganese chloride ($MnCl_2$). Table 2 presents a summary of a number of animal studies with exposure to manganese dioxide, and Table 3 presents some studies with the more readily soluble manganese chloride. Both tables are organized according to method of administration. Only a few of these studies cover inhalation exposure. Regardless of how the animals are exposed, manganese affects primarily their nervous systems and respiratory organs – the same organs it affects in people. There is apparently no difference in the types of effects caused by the two substances. It is possible that manganese chloride, the more soluble of the two, produces effects at lower exposures.

Table 2. Effects of exposure to manganese dioxide observed in experimental animals.

Species	Exposure	Effect	Ref.
Mouse	Inhalation: Aerosol, 109 mg/m^3, 3 hours	Lowered resistance to bacterial and viral respiratory infections	32
Monkey	Inhalation: Aerosol, 0.011, 0.112 and 1.15 mg Mn/m^3 24 hrs/day for 9 months	Accelerated growth, elevated Hb levels at high dose. Dose-dependent elevation of Mn levels in kidneys, lungs, spleen, blood. No exposure-related effects on lung function, tremor or EMG.	51
Rat	Intratracheal: 10 mg Observation up to 18 months	Emphysema after 1-2 hours, alveolar inflammation, large numbers of macrophages. Lungs normal after about 1 year.	27
Guinea pig	Intratracheal: 50 mg Observation up to 180 days	Day 7: proliferation of macrophages. Day 60: proliferation of fibroblasts.	54
Rabbit	Intratracheal: 250 mg/kg b.w. Observation up to 8 months	Enzyme effects in testes; after 8 months calcified spermatic ducts.	6
Rabbit	Intratracheal: 400 mg Observation up to 24 months	Paralysis of rear legs. Neuron degeneration in brain.	5
Macaque	Subcutaneous: 0.25, 0.5 or 1.0 g, once a week for 9 weeks. Observation up to 3 months	Low-dose group: hand tremor, disturbed balance after about 50 days. Medium-dose group: Same after about 35 days. High-dose group: Same after about 14 days.	50
Macaque	Subcutaneous: 0.1 g once a month for 26 months	Effects on dopaminergic neurons and D1 receptors.	16
Macaque	Subcutaneous: 0.4 g 11 times in 4 months + 1 time 12 months later	Unsteady gait, hypoactivity, brain damage.	17
Rhesus	Intramuscular: 2 g + 2 g two months later. Observation up to 24 months	Indications of poisoning after 9 months. Brain damage after 14 months, particularly in some areas	38
Mouse	In food: 2g Mn/kg food, 100 days	Reduced numbers of white blood cells	24
Mouse	In food: 2g Mn/kg food, 12 months	Reduced dopamine level in brain. (MnO_2 more toxic than Mn^{2+})	25

Table 3. Effects of exposure to manganese chloride observed in experimental animals

Species	Exposure	Effect	Ref.
Rat	Intraperitoneal: 8 mg/kg b.w./day 180 days	Effects on testes. Neuron degeneration after 120 days.	4, 10
Rat	Intraperitoneal: 8 mg/kg b. w./day 120 days	Enzyme effects in brain.	46
Monkey	Intravenous: 5-10 mg/kg b. w., 6-7 times at intervals of at least a week; total time 450 days, total dose 50-60 mg/kg	Lethargy, Impairment in motor performance, Tremor at a cumulative dose of 40 mg/kg.	36
Rabbit	Intravenous: 3.5 mg/kg b. w./day 30 days	Degenerative changes in testes.	22
Rat	Intratracheal: 1 ml 5% or 0.5% solution Observation 8 days	5%: All animals died of lung edema within a few minutes. 0.5%: One third died of lung edema within an hour.	27
Rat	Intracerebral: 12.5, 25, 50 or 100 µg	Dopamine reduction lasting at least 90 days, maximum after 3 days.	49
Rat	Gavage: 50 µg Observation 60 days	Enzyme effects in brain. Neuron degeneration.	7
Rat	In drinking water: 1 or 10 mg/ml Observation up to 360 days	Enzyme effects in brain.	3, 8
Mouse	Mothers: 5 mg/ml in drinking water Pups: via milk, followed by 3 µg/ml in drinking water	Increased motor activity. Enzyme effects in brain.	9
Mouse	In feed: 2 g Mn/kg feed Observation 100 days	Slower growth. Reduced number of blood cells	24

Human data

Effects on the central nervous system

Several years of occupational exposure to high concentrations of manganese (usually over 1000 µg/m^3) can cause manganism. The onset of the illness is marked by psychological symptoms such as emotional instability, behavior disturbances and in severe cases even hallucinations. This phase is followed by neurological symptoms: muscular weakness, speech impairment, headaches and symptoms resembling those of Parkinson's disease (39).

Several studies of the CNS effects of occupational exposure to low concentrations of manganese have been published in the past few years (11, 21, 29, 35, 40, 47). The studies were initiated because effects at low exposure levels resemble those of clinical cases of

manganism, but the threshold level for appearance of these effects is not known. The results of these studies are summarized in Table 4.

In a study from Taiwan (21), psychometric tests were given to four small groups: 17 symptom-free manganese workers, 4 manganese workers with the diagnosis of Parkinson's disease; 8 patients with a diagnosis of Parkinson's and no exposure to manganese; and a control group of 19 persons. The relevance of this study is difficult to assess, since the report is unclear on many points. The criteria for choosing the study groups are not adequately described. "Symptom-free workers," for example, seem to have been chosen simply on the basis of having no symptoms. The tests used are traditional clinical tests designed to diagnose severe brain damage, and are definitely not as sensitive as the tests used in other modern studies. For these reasons, the results of this study are not included in the summary in Table 4.

In a Belgian study (40), 92 workers exposed to MnO_2 in battery manufacture and 101 unexposed controls were examined in an attempt to establish the lowest level at which CNS symptoms appear. The studied group consisted of fairly young workers (aged 22 to 50, average age 31.3) with relatively short exposures (0.2 to 17.7 years, average 5.3). Their current exposures to manganese in total dust and in the respirable fraction were measured with personal monitors, and showed a geometric mean of 948 $\mu g/m^3$ (range 46 to 10,840 $\mu g/m^3$). The control group was recruited from a chemical processing industry in which there was no known exposure to neurotoxic substances. Effects measured included neuropsychological symptoms, respiratory symptoms, lung function, psychological performance, various biological parameters (serum content of calcium, iron and some hormones, standard hematological analysis), and concentrations of manganese, lead, cadmium and mercury in urine and blood. Two exposure indices for total occupational exposure were calculated for each worker: one based on Mn in total dust (range 191 – 27,465 $\mu g\ Mn/m^3$ x year) and one based on Mn in the respirable fraction (40 – 4433 $\mu g\ Mn/m^3$ x year). There was no statistically confirmed connection between these exposure indices and the manganese content of blood or urine. When the workers were divided into six groups according to manganese in urine, however, a correlation with the measured air concentrations of Mn could be established.

Regarding effects on respiratory organs, there were no differences between the exposed group and controls, neither increase of symptoms nor effects on spirometry. Nor was it possible to determine a difference between the groups with regard to reported CNS symptoms. However, there were clear differences in results on several performance tests (reaction time, eye-hand coordination and hand tremor), on which the exposed group did less well than controls.

No significant correlations could be established between biological concentrations and either exposure index (respirable fraction or total dust). For the results of the reaction time, eye-hand coordination and hand tremor tests, however, there was a definite correlation between the exposure indices and the magnitude of the effects. Abnormal test results were clearly more prevalent in groups with higher exposure. The authors considered it impossible to identify a threshold value for the appearance of effects, and used logistic regression to determine the exposure at which there was a significant increase in the risk of

effects on hand tremor. The regression analysis showed that hand tremor increased significantly when the total dose exceeded 3575 μm Mn/m^3 x year for total dust and 730 μg Mn/m^3 x year for the respirable fraction. Dividing these results by the average exposure time yields levels of 674 $\mu g/m^3$ for total dust and 138 $\mu g/m^3$ for the respirable fraction. It should be borne in mind that this estimate of the critical exposure level is based on data from a group of young workers with relatively little time in exposed jobs.

A small group of 17 manganese-exposed workers was studied at two plants in Singapore (11, 12) where manganese ore was ground and packed for further shipping. Before 1985 exposure levels were above 5000 $\mu g/m^3$, but since that date exposure to manganese in total dust has not exceeded 1000 $\mu g/m^3$ and had gradually been reduced to about 30 $\mu g/m^3$ by 1991. The geometric mean for manganese concentrations in air during the 1981 –1991 period was 1590 $\mu g/m^3$ The workers had been employed an average of 7.4 years (SD = 4.3) and 12 of those examined had been employed for more than five years when the study was made. A control group was recruited from administrative staff at a hospital. No differences between exposed subjects and controls could be observed in clinical neurological examination or in tests of neural conductivity in motor and sensory nerves. The subjects exposed to manganese reported more vegetative symptoms and did not perform as well on tests of motor ability, coordination, manual dexterity, hand tremor and memory. The authors conclude that "…this result may be suggestive of an early Parkinson-like disorder." Thirteen of the exposed subjects and 16 controls were also given balance tests. Clear differences between exposed subjects and controls could be noted on some of these parameters also (12). No correlation between exposure level and effect could be established.

In a Canadian study (35) at a foundry where manganese alloys were produced, 74 exposed workers were compared to paired controls. The exposure, which averaged 16.7 years, was to manganese in the form of oxides, and air concentrations averaged 1180 $\mu g/m^3$ for total dust and 120 $\mu g/m^3$ for the respirable fraction (geometric means were 220 and 30 $\mu g/m^3$ respectively). The controls were recruited from the same town, and the groups were matched with regard to a fairly large number of relevant variables. A large battery of tests were used to measure effects. They included motor tests (finger tapping, hand tremor, grip strength, eye-hand coordination), sensory tests (visual acuity, color discrimination, contrast sensitivity, odor threshold and vibration threshold), alertness, concentration and memory tests (number memory, word memory, coding, simple reaction time and choice reaction time), cognitive flexibility and mood (POMS). The results showed effects on several reported symptoms commonly associated with manganese exposure, notably fatigue, forgetfulness, concentration difficulties and reduced potency. Effects were also seen in several of the performance tests, including motor tests, in which the exposed group performed less well than controls. The results of some cognitive tests showed similar differences between the groups. The authors conclude that "These findings, which are consistent with current knowledge on the site and mechanisms of manganese activity in the brain, suggest that manganism probably progresses infraclinically on a continuum; initial manifestations can be observed in well-designed population studies, using sensitive testing methods." No analyses of dose-response or dose-effect relationships were given.

In an Italian study at a foundry where manganese alloys were produced (29), 58 exposed workers were tested during a period of layoffs. The workers were divided into three groups according to exposure level, which was measured as μg Mn/m^3 (total dust). One group consisted of workers from the ovens, where levels during the previous decade had dropped from 1590 to 270 μg/m^3; one group was maintenance workers, where levels had dropped from 319 to 124 μg/m^3; and one group was from other parts of the factory, where levels had dropped from 70 to 27 μg/m^3 (all these values are geometric means). The authors report that 95% of the manganese was in the form of oxides, and that the respirable fraction made up 50 – 60% of total dust. The time between the most recent exposure and the examination ranged from 1 to 42 days (median 13 days). Manganese concentrations in blood and urine were used as a measure of internal exposure. A cumulative exposure index was also calculated for each subject. No control group was used in this study.

The effects of exposure were measured with seven different psychological performance tests. The groups exposed to the two higher manganese concentrations did less well on the tests. The inferior performance was seen on tests of addition, coding, finger-tapping and memory. A dose-effect correlation could be established for several of the test results: the results of four of the tests were correlated to manganese in blood, and one of the test results was correlated to manganese in urine and to the calculated cumulative exposure index. The correlations showed a tendency to increase with both duration of employment and duration of layoff.

A Swedish study of welders (48) reports results for a small group (N = 12) exposed to manganese who were compared with welders working with ordinary steel (N = 39). These welders work on tracks for the Swedish state railways, and one of their jobs is to put a layer of manganese on the rails after they have been laid, using a special electrode. The work is dependent on the outdoor temperature and can only be performed during warm weather, and is done for only a few weeks per worker per year. The effects were measured in late winter. Exposure was measured as the number of hours at the arc with manganese welding, and as manganese in blood. Blood lead was also checked, as was aluminum in blood and urine. Only three measures of air concentrations have been made around this type of work, and these yielded time-weighted averages of 100, 500 and 900 μg/m^3. The results of this study indicated no differences between manganese welders and other welders with regard to manganese content in blood. No differences in lead or aluminum were observed, either. Regarding effect measures, the manganese welders had more symptoms involving the peripheral nervous system and less restful sleep, and had poorer scores on five different measures of motor function.

A group of 35 foundry workers, exposed to about 460 μg/m^3 (geometric mean; range 46 – 980 μg/m^3) for an average of 14.5 years were recently examined. The examination included a test of motor function (28). Exposed workers tended to perform less well than controls, and a dose-response relationship could be established since performance on that test correlated with manganese concentration in blood (r = 0.42).

Table 4. Results of some studies of occupational exposure to manganese in which CNS effects were investigated.

Occupation exposed/controls	Number of exposed/ controls	Exposure level, $\mu g/m^3$ (geom. mean or range)	Effects	Ref.
Battery manufacture / chemical industry	92 / 101	≈ 950	Worse scores on tests of motor function, reaction time; Dose-effect relationship	40
Ore mill / hospital	17 / 17	≈1590	Worse scores on tests of motor function, reaction time, memory	11
	13 / 16	≈ 1590	Impaired balance	12
Foundry / paired controls	74 / 74	≈ 220	Worse scores on tests of motor function, cognition; More symptoms (central & autonomic nervous system, motor, sensory)	35
Foundry / –	19 / –	27 – 70	None	29
	19 / –	120 – 320	Dose-related decline in performance (motor, memory, cognition)	
	20 / –	270 – 1590		
Foundry / electricians	35 / 37	46 – 980	Worse scores on tests of motor function, memory, cognition	28

Effects on respiratory organs

Inhalation of MnO_2 or Mn_3O_4 causes an inflammatory reaction in the lungs (44). This reaction does not seem to be specific for manganese, however, since it also occurs with inhalation of particles of other substances (2). An increased vulnerability to bacterial infection seems to be a secondary effect of the lung irritation (1).

Two Belgian studies of occupational exposure to manganese report both symptom assessments and lung function tests (40, 41). The workers in one of the studies (41) were exposed to manganese in the form of both salts and oxides. The exposure level was 940 $\mu g/m^3$ (geometric mean), and the average duration of employment was 7.1 years (range 1–19 years). An elevated frequency of respiratory symptoms was documented for those exposed to manganese, both smokers and non-smokers. There was also an elevated risk of acute bronchitis. On the spirometry tests, manganese had an effect on FVC (Forced Vital Capacity), though no dose-response relationship could be established. The results indicate that manganese has slight effects on the respiratory passages at a level as low as about 1000

μg/m^3 . The subjects in the other study (40) were workers exposed to manganese oxides only, and no differences were found in either the spirometry tests or symptoms, despite about the same level of exposure (≈ 1000 μg/m^3). The authors explain the different results of these two studies with the different biological availability of water-soluble manganese chloride and the sparingly soluble manganese oxides.

According to WHO (53), occupational exposures to air concentrations below 300 μg/m^3 should have no effects on the lungs.

Other effects

Regarding hematological effects, there are some contradictory results in both human and animal studies. The only effects reported from the well-controlled studies of recent years are on the number of white blood cells. In a study of workers exposed to various manganese salts (about 1000 μg/m^3) in a battery factory (41), they were found to have a higher number of white blood cells (neutrophilic leucocytes only) than controls ($p < 0.001$). Values exceeding the 95th percentile in the control group were found in 21% of the exposed group. The difference could not be explained by smoking habits, since the number of smokers was larger in the control group and the effects of manganese exposure and smoking were independent of each other.

Elevated numbers of white blood cells have recently been reported in a group of foundry workers exposed to an average 460 μg/m^3 (geometric mean; range 210 – 890 μg/m^3) (28). The average duration of employment in exposed jobs was 14.5 years. Elevated numbers of neutrophilic leucocytes and lymphocytes were observed in the study. The difference can not be explained by smoking in this case, either, since manganese was shown to have a significant effect regardless of smoking habits.

Effects on fertility, libido and potency have been observed with occupational exposure to manganese (26, 35, 52). In one study of 85 industrial workers exposed to manganese, they were found to have lower fertility than a control group. The exposure level was 940 μg/m^3 (total dust, geometric mean; range 70 – 8610 μg/m^3). The number of children was lower than expected in two of three age groups (16 – 25 and 26 – 35), but no effects were observed in the third age group (36 – 45). In the Swedish study of foundry workers (52) a reduced sex drive was one of two symptoms that differentiated the exposed group from controls. In the Canadian study (35) made at a foundry where 74 workers were compared with paired controls, the exposed group had a higher frequency of three symptoms: ”Difficulty in maintaining an erection,” ”Loss of libido,” and ”Difficulty ejaculating.” Some support for effects on fertility is also provided by animal studies in which injections of manganese dioxide or manganese chloride have affected enzyme activity in testes and caused sclerosis in the ducts (4, 6, 21; see also Tables 2 and 3).

Mutagenicity, carcinogenicity, teratogenicity

Manganese in ion form can replace magnesium in DNA polymerase and thus disrupt DNA replication (14), but it is not clear whether this constitutes a risk for genetic effects in humans.

There are only a few cancer studies of manganese, and the results are mixed. Exposure via respiratory passages has not been associated with any form of cancer. In a cancer study in which rats and mice were given manganese sulfate in food, the rats showed no indication of cancer but the mice showed a marginal increase of follicular adenomas in thyroidea. The feed given the mice contained 1500, 5000 or 15,000 ppm manganese sulfate, equivalent to approximately 160, 540 or 1800 mg/kg body weight/day for males and 200, 700 or 2250 mg/kg/day for females (37).

Rats (Fischer-344) and mice (Swiss albino) given intramuscular injections of a solution containing manganese dioxide or manganese in powder form showed no effects when compared with controls. Each injection contained 3 or 10 mg manganese, and the animals were injected up to nine times (18).

In the judgement of the EPA (15), available data do not provide an adequate basis for assessing the carcinogenicity of manganese. The IARC has made no assessment of manganese.

Dose-effect / dose-response relationships

Effects on respiratory passages and hematological parameters have been found at exposures to 1000 $\mu g/m^3$ or somewhat lower (total dust). Effects on the nervous system have been demonstrated at total dust contents around 200 $\mu g/m^3$. For the respirable fraction, effects appear at concentrations around 100 $\mu g/m^3$. It has not been possible to establish a threshold value (NOAEL/LOAEL) for effects on the central nervous system.

Conclusions

The critical effects of occupational exposure to manganese are its effects on the nervous system, which have been shown to appear at average levels around 200 $\mu g\ Mn/m^3$ (total dust).

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Consensus Report for Platinum and Platinum Compounds

June 4, 1997

This report is based on a criteria document compiled jointly by the Nordic Expert Group and the Dutch Expert Committee (DECOS) (46).

Chemical and physical data.

Substance	Chemical formula	CAS No.	Mol weight	Melting point (°C)	Boiling point (°C)
Platinum	Pt	7440-06-4	195.09	1768	3825
Hexachloroplatinic acid	H_2PtCl_6	16941-12-1 18497-13-7	409.8l	60	
Platinum (II) chloride	$PtCl_2$	10025-65-7	265.99	581 (d)	
Platinum (IV) chloride	$PtCl_4$	37773-49-2 13454-96-1	336.89	327 (d)	
Ammonium tetrachloroplatinate (II)	$(NH_4)_2PtCl_4$	13820-41-2	372.97	(d)	
Ammonium hexachloroplatinate (IV)	$(NH_4)_2Pt\ Cl_6$	16919-58-7	443.87	380 (d)	
Potassium tetrachloroplatinate (II)	K_2PtCl_4	10025-99-7	415.09	500 (d)	
Potassium hexachloroplatinate (IV)	K_2PtCl_6	16921-30-5	485.99	250 (d)	
Sodium hexachloroplatinate (IV)	Na_2PtCl_6	16923-58-3	453.77	250 (d)	

(d) = decomposes

Platinum is a silver-white, relatively soft precious metal (7, 23, 32). It is extremely resistant to chemicals, and about the only thing that will affect it at room temperature is aqua regia (28). Platinum has great ability to form complexes, and can form numerous

different complexes with tetra- and hexa-coordination (16, 23, 32). The most common valences for platinum are +2 and +4 (16, 60). Most of the tetrachloroplatinates are soluble in water, whereas the hexachloroplatinates vary in this respect (77). The water-soluble compounds include platinum (IV) chloride, platinum (IV) sulfate and hexachloroplatinic (IV) acid (45, 77, 86).

Occurrence, use

Metallic platinum and platinum alloys are widely used in industry because they are very good catalysts. The metal is used – to take a few examples – in the petrochemical industry to upgrade the octane of gasoline, in the basic chemical industry for production of nitric acid and sulfuric acid, and in the automobile industry in the production of catalytic converters (7, 35, 60). Metallic platinum and platinum alloys are also used because of their durability and resistance to corrosion at a range of temperatures, and are found in some types of factory and laboratory equipment: electrochemical anodes, spinnerettes for viscose fiber, crucibles for molten glass etc. Platinum is also used in the electronics industry and in the production of jewelry, ceramic glass, dental material and medical implants (7, 16, 35, 60).

Hexachloroplatinic (IV) acid and some platinum salts are formed and used in refining metallic platinum (from ores or in recycling) (4, 23, 64, 69). Hexachloroplatinic (IV) acid and soluble platinum salts may also be used in the production of catalytic converters, in plating on electrodes, wire, airplane components, jewelry etc., and in the photographic industry (6, 22, 28, 31, 52, 74, 90).

Uptake, distribution, excretion

Daily intake of platinum in food is estimated in an Australian study (83) to be about 1.4 µg Pt (1.15 – 1.73 µg Pt). In the same study, excretion in feces is reported to be 0.61 – 0.73 µg Pt /day, and in urine 0.76 – 1.07 µg Pt/day. This information leads to the conclusion that quite a bit of the platinum taken in is absorbed, but further studies are necessary to establish this with certainty. Uptake of platinum and platinum compounds in work environments can occur via inhalation or by swallowing dust particles. Elevated platinum levels have been reported in blood and urine of persons occupationally exposed to metallic platinum, but no definite correlations between air concentrations and concentrations in blood/serum or urine were found (1, 70). Slow excretion of the metal was indicated in one study (1) in which little reduction of the platinum in urine and serum could be shown after a brief exposure-free period (15 days).

Data from animal experiments indicate that uptake of orally administered metallic platinum and various platinum compounds is small, but related to solubility and particle size (2, 3, 13). In a study with rats, uptake of platinum (IV) chloride was roughly estimated to be ‹ 1% of the dose (57, 58). No quantitative data on uptake of platinum via inhalation were found. Excretion data (rats), however, indicate that minor amounts are absorbed during short-term exposures (48 minutes) to metallic platinum, platinum (IV)

oxide, platinum (IV) sulfate or platinum (IV) chloride (air concentrations 5 – 8 mg/m^3), but the relative amounts of uptake via lungs and digestive tract could not be determined (59). Immediately after the exposures there was accumulation of platinum in the digestive tract and respiratory passages. Most of it was excreted from the digestive tract within 24 hours, but elimination from the lungs was much slower. Platinum (IV) sulfate was eliminated from lungs somewhat faster than the metal or the oxide. After exposure to metallic platinum (7 – 8 mg/m^3) the highest platinum concentrations were found in lungs, trachea, kidneys and bone; very little platinum was found in brain tissue (59). After oral administration of platinum to mice and rats, the highest concentrations have often been found in kidneys (2, 3, 13, 26, 48, 57, 58, 65). Platinum has been identified in very small amounts in fetuses (mice, rats) after administration of platinum as metal or salt (40, 50, 57). Platinum has also been found in the milk of rats given oral doses of platinum (IV) chloride (41).

Toxic effects

Human data

There are few reports of acute poisoning attributed to platinum exposure. In one case, nausea, vomiting, diarrhea and leg cramps were reported about 12 hours after swallowing 600 mg potassium tetrachloroplatinate (II), and medical examination revealed acute kidney damage, inflammation in stomach and intestines, mild hepatitis and other effects. The initial serum concentration was 245 µg Pt/dl, and the urine concentration was 4200 µg Pt/L (90).

There are many reported cases of eye irritation, respiratory symptoms and/or skin reactions (e.g. urticaria) resulting from occupational exposure to hexachloroplatinic acid and some platinum salts (46). Duration of exposure before the appearance of symptoms has ranged from one week to over 20 years (46). There are no reports of respiratory symptoms attributed to exposure to metallic platinum (31, 44, 73, 87), and only one reported case of a skin reaction (dermatitis) (72). It has sometimes been possible to show an immunological etiology for these symptoms, usually with a prick test using platinum salts or by identification of specific IgE antibodies in serum (in vitro) (46). In the other cases of respiratory symptoms, a non-specific irritative effect of platinum salts can not be excluded (9, 11, 88). The acute symptoms of allergy to platinum salts usually disappear when exposure is terminated (47, 66), but there may be a residual non-specific hyperreactivity in respiratory passages and/or a residual positive reaction to prick tests (4, 17, 54). Dermatitis, which has been reported in employees at platinum refineries, is often attributed to other irritating substances (14, 30).

Respiratory symptoms (sneezing, coughing, shortness of breath etc.) were reported in 52 of 91 workers (57%) in four refineries where platinum concentrations in air ranged from 0.9 to 1700 µg/m^3 (21, 31). In one of the refineries, where measured air concentrations ranged from 0.9 to 3.2 µg/m^3, 5 of 7 workers reported minor symptoms such as sneezing and runny nose (21, 31). In other older studies (51, 63, 66, 69) the estimated prevalence of symptoms involving eyes, respiratory passages and/or skin in refinery workers ranges from 60 to 88%, but no air concentrations of platinum are reported. In a retrospective

cohort study (84), 91 workers were followed from 1973-1974 until 1980. There were 49 subjects (54%) with respiratory symptoms, and 22 of 84 persons (26%) had a positive reaction to a prick test with platinum salts. It was shown that smokers have an elevated risk of sensitization to platinum salts. No monitoring data are presented in this study.

A study of 107 workers who worked with recycling platinum in 1981 is described in three other reports (4, 8, 17). Rhinitis was reported in 44%, and asthma in 29% of them (the diagnoses were made after interviews with the subjects). A prick test with platinum salts yielded a positive reaction in 14% of the subjects, and the prevalence was reported to vary with the air concentration: e.g. sensitization to platinum salts was reported in two of three (67%) workers in a part of the refinery where the average concentration was 27.1 $\mu g/m^3$, but in only 2 of 14 workers (14%) in other parts of the refinery where the average concentration was 10.7 $\mu g/m^3$, and in 2 of 19 workers (11%) in the laboratories, where the platinum concentration never exceeded 2.0 $\mu g/m^3$ on any monitoring occasion (average concentration 0.4 $\mu g/m^3$). A strong correlation between smoking and a positive reaction on the prick test was also reported in this study.

In the past few years the prevalence of symptoms in platinum-exposed workers has generally been reported to be lower than it used to be. In one study (15), it is reported that 15 of 65 workers (23%) had work-related symptoms (conjunctivitis, rhinitis, cough, shortness of breath), and that the symptoms were more common among personnel with high platinum exposure than among those with moderate or low exposure (52%, 4%, 14%) but further data on exposure levels were not given. The group with work-related symptoms had normal lung function at the beginning of the week, but showed a decline ($p = ‹ 0.05$) in some measures of lung function (FEV_1, FEF_{25}) as the work week progressed. Twelve of 64 workers (18.7%) had a positive reaction to platinum salts in a prick test: of these 12, 9 were in the group with work-related symptoms and 2 in the group with symptoms not judged to be work-related. The air concentrations of platinum salts in total dust were measured a few times in 1984 and 1986, and reported to be ‹ 0. 2 $\mu g/m^3$ in 1984 and 0.08 – 0.1 $\mu g/m^3$ in 1986 with stationary monitoring, and ‹ 0.05 $\mu g/m^3$ with personal monitors in 1986. It was also reported that 2.0 $\mu g/m^3$, the exposure limit in force at the time, was not exceeded.

In another study (55, 56), work-related symptoms (conjunctivitis, rhinitis, asthma, skin reactions) were observed in 2 of 24 workers (8%) at a platinum refinery. Prick tests with a hexachloroplatinate solution were given to 20 workers, and 4 (20%) had a positive reaction. One of these was in the group with work-related symptoms, and three were in the group with symptoms not classified as work-related (one of these, however, developed work-related asthma after the study). It was reported that the risk of developing an allergy to platinum salts did not increase with smoking, and it was shown that the workers in the group with work-related symptoms had higher exposure to platinum salts than workers in the other studied groups. No details were given regarding exposure levels, but it was reported that the air concentration of platinum salts was generally below 0.08 $\mu g/m^3$ (55, 56).

In an incompletely reported study of 261 workers who were followed for at least 2.5 years (1989-1992), it is stated that no cases of allergy were found in places where the air

concentration of soluble platinum salts was below 0.01 μg/m^3. A total of 8 persons (3%) were reported to be allergic to platinum salts, but no monitoring data were presented. The air concentrations were considered to be generally lower than average for platinum refineries, however (53).

In one study (55), bronchial provocation tests with methacholine and platinum salts given to 27 workers who had quit their jobs because of work-related symptoms revealed effects on lung function in 22 of them. The authors state that the provocation dose was equivalent to the amount that a worker inhales (2 x 10^{-8} g/minute) at an exposure level of 2 μg/m^3, but no further details of the calculation are given.

Animal data

Different platinum compounds vary quite a bit in their acute toxicity. Water-soluble compounds, however, usually have greater acute toxicity than insoluble compounds in the same group (25, 26, 35, 60). LD_{50} values ranging from 25 to 240 mg/kg (rats) have been reported for oral administration of e.g. ammonium tetrachloroplatinate (II), ammonium hexachloroplatinate (IV), potassium tetrachloroplatinate (II), sodium hexachloroplatinate (IV) and platinum (IV) chloride (25, 35).

Single injections of hexachloroplatinic (IV) acid, potassium tetrachloroplatinate (II), potassium hexachloroplatinate (IV), or platinum (IV) chloride have resulted in extensive kidney damage, severe histopathological changes in the thymus, and effects on enzymes that regulate heme biosynthesis, drug metabolism or DNA synthesis (20, 27, 49, 61, 85). Repeated oral administration of soluble platinum salts – platinum (IV) chloride, platinum (IV) sulfate tetrahydrate, potassium tetrachloroplatinate (II) – has resulted in lower weight gain, higher kidney weights, effects on liver enzymes and, at lower doses, reduced kidney function and effects on blood parameters (26, 27, 58, 65). Oral administration of metallic platinum has been reported to increase the number of red blood cells (12, 13).

A few inhalation studies were found. In a sketchily reported Russian study (67), effects on several parameters were seen in rats exposed for prolonged periods (not quantified) to 18.6 mg/m^3 ammonium chloroplatinate (IV). At an exposure level of 4.5 mg/m^3 the effects were reported to be slight and reversible.

Hyperreactivity in respiratory passages, expressed as significant changes in some lung function parameters, is reported in a study in which monkeys were exposed to 216 μg/m^3 sodium hexachloroplatinate (IV) 4 hours/day, 2 days/week for 12 weeks, and 2 weeks later exposed to a provocation dose of platinum salts (aerosol). The provocation produced no indications of bronchial hyperreactivity at a dose level of 1940 μg/m^3 or when the platinum salt had been applied repeatedly to the skin for 12 weeks. According to the authors, the amount of platinum salts the monkeys had been exposed to at an air concentration of 200 μg/m^3 was three to four times the amount that a worker is exposed to in a week at an exposure level of 2 μg/m^3. The results indicated a pharmacological or irritant-mediated mechanism for bronchial constriction with acute exposure, since bronchial provocation with sodium hexachloroplatinate (IV) revealed some deterioration of lung function in animals in all groups (significant in controls at the highest dose) (11). A later study with monkeys reports that exposure to 177 μg/m^3 ammonium hexachloroplatinate (IV) 6

hours/day, 5 days/week for 12 weeks had no significant effect (average value) on reactivity to platinum salts or methacholine (compared with reactivity to these substances in provocation tests given before the exposures), whereas the provocation results after exposure to 208 $\mu g/m^3$ ammonium hexachloroplatinate (IV) combined with 1 ppm ozone indicated an increase of both specific and non-specific bronchial hyperreactivity. The combined exposure also increased the incidence of positive reactions to skin tests with Pt (intracutaneous injections) (10).

Immunological reactions have been observed in experimental animals after administration of platinum salts. In one study with mice, administration of sodium hexachloroplatinate (IV), ammonium hexachloroplatinate (IV), or sodium tetrachloroplatinate (II) yielded a dose-dependent lymph node activation, and it was observed that only about a fifth of the original dose was needed to trigger a secondary reaction (71). Ammonium tetrachloroplatinate (II) was classified as extremely sensitizing when tested in the guinea pig maximization test (5).

Some platinum salts have been tested on rabbits for irritation of skin and eyes. Among the compounds reported to cause moderate to severe skin irritation are ammonium tetrachloroplatinate (II), sodium hexahydroxyplatinate (IV), and tetraammine platinum (II) chloride. Sodium hexachloroplatinate (IV) and potassium tetrachloroplatinate (II) were reported to cause eye irritation, and tetraammine platinum (II) chloride, diammine dinitroplatinum (II) and ammonium tetrachloroplatinate (II) were strongly irritating or corrosive when applied to eyes (28, 35).

Mutagenicity, carcinogenicity

Numerous platinum compounds have been tested in various in vitro test systems, and many of them have been found to be genotoxic/mutagenic (46). In tests with *Salmonella typhimurium* (usually without metabolic activation), mutagenic activity has been shown for hexachloroplatinic (IV) acid, platinum (IV) chloride, ammonium hexachloroplatinate (IV), potassium tetrachloroplatinate (II), cis-potassium dichlorodinitroplatinate (II), ammonium ammine trichloroplatinate (II), potassium ammine trichloroplatinate (II), chlorotriammine platinum (II) chloride, and tetraammine platinum (II) chloride (28, 38, 42, 63, 82). In one study, positive results were reported for platinum (IV) chloride, hexachloroplatinic (IV) acid, and ammonium hexachloroplatinate (IV) in tests with *E. coli* and/or *Bacillus subtilis* (38). Various types of genotoxicity (DNA inhibition, chromosomal malsegregation) have also been reported in yeast in a few tests with platinum (IV) chloride and potassium tetrachloroplatinate (II) (24, 76). Tests on mammalian cells in vitro (without addition of metabolic systems) have shown mutagenic activity for platinum (IV) chloride, platinum (IV) sulfate, potassium tetrachloroplatinate (II), potassium hexachloroplatinate (IV), potassium ammine itrichloroplatinate (II) and chlorotriammine platinum (II) chloride (18, 29, 36, 39, 68, 75, 78, 79, 80, 81). Mutagenic effects were also reported in a study of fruit flies (in vivo) after oral administration of a solution of platinum (IV) chloride (89).

No relevant cancer studies of platinum compounds used in industry were found in the literataure. The cancer drug cisplatin and a few other cis-platinum (II) coordination

complexes with tumor-inhibiting effects have been shown to be carcinogenic to experimental animals (33, 34, 43).

Reproduction toxicity

No notable effects on fetuses (fetus weight, number of resorptions, number of fetuses with developmental aberrations) or placenta (weight) were reported in a study (12) in which rats were given metallic platinum or platinum (IV) chloride in feed before and during gestation (up to 100 mg Pt/kg feed; total 7 weeks). Nor were effects observed on young (weight, hematological parameters) of rats given platinum (IV) chloride or platinum (II) chloride in feed (up to 100 mg Pt/kg feed) during lactation (41). Effects on young were also investigated in a study in which mice were given a dose of platinum (IV) sulfate (200 mg Pt/kg body weight, per os) or sodium hexachloroplatinate (IV) hexahydrate (20 mg Pt/kg, subcutaneous) during gestation or lactation (19). Administration of platinum (IV) sulfate during gestation resulted in reduced body weight in young (up to day 45 after birth), but it could be shown that pups of unexposed mothers who were cared for by platinum -exposed mothers also had reduced body weight. When platinum (IV) sulfate was given to the mothers during lactation (day 2), the pups were reported to be less active than normal. Administration of sodium hexachloroplatinate (IV) on day 12 of gestation resulted in reduced activity in pups.

Injection of platinum (IV) chloride into the testes of male rats is reported to cause necrosis and reduced testes weight. When the substance was injected in lower doses (total dose 27 mg/kg b.w.) under the skin of mice for 30 days, it resulted in lower testes weights and inhibited spermatogenesis (37).

Dose-effect / dose-response relationships

The only reported effects of occupational exposure to soluble platinum salts are allergy and irritation. There are no data at all on the effects of human exposure to metallic platinum and insoluble platinum salts. Reliable measures of air concentrations are sparse, and it is therefore difficult to determine an exposure level at which allergy might be induced. In one study (4), however, it is reported that sensitization to platinum salts (expressed as a positive prick test) could be shown in 2 of 3 workers (67%) in a part of a refinery where the average concentration was 27.1 $\mu g/m^3$, in 2 of 14 workers (14%) where the average concentration was 10.7 $\mu g/m^3$, and in 2 of 19 workers (11%) where the average concentration was 0.4 $\mu g/m^3$ and reportedly did not exceed 2.0 $\mu g/m^3$ on any monitoring occasion. There are also indications that persons previously sensitized to platinum salts can develop symptoms of respiratory allergy at air concentrations below 2 $\mu g/m^3$ – possibly as low as 0.08 – 0.1 $\mu g/m^3$ (15, 55, 56).

Effects on kidneys, thymus and testes have been observed in animals exposed to soluble platinum salts. The exposure-effect relationships observed in animal experiments are summarized in Table I.

Table 1. Exposure-effect relationships observed in experimental animals given soluble platinum salts.

Substance	Exposure	Species	Effects	Ref.
H_2PtCl_6	i.p. 40-50 mg/kg single dose	Rat	LD_{50}, kidney damage, thymus damage	85
$PtCl_4$	i.p. 4.7 mg/kg/day 2 days	Rat	Decreased aminopyrine demethylase activity; somewhat longer hexobarbital-induced sleep	27
$PtCl_4$	i.p. 4.7 mg/kg single dose	Rat	Inhibited DNA synthesis in spleen	20
Pt Cl_4	s.c. 0.9 mg/kg/day 30 days	Mouse	Reduced testes wight, inhibited spermatogenesis	37
$Pt(SO_4)_2x4H_20$	750 mg/L in drinking water, 8 days (≈140 mg/kg/day)	Rat	Lower weight gain, reduced aniline hydroxylase activity	26, 27
$PtCl_4$	550 mg/L in drinking water, 29 days (≈74 mg/kg/day)	Rat	Lower weight gain, higher relative kidney weight	26
$PtCl_4$	50 ppm Pt in feed, 4 weeks (≈8.6 mg/kg/day)	Rat	Rise in plasma creatinine, slightly lower erythrocyte count and hematocrit	65

Conclusions

The critical effect of occupational exposure to soluble platinum salts is effects on the respiratory passages. It has been shown that smokers have an elevated risk of sensitization to platinum salts. Metallic platinum has not been associated with respiratory effects. There are no data from which to determine a critical effect for exposure to metallic platinum or insoluble platinum compounds.

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Consensus Report for Tetrachloroethane

June 4, 1997

This report is based primarily on a criteria document produced by the Nordic Expert Group (44).

Chemical and physical data. Uses.

1,1,1,2-Tetrachloroethane

CAS No:	630-20-6
Synonym:	asymmetric tetra
Formula:	$ClH_2C–CCl_3$
Molecular weight:	167.84
Boiling point:	130.5 °C
Melting point:	- 68.7 °C
Vapor pressure:	0.66 kPa (20 °C)
Saturation concentration in air:	0.65% (20 °C) (= 45.3 mg/m^3)
Conversion factors:	1 ppm = 6.96 mg/m^3 (20 °C)
	1 mg/m^3 = 0.144 ppm (20 °C)

1,1,2,2-Tetrachloroethane

CAS No:	79-34-5
Synonyms:	acetylene tetrachloride, *sym*-tetrachloroethane, 1,1-dichloro-2,2-dichloroethane, symmetric tetra
Formula:	$Cl_2HC–CHCl_2$
Molecular weight:	167.84
Boiling point:	146.5 °C
Melting point:	- 42.5 °C
Vapor pressure:	0.68 kPa (20 °C)
Saturation concentration in air:	0.67% (20 °C) (= 46.7 mg/m^3)
Solubility in water:	0.3% (20 °C)
Conversion factors:	1 ppm = 6.96 mg/m^3 (20 °C)
	1 mg/m^3 = 0.144 ppm (20 °C)

Tetrachloroethane (TCE) occurs in two isomeric forms: 1,1,1,2-tetrachloroethane (1,1,1,2-TCE) and 1,1,2,2-tetrachloroethane (1,1,2,2-TCE). Both isomers are heavy, colorless, non-flammable liquids (36, 78). Contact with hot metal or open flame may result in formation of poisonous phosgene gas (36). TCE is soluble in several organic solvents – ethanol, diethyl ether, benzene, chloroform, etc.– but its solubility in water is extremely

low (4, 44, 78). 1,1,2,2-TCE has a sweet smell (36, 73) and in one work (1) the average odor threshold is reported to be 10 mg/m^3 (1.5 ppm). Another work (40) reports that the odor is recognizable at 20 mg/m^3 and that the sense of smell is deadened at high concentrations.

1,1,1,2-TCE is not produced on an industrial scale, but frequently occurs as a by-product in chlorination of C_2 hydrocarbons (78), and is found as a contaminant in e.g. trichloroethylene and tetrachloroethylene (8). 1,1,2,2-TCE was once widely used as an intermediate in the production of other chlorinated hydrocarbons, and also had widespread use as a solvent. The substance was used in a wide variety of industries, ranging from synthetic fibers, electronics and pesticides to production of artificial pearls. It had a special use in the aviation industry: to impregnate the varnish on airplane wings (3, 4, 56, 60, 73). The use of 1,1,2,2-TCE has been cut back considerably in recent decades, and it now occurs primarily as an unisolated intermediate in the production of trichloroethylene. Manufacture of 1,1,2,2-TCE as an end product is reported to be extremely limited. However, 1,1,2,2-TCE may sometimes be isolated and used in production of trichloroethylene, tetrachloroethylene and 1,2-dichloroethylene. It is possible that minor amounts of 1,1,2,2-TCE are also used as solvents and pesticides (44, 67). Neither 1,1,2,2-TCE nor 1,1,1,2-TCE may be present in concentrations exceeding 0.1% by weight in chemicals or products sold to the public (44).

Uptake, biotransformation, excretion

TCE can be absorbed via both lungs and digestive tract (see toxicity data), but quantitative data are sparse. In one study (51) it is reported that when a subject inhaled a vapor of ^{38}Cl-labeled 1,1,2,2-TCE (one breath), 3.3% of the absorbed dose was exhaled within an hour. In another study, in which rats were exposed to 2450 mg/m^3 (352 ppm) 1,1,1,2-TCE or 2440 mg/m^3 (350 ppm) 1,1,2,2-TCE for 6 hours, there were indications of considerable uptake via lungs (21). There is virtually no information on skin uptake, but data from the EPA on the permeability of human skin (permeability coefficient) indicate that 1,1,2,2-TCE has limited ability to penetrate skin (44, 79). However, extensive skin contact can lead to a significant uptake: according to a calculation in Reference 44, about 10.8 mg/hour via contact with the palms of both hands (about 400 cm^2).

Both 1,1,1,2-TCE and 1,1,2,2-TCE are metabolized to a great extent. In a study with mice, within 4 hours after an intravenous injection of ^{14}C-1,1,2,2-TCE in the mucous membranes of the respiratory passages and upper alimentary tract, the highest concentrations of radioactivity were found in liver, gall bladder, adrenal cortex and testes (interstitial tissue), and it could be established that a large portion of the radioactivity was irreversibly bound in metabolites (17).

Biotransformation of 1,1,1,2-TCE involves both oxidative and reductive metabolism (8). In an inhalation study in which rats were exposed to 2450 mg/m^3 (352 ppm) for 6 hours, the maximum metabolism rate (V_{max}) was determined to be 6.39 mg/kg/hour (21). Excretion of trichloro compounds (trichloroacetic acid, trichloroethanol) in urine has been demonstrated in several studies (33, 43, 50). In one study (33) with rats, the amount of

trichlorinated compounds in urine (mostly trichloroethanol) is reported to be more than 20 times greater after exposure to 1,1,1,2-TCE than after exposure to 1,1,2,2-TCE; another study (50) with mice and rats reports that trichloroethanol/trichloroacetic acid was the principal metabolite for both isomers. Reductive metabolism of 1,1,1,2-TCE has been demonstrated in several studies (71, 74) and significant quantities of 1,1-dichloroethylene have been identified in vivo (rat blood) as well as in vitro after administration of 1,1,1,2-TCE (71). In a comparative in vitro study (rat liver microsomes) it is reported that under anaerobic conditions 1,1,1,2-TCE was reduced much more rapidly than 1,1,2,2-TCE (71).

1,1,2,2-TCE is metabolized mostly by oxidative metabolism. In an inhalation study in which rats were exposed for 6 hours to 2440 mg/m^3 (350 ppm) 1,1,2,2-TCE, the maximum metabolism rate (V_{max}) was determined to be 12.9 mg/kg/hour (21). One of the primary metabolic pathways involves incremental hydrolytic splitting of the carbon-chlorine bond via dichloroacetic acid (urine metabolite) to glyoxylic acid (urine metabolite) and subsequent transformation, notably to carbon dioxide. In vitro studies have indicated an alternative metabolic pathway via dichloroacetyl chloride (reactive metabolite) instead of dichloroacetaldehyde for transformation of 1,1,2,2-TCE to dichloroacetic acid (7, 9, 24, 60). 1,1,2,2-TCE can also undergo elimination of hydrogen chloride and form trichloroethylene, which then yields the urine metabolites trichloroacetic acid and trichloroethanol (8, 33, 50). Small amounts of tetrachloroethylene (trichloroacetic acid and oxalic acid in later steps) can also be formed with oxidation of 1,1,2,2-TCE (85). Reductive dechlorination and formation of free radicals have been indicated in some studies with 1,1,2,2-TCE and the metabolites dichloroacetic acid and trichloroacetic acid (37, 60, 72).

Both 1,1,1,2-TCE and 1,1,2,2-TCE are excreted mostly as metabolites. In a study (85) in which mice were given intraperitoneal injections of ^{14}C-1,1,2,2-TCE, it is reported that about three fourths of the dose was excreted within 48 hours, most of it as metabolites during the first 24 hours. In another study with mice and rats (50), it was shown that about half of an oral dose of ^{14}C labeled 1,1,2,2-TCE and about 90% of a dose of ^{14}C-1,1,1,2-TCE were excreted within 48 hours, mostly as metabolites. A calculation based on perfusion rate, tissue volume and distribution coefficient (oil/blood) indicates that 1,1,2,2-TCE accumulates in human fat to some extent but is eliminated fairly quickly, with a half time of about 34 hours (44).

Toxic effects

Animal data

With inhalation and oral administration, 1,1,1,2-TCE has higher LC_{50} and LD_{50} values than 1,1,2,2-TCE. The LD_{50} for rats has been reported to be 670 mg/kg for the first substance and 250 mg/kg for the second. The reported LC_{50} for rats (4 hours) is 14,600 mg/m^3 (2100 ppm) for the first substance, and 8600 mg/ m^3 for the second (44, 64). The lowest reported LC_{50} (mice, 2 hours) for 1,1,2,2-TCE is 4500 mg/m^3 (44). With dermal application to rabbits, an LD_{50} of 20 g/kg has been reported for 1,1,1,2-TCE (44).

With short-term exposure to high concentrations of TCE in air, the toxic picture is distinguished mostly by CNS symptoms (38, 39, 52, 59). The anesthetic qualities of tetrachloroethane have been demonstrated, for example, in a study with cats (39), in which exposure to 5700 mg/m^3 1,1,2,2-TCE resulted in slight narcosis after a bit over 4 hours. CNS effects were also reported in cats that had been exposed to an average 1400 mg/m^3 6 to 7 hours/day for 4 weeks (18 exposures) (39).

Damage to liver (e.g. fatty degeneration), kidneys, intestinal mucosa, eyes etc. has been observed in animal experiments with single or brief exposures to TCE in high concentrations (18, 26, 29, 44, 52). Short-term exposures to low air concentrations are reported to affect primarily the liver. In one study, rats were exposed for 4 hours to 1,1,2,2-TCE in concentrations ranging from 410 to 4200 mg/m^3, and diffuse fatty degeneration was noted even at the lowest dose (64). Another inhalation experiment with rats (14, 44) reports an increase of aminotransferases (ASAT, ALAT) in serum 24 hours after a 6-hour exposure to 1,1,2,2-TCE in air concentrations of 70 and 690 mg/m^3 (10 and 100 ppm), although histopathological examination revealed no clear changes in liver. However, histopathological changes in liver were reported in another experiment in which rats were repeatedly exposed to 15 mg/m^3 1,1,2,2-TCE for 10 days (23, 62).

Prolonged exposure of rabbits (6 months) and rats (12 months) to 3430 mg/m^3 (500 ppm) 1,1,1,2-TCE was reported to cause liver damage in the form of centrilobular necroses and microvacuolization (30, 76). Exposure to 3900 mg/m^3 (560 ppm) 1,1,2,2-TCE for 15 weeks also caused liver changes in rats (44, 75). No effects on kidneys, lungs, adrenals, ovaries or uterus were observed in histopathological examination. In a study designed to discover glomerulopathy in rats, small changes in glomeruli were noted after exposure to 3600 mg/m^3 (516 ppm) 1,1,2,2-TCE for 13 weeks (13, 44). A long-term experiment in which rats were exposed to 13.3 mg/m^3 1,1,2,2-TCE for 9 months resulted in reduced ACTH level in pituitaries (the change was greatest on the first examination, i.e. after 4 months of exposure), and minor, transient changes in liver lipids, body weight etc. (62).

In a long-term study, one monkey was given a fluctuating exposure ranging from 6960 to 27,800 mg/m^3 (1000 – 4000 ppm) unspecified TCE for a total of 190 2-hour sessions over a period of 9 months; it developed diarrhea and loss of appetite (anorexia) after the 12th exposure and became nearly unconscious (for 20 to 60 minutes) starting with the 15th exposure. Hemoglobin levels and erythrocyte counts dropped 3 – 4 months after the exposures were begun, but this was followed by an increase. The histopathological examination revealed centrilobular fatty degeneration and vacuolization in the liver. No exposure-related effects were seen on heart, lungs, kidneys, pancreas or testes (29).

With oral administration of 1,1,1,2-TCE to mice (250 mg/kg/day, 5 days/week for 103 weeks, or 500 mg/kg/day, 5 days/week for 65 weeks) and rats (125 or 250 mg/kg/day, 5 days/week for 103 weeks), CNS toxicity and liver damage were observed in mice in the high-dose group, and CNS toxicity in rats in the high-dose group (30, 58). Other studies with oral administration (doses of 300 to 500 mg/kg) of 1,1,1,2-TCE to rats, guinea pigs and rabbits for various lengths of time also report indications of liver damage (30).

Oral administration of 1,1,2,2-TCE to mice (0, 100 – 200 or 200 – 400 mg/kg/day, 5 days/week for 78 weeks) resulted in a dose-related increase in mortality. Many deaths

among males in the high-dose group (week 69 – 70) were due to acute tubular nephrosis (53). There was also an increase of early deaths among females in the high-dose group. The same study also reports a dose-related negative effect on growth in rats given 40 – 65 mg/kg/day or 80 – 130 mg/kg/day 1,1,2,2-TCE for up to 78 weeks. In another study (mice), intraperitoneal injections of 1,1,2,2-TCE, 300 or 600 mg/kg, resulted in biochemical effects in liver, and females in the high-dose group had reduced liver weights (60).

To clarify the acute neurochemical effects of 1,1,2,2-TCE, the concentration of neurotransmitters and metabolites in various parts of the brains of male rats were measured after oral doses of 1,1,2,2-TCE (50 mg/kg). It was found that the levels of the serotonin metabolite 5-hydroxyindole acetic acid (mesencephalon), dopamine (medulla oblongata) and serotonin (medulla oblongata) rose significantly (35).

1,1,2,2-TCE is reported to be strongly irritating to skin and mucous membranes (36).

Human data

There are several reported deaths due to oral intake of unknown quantities of 1,1,2,2-TCE. These cases are characterized by effects on the central nervous system, including loss of consciousness, and death occurred within 12 hours (16, 19, 41, 45). Temporary loss of consciousness has been reported after oral intake of 3 ml (about 60 – 80 mg/kg body weight) 1,1,2,2-TCE (65).

Many cases of poisoning have also occurred during work with 1,1,2,2-TCE, especially in the European aircraft industry in the early 1900s. In some cases the primary symptoms of poisoning involved the digestive tract. Jaundice and enlarged livers were observed, and in fatal cases severe liver damage was found at autopsy (19, 27). In other cases, there were neurological symptoms in addition to nausea and loss of appetite (27). Changes in hematological parameters, including increase of large mononuclear cells, have sometimes been observed to precede the clinical symptoms of poisoning (48).

There are a few studies in which both the symptoms of exposed persons and the air concentrations of TCE are reported. In one study, two volunteers were exposed to 1,1,2,2-TCE in concentrations of 20 to 2300 mg/m^3 for periods of up to 30 minutes. Exposure to 20 – 90 mg/m^3 for 10 minutes was reported to have no noteworthy effects. With exposure to 800 mg/m^3 it was observed that the odor was no longer discernible after 10 minutes, and slight nausea was felt at the end of the 20-minute exposure. Exposure to 1000 mg/m^3 resulted in dizziness after 10 minutes, irritated mucous membranes after 12 minutes and drowsiness after 20 minutes. At an air concentration of 1800 mg/m^3 the subjects became dizzy after only 5 minutes, and the exposure (10 minutes) also resulted in irritation of mucous membranes in eyes, nose and mouth (40).

In a Hungarian study (34, 44) it is reported that about half of the workers in a penicillin factory had indications of poisoning, including digestive disorders, headaches and weight loss. Many of these workers also had enlarged livers and abnormal results on tests of liver function. The concentration of 1,1,2,2-TCE in different processes ranged from 10 to 1700 mg/m^3 (1.5 to 247 ppm). The health of the workers improved when the work environment

was improved, and most of them were reported to be free of symptoms when the maximum air concentration of 1,1,2,2-TCE was 250 mg/m^3 (36 ppm).

A Japanese study (28) reports air concentrations of TCE ranging from 490 to 1560 mg/m^3 (70 to 224 ppm) in three factories where artificial pearls were produced. Medical examination of 18 workers revealed deviations from normal results in many of them: neurological symptoms, low erythrocyte counts and/or relative lymphocytosis, etc. After the air concentration of TCE was reduced to 0 – 140 mg/m^3 (20 ppm) it was observed that the proportion of workers with abnormal test results (blood) declined substantially.

In a study of 380 workers in 23 factories in India where 1,1,2,2-TCE was used as a solvent for cellulose acetate, it is reported that symptoms of poisoning appeared after about 3 months of exposure. Air concentrations (average) were determined to be 63 to 680 mg/m^3 (9 to 98 ppm), but frequent skin contact with the substance in liquid form was also common. Among the most exposed persons, CNS symptoms (e.g. finger tremor, headache, dizziness) were most common, but symptoms involving the digestive system (loss of appetite, nausea, vomiting, stomach cramps) were also widespread. Enlarged livers or jaundice were not seen. There appeared to be a dose-response relationship for tremor, but the importance of e.g. skin exposure to 1,1,2,2-TCE can not be assessed (42).

In an Italian study (22, 44), 75 persons exposed to TCE were examined for effects on heart and circulatory system. No significant differences from normal values were observed in clinical examinations (including pulse, ECG). Air concentrations (average values) around production of TCE were reported to range from 2.6 mg/m^3 to 9.3 mg/m^3, but a peak of 22 mg/m^3 was also measured. In other occupational contexts (including laboratory work and production of trichloroethylene and tetrachloroethylene), concentrations of TCE ranged from 35 to 104 mg/m^3 with occasional peaks of 278 mg/m^3.

In a retrospective cohort study (1946 – 1976) of 1,099 men who were exposed to 1,1,2,2-TCE for brief periods (5 weeks to 1 year), there was no significant increase in mortality due to heart/circulatory diseases. Nor was there a significant increase of total mortality, or deaths due to cancer or liver cirrhosis. No exposure data are given in this study (57).

Mutagenicity

1,1,1,2-TCE has yielded negative results in most studies with bacteria, yeast or moulds (25, 46, 47, 61, 81, 82), but mutagenic/genotoxic effects were observed in a study with *Salmonella typhimurium* and in a study with *Aspergillus nidulans* (12, 67). In tests on mammalian cells in vitro, 1,1,1,2-TCE has caused sister chromatid exchanges and mutations, but negative results were obtained in other tests of DNA repair, cell transformation or chromosome aberrations (20, 47, 68, 69, 77, 83). A study with Drosophila, in which genetic damage in somatic cells was examined after inhalation exposure of larvae (1000 ppm) also yielded negative results (80).

1,1,2,2-TCE has also been tested in several in vitro test systems. Most studies with *Salmonella typhimurium* have yielded negative results (25, 47, 55, 61, 81), but in some studies 1,1,2,2-TCE has been reported to be mutagenic (2,46, 67). In genotoxicity tests

with yeasts/moulds, positive results were obtained in two of three studies (6, 12, 54). DNA damage has also been indicated in some tests with *E. coli* (2, 15). In tests with mammalian cells in vitro, sister chromatid exchange (10, 20) and cell transformation (two studies) have been observed (10, 11, 47, 77), but DNA repair and chromosome aberrations have not been reported (20, 47, 83). A few in vivo studies were also found. In one study with mice, no increase of DNA repair synthesis or DNA replication synthesis was observed in hepatic cells (with equivocal result regarding S-phase synthesis in females) after oral administration of 50 – 1000 mg/kg or 200 – 700 mg/kg 1,1,2,2-TCE (49). In a gene mutation test with Drosophila (sex-linked recessive lethals) it was concluded that 1,1,2,2-TCE was not mutagenic after injection of 800 ppm or oral administration of 1500 ppm (84). Monitoring of genetic damage in somatic cells after inhalation exposure (500 ppm) of larvae also yielded negative results (80).

On the basis of the covalent bonding index for hepatic DNA (in vivo: mice, rats), 1,1,1,2-TCE has been classified as a weak to moderate initiator of genotoxic activity and 1,1,2,2-TCE as a moderate initiator of genotoxic activity (8, 9).

Carcinogenicity

In a cancer study, mice were given 1,1,1,2-TCE by gavage 5 days/week, 250 mg/kg/day for 103 weeks or 500 mg/kg/day for 65 weeks (all the animals in the high-dose group died or were killed after 65 weeks). A significant, dose-related increase in the incidence of hepatocellular adenomas was observed in both males (controls 6/48; low-dose 14/46; high-dose 21/50) and females (4/49, 8/46, 24/48), and a dose-related increase of hepatocellular carcinomas ($p < 0.05$) was observed in females (1/49, 5/46, 6/48). Rats were given 1,1,1,2-TCE by gavage, 125 or 250 mg/kg/day, 5 days/week for 103 weeks: there was a statistically significant increase in the incidence of fibroadenomas in mammary glands of females in the low-dose group, but not in the high-dose group (6/49, 15/49, 7/46) (30).

One study (53) with oral administration of 1,1,2,2-TCE to mice (100 – 200 or 200 – 400 mg/kg/day, 5 days/week for up to 78 weeks) reports a significant, dose-related increase of hepatocellular carcinomas in both males and females. Liver carcinomas were observed in 2/19 untreated controls, 1/18 vehicle controls, 13/50 males in the low-dose group, and 44/49 males in the high-dose group. The corresponding figures for females were 0/19, 0/20, 30/48, and43/47. Rats given 1,1,2,2-TCE by gavage (80 – 130 mg/kg/day or 40 – 65 mg/kg/day, 5 days/week for up to 78 weeks) showed no significant increase in incidence of any tumor type. Two of 49 males in the high-dose group, however, developed liver carcinomas, and one other animal in this group had neoplastic changes (nodules) in the liver (53). In a 24-week study (70), mice were given intraperitoneal injections of 80, 200 or 400 mg/kg 1,1,2,2-TCE 3 times/week (total 5, 18 or 16 injections) and examined for the occurrence of lung adenomas. The highest dose resulted in a slightly elevated incidence of lung tumors (not statisticallly significant), but by the end of the study most of the animals in this dose group had died.

In an initiation-promotion study (47, 66), rats were given oral doses of 200 mg/kg 1,1,1,2-TCE or 100 mg/kg 1,1,2,2-TCE, as initiator or as promotor (5 days/week for 7

weeks); 1,1,2,2-TCE (but not 1,1,1,2-TCE) induced an increase of GGT+ (gamma-glutamyl transferase) foci in liver. 1,1,2,2-TCE administered in accordance with the promotion protocol induced a significant increase of GGT+ foci both with and without the use of known initiators. The results indicate that 1,1,2,2-TCE is a complete carcinogen, with a slight ability to function as initiator and a strong ability to function as promotor.

In the judgement of the IARC, there is ”limited evidence” that 1,1,1,2-TCE and 1,1,2,2-TCE are carcinogenic to experimetal animals, but it is not possible to determine whether either substance is carcinogenic to humans (31). In the overall IARC assessment, both substances are placed in Group 3: ”not classifiable as to its carcinogenicity to humans” (31). It should be observed that the TCE metabolites trichloroethylene, tetrachloroethylene, dichloroacetic acid and trichloroacetic acid have been shown to be carcinogenic in animal experiments (32). The two latter metabolites have been shown to induce liver tumors in mice (5, 32). The overall assessments of the IARC for trichloroethyene and tetrachloroethylene are that these substancess are ”probably carcinogenic to humans” (Group 2A) (32). The overall assessments of the IARC for dichloroacetic acid and trichloroacetic acid are that these substances are ”not classifiable as to its carcinogenicity to humans” (Group 3) (32).

Reproduction toxicity

In an incompletely reported study with rats (30, 76), it is stated that pups born to mothers exposed to 1,1,1,2-TCE either orally or by inhalation (dose not reported) died within two days of birth. No other reproductive disturbances were reported. Another study reports that 1,1,2,2-TCE was embryotoxic to mice with intraperitoneal injection during gestation (63). An increased number of post-implantation losses was observed in one strain of mice (700 mg/kg on day 9 or 400 mg/kg/day on days 7-14), and an increase in the number of non-pregnant females was reported in another strain of mice (300 mg/kg/day, days 1 – 14). A slight increase in the number of fetuses with aberrations (both strains) was also noted (63). When male rats were exposed to 13.3 mg/m^3 1,1,2,2-TCE for 9 months and then mated with untreated females, there were no effects on litter size, birth weight, sex distribution, growth or neonatal mortality. Nor did the young show any deformities (62).

Dose-effect / dose-response relationships

There are very little data on human exposure that can be used as a basis for establishing a dose-effect or dose-response relationship for either 1,1,1,2-TCE or 1,1,2,2-TCE. The effects of acute inhalation exposure on human subjects are summarized in Table 1.

The dose-effect relationships observed in animal experiments are summarized in Table 2.

Table 1. Acute effects of inhalation of 1,1,2,2-TCE experienced by two volunteers (from Reference 40).

Concentration	Effect
1800 mg/m^3 (259 ppm) 5 – 10 minutes	Dizziness, irritation of mucous membranes
1000 mg/m^3 (144 ppm) 10 – 20 minutes	Dizziness, irritation of mucous membranes, fatigue
800 mg/m^3 (115 ppm) 20 minutes	Slight nausea
20 – 90 mg/m^3 (2.9 – 13 ppm) 10 minutes	No effects

Table 2. Exposure-effect relationships observed in laboratory animals with inhalation exposure to 1,1,2,2-TCE.

Concentration	Exposure time	Species	Effect	Ref.
6960 – 27,800 mg/m^3	190 2-hour sessions, 6 days/week, 9 months	Monkey	CNS effects, diarrhea, loss of appetite, temporary drop in erythrocytes and hemoglobin, fatty degeneration and vacuolization in liver	29
5700 mg/m^3	4 hrs 15 minutes	Cat	Slight narcosis	39
3900 mg/m^3	5 – 6 hrs/day, 5 days/week, 15 weeks	Rat	Increased relative liver weights, indications of liver hyperplasia, granulation and vacuolization foci in liver, slight reduction of hematocrit	44, 75
1400 mg/m^3	6 – 7 hrs/day, 18 sessions	Cat	CNS effects	39
410 mg/m^3	4 hrs	Rat	Diffuse fatty degeneration in liver	64
70 mg/m^3	6 hrs	Rat	Increases in ASAT, ALAT	14, 44
15 mg/m^3	4 hrs/day, 4 or 8 sessions in 10 days	Rat	Slight inflammatory changes, including small necrotic foci and fat accumulation in liver	23, 62
13.3 mg/m^3	4 hrs/day, 9 months	Rat	Reduced ACTH in pituitary, minor, temporary changes including liver lipid content (increase at 9 months) and body weight (reduction at 4 months)	62

Conclusions

Occupational exposure to 1,1,2,2-TCE has effects on liver, digestive tract and central nervous system, but data on human exposure provide an insufficent basis for establishing a critical effect. Judging from animal experiments, the critical effect of exposure to 1,1,1,2-TCE and 1,1,2,2-TCE is cancer. Liver tumors have been observed in mice after oral administration of both substances, but the mechanism behind the TCE-induced liver carcinogenesis is not clear. Both isomers can bind to DNA and have shown some mutagenic/genotoxic activity in vitro. TCE can penetrate the skin.

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Summary

Lundberg P (ed). Scientific Basis for Swedish Occupational Standards. XVIII. *Arbete och Hälsa* 1997;25, pp 1-78.

Critical 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 National Institute for Working Life between July, 1996 and June, 1997.

Key Words: Cyanoacrylates, Diethyleneglycol ethylether + acetate, Ethene, Inorganic Manganese, Occupational Exposure Limit (OEL), Platinum + Platinum compounds, Potassium aluminium fluoride, Scientific Basis, Tetrachloroethane.

Sammanfattning

Lundberg P (ed). Vetenskapligt underlag för hygieniska gränsvärden. XVIII. *Arbete och Hälsa* 1997;25, s 1-78.

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 juli 1996 - juni 1997.

Nyckelord: Cyanoakrylater, Dietylenglykoletyleter + acetat, Eten, Hygieniskt gränsvärde, Kaliumaluminiumfluorid, Oorganiskt mangan, Platina och platinaföreningar, Tetrakloretan, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 1997:24.

APPENDIX

Consensus Reports in previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	
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, C_{10}-C_{15}	June 1, 1983	1983:36	(IV)
Aliphatic monoketons	September 5, 1990	1992:6	(XII)
Allyl alcohol	September 9, 1986	1987:39	(VIII)
Allylamine	August 25, 1982	1983:36	(IV)
Allyl chloride	June 6, 1989	1989:32	(X)
Aluminum	April 21, 1982	1982:24	(III)
revised	September 14, 1994	1995:19	(XVI)
p-Aminoazobenzene	February 29, 1980	1981:21	(I)
Ammonia	April 28, 1987	1987:39	(VIII)
Amylacetate	March 23, 1983	1983:36	(IV)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
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)
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)
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)
Butylamine	August 25, 1982	1983:36	(IV)
Butyl glycol	October 6, 1982	1983:36	(IV)
Cadmium	January 18, 1980	1981:21	(I)
revised	February 15, 1984	1984:44	(V)
revised	May 13, 1992	1992:47	(XIII)
Calcium nitride	January 27, 1993	1993:37	(XIV)
Caprolactam	October 31, 1989	1991:8	(XI)
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)
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)
Coal dust	September 9, 1986	1987:39	(VIII)
Cobalt	October 27, 1982	1983:36	(IV)
Copper	October 21, 1981	1982:24	(III)
Cotton dust	February14, 1986	1986:35	(VII)
Creosote	October 26, 1988	1989:32	(X)
Cumene	June 2, 1982	1982:24	(III)
Cycloalkanes, C_5-C_{15}	April 25, 1984	1984:44	(V)
Cyclohexanone	March 10, 1982	1982:24	(III)
Cyclohexanone peroxide	February 13, 1985	1985:32	(VI)
Cyclohexylamine	February 7, 1990	1991:8	(XI)
Diacetone alcohol	December 14, 1988	1989:32	(X)
1,2-Dibromo-3-chloropropane	May 30, 1979	1981:21	(I)
Dichlorodifluoromethane	June 2, 1982	1982:24	(III)
1,2-Dichloroethane	February 29, 1980	1981:21	(I)
Dichloromethane	February 29, 1980	1981:21	(I)
Dicumyl peroxide	February 13, 1985	1985:32	(VI)
Dicyclopentadiene	March 23, 1994	1994:30	(XV)
Diethanolamine	September 4, 1991	1992:47	(XIII)
Diethylamine	August 25, 1982	1983:36	(IV)
2-Diethylaminoethanol	January 25, 1995	1995:19	(XVI)
Diethylene glycol	September 16,1992	1993:37	(XIV)
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)
Diisopropylamine	February 7, 1990	1991:8	(XI)
N,N-Dimethylacetamide	March 23, 1994	1994:30	(XV)
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)
Dimethylhydrazine	January 27, 1993	1993:37	(XIV)
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	April 8, 1981	1982:9	(II)
Dipropylene glycol	May 26, 1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12, 1990	1992:6	(XII)
Disulfiram	October 31, 1989	1991:8	(XI)
Enzymes, industrial	June 5, 1996	1996:25	(XVII)
Ethanol	May 30, 1990	1991:8	(XI)
Ethanolamine	September 4, 1991	1992:47	(XIII)

Ethylacetate	March 28, 1990	1991:8	(XI)
Ethylamine	August 25, 1982	1983:36	(IV)
Ethylamylketone	September 5, 1990	1992:6	(XII)
Ethylbenzene	December 16, 1986	1987:39	(VIII)
Ethylchloride	December 11, 1991	1992:47	(XIII)
Ethylene chloride	February 29, 1980	1981:21	(I)
Ethylene diamine	August 25, 1982	1983:36	(IV)
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Ethyleneglycol monoisopropylether	November 16, 1994	1995:19	(XVI)
Ethyleneglycol monopropylether + acetate	September 15, 1993	1994:30	(XV)
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Furfuryl alcohol	February 13, 1985	1985:32	(VI)
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Glycol ethers	October 6, 1982	1983:36	(IV)
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3-Heptanone	September 5, 1990	1992:6	(XII)
Hexachloroethane	September 15, 1993	1994:30	(XV)
Hexamethylenediisocyanate	April 8, 1981	1982:9	(II)
Hexamethylenetetramine	August 25, 1982	1983:36	(IV)
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)
Hydrogen fluoride	April 25, 1984	1984:44	(V)
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)
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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)
Lead, inorganic	February 29, 1980	1981:21	(I)
revised	September 5, 1990	1992:6	(XII)
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)
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Methacrylates	September 12, 1984	1985:32	(VI)
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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)
Methylene chloride	February 29, 1980	1981:21	(I)
4,4'-Methylene dianiline	June 16, 1987	1987:39	(VIII)
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Methyl ethyl ketone peroxide	February 13, 1985	1985:32	(VI)
Methyl formare	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)
Methyl mercaptane	September 9, 1986	1987:39	(VIII)
Methyl methacrylate	March 17, 1993	1993:37	(XIV)
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Methyl-t-butyl ether	November 26, 1987	1988:32	(IX)
Mixed solvents, neurotoxicity	April 25, 1985	1985:32	(VI)
Molybdenum	October 27, 1982	1983:36	(IV)
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)
Natural crystallinic fibers (except asbestos)	June 12, 1991	1992:6	(XII)
Nickel	April 21, 1982	1982:24	(III)
Nitroethane	April 4, 1989	1989:32	(X)
Nitrogen oxides	December 11, 1985	1986:35	(VII)
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Nitrotoluene	February 20, 1991	1992:6	(XII)
Nitrous oxide	December 9, 1981	1982:24	(III)
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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)
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Selenium	December 11, 1985	1986:35	(VII)
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Silica	March 13, 1996	1996:25	(XVII)
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Strontium	January 26, 1994	1994:30	(XV)
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Synthetic organic and inorganic fibers	May 30, 1990	1991:8	(XI)
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Terpenes, mono-	February 17, 1987	1987:39	(VIII)
Tetrabromoethane	May 30, 1990	1991:8	(XI)
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	!989:32	(X)
Thioglycolic acid	June 1, 1994	1994:30	(XV)
Thiourea	December 1, 1987	1988:32	(IX)
Thiram	October 31, 1989	1991:8	(XI)
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Titanium dioxide	February 21, 1989	1989:32	(X)
Toluene	February 29, 1980	1981:21	(I)
Toluene-2,4-diisocyanate	April 8, 1981	1982:9	(II)
Toluene-2,6-diisocyanate	April 8, 1981	1982:9	(II)
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)

Triethylamine	December 5, 1984	1985:32	(VI)
Trimellitic anhydride	September 12, 1989	1991:8	(XI)
Trimethylolpropane	November 16, 1994	1995:19	(XVI)
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Vanadium	March 15, 1983	1983:36	(IV)
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Wood dust	June 17, 1981	1982:9	(II)
Xylene	February 29, 1980	1981:21	(I)
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Zinc dimethyl dithiocarbamate	September 12, 1989	1991:8	(XI)
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Sent for publication October 29, 1997

Instructions to authors

Content
Most articles published in Arbete och Hälsa are original scientific work, but literature surveys are sometimes published as well. The usual language is Swedish. Doctoral theses, however, are usually written in English.

Manuscript
The manuscript must be submitted in six copies. Detailed instructions can be obtained from the Institute's Department of Information. The manuscript is printed by photo offset in the same form in which it is received. It is introduced by a title page containing the title (in capital letters) in the center. Below the title are the names of the authors. In the upper left-hand corner is Arbete och Hälsa, followed by the year and the issue number (e.g. 1994:22) This number is assigned after the manuscript has been approved for publication, and can be obtained from Eric Elgemyr in the Department of Information (telephone: (+46)8/617 03 46).

A brief foreword may be presented on page 3, explaining how and why the work was done. The foreword should also contain the acknowledgements of persons who participated in the work but who are not mentioned as authors. The foreword is signed by the project leader or the division manager. Page 4 should contain the table of contents, unless the manuscript is extremely short.

Summary
Summaries in Swedish and English are placed after the text, preceding the reference list. A summary should be no more than 100 words long. It should begin with complete reference information (see below for format). The texts should be followed by no more than 10 key words, in both Swedish and English.

References
The references are placed after the summaries. They are arranged alphabetically and numbered consecutively. They are referred to in the text by a number in parentheses. Unpublished information is not taken up in the reference list, only in the text: Petterson (unpublished, 1975).
When a work by more than two authors is referred to in the text, only the first name is given: Petterson et al. All the authors are given in the reference list. In other respects, the references should follow the Vancouver system.
Abbreviations for periodicals are those given in the Index Medicus.
For articles that are not written in English, German, French or one of the Nordic languages, the English translation of the title is usually given, with a note on the original language.

Examples:
a. Articel
1. Axelssson NO, Sundell L. Mining, lung cancer and smoking. *Scand J Work Environ Health* 1978;4:42–52.
2. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health* 1990;16, Suppl. 1: 55-58.
3. Bergkvist M, Hedberg G, Rahm M. Utvärdering av test för bedömning av styrka, rörlighet och koordination. *Arbete och Hälsa* 1992;5.
b. Chapter in book
1. Birmingham DJ. Occupational dermatoses. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology Vol.1*. 3rd ed. New York: John Wiley, 1978: 203–235.
c. Book
1. Griffin MJ. *Handbook of human vibration*. London: Academic, 1990.
2. Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's toxicology*. 3rd ed. New York: Macmillan, 1986.
d. Report
1. Landström U, Törnros J, Nilsson L, Morén B, Söderberg L. *Samband mellan vakenhetsmått och prestationsmått erhållna vid körsimulatorstudie avseende effekter av buller och temperatur*. Arbetsmiljöinstitutet, 1988 (Undersökningsrappport 1988:27).
e. Articles written in langueges other than English, French, German or one of the Nordic languages
1. Pramatarov A, Balev L. Menstrual anomalies and the influence of motor vehicle vibrations on the conductors from the city transport. *Akushersto Ginekol* 1969;8:31-37 (in Russian, English abstract).
f. Article in conference proceedings
1. Mathiassen SE, Winkel J, Parenmark G, Malmkvist AK. Effects of rest pauses and work pace on shoulder-neck fatigue in assembly work. *Work and Health Conference*. Copenhagen 22–25 February 1993: 62–63 (Abstract).
2. van Dijk F, Souman A, deVries F. Industrial noise, annoyance and blood pressure. In: Rossi G, ed. *Proceedings of the Fourth International Congress on Noise as a Public Health Problem*. Milano: Centro Ricerche e Studi Amplifon, 1983: 615-627.

Figures and tables
Figures are placed in the text and numbered in order of appearance. The figure text is below the figure. The tables are placed in the text and numbered in order of appearance. The table text is placed above the table. Tables are normally placed at the top or bottom of a page, or immediately above a subhead.

1996

30 V Skaug. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 121. Refractory Ceramic Fibres.

1997

1 A Kjellberg, K Holmberg, U Landström, M Tesarz och T Bech-Kristensen. Lågfrekvent buller: En prövning av sambandet mellan några tekniska utvärderingsmått och upplevd störning.

2 K Kemmlert. On the Identification and Prevention of Ergonomic Risk Factors, with Special Regard to Reported Occupational Injuries of the Musculo-skeletal System.

3 F Chen. Thermal Responses of the Hand to Convective and Contact Cold – with and without Gloves.

4 L Gonäs and A Spånt. Trends and Prospects for Women's Employment in the 1990s. Submitted to the European Commission Network of Experts on the Situation of Women in the Labour Market.

5 L Barregård, L Ehrenström, K Marcus och L-E Sandén. I. Vibrationsskador hos bilmekaniker. **B Meding, L Barregård och K Marcus.** II. Handeksem hos bilmekaniker.

6 J-O Levin (red). Principer och metoder för provtagning och analys av ämnen på listan över hygieniska gränsvärden.

7 A Kjellberg, P Muhr och B Sköldström. Trötthet efter arbete i buller – en registerstudie och tre fältstudier.

8 L Laflamme och E Menckel. Elevskador i ett arbetsmiljöperspektiv. Vad kan vi lära av kommunbaserade skolstudier?

9 L Karlqvist. Assessment of physical work load at visual display unit workstations. Ergonomic applications and gender aspects.

10 M Döös. Den kvalificerande erfarenheten. Lärande vid störningar i automatiserad produktion.

11 H Stouten. DECOS and SCG Basis for an Occupational Standard. Isopropyl acetate.

12 R-M Högström, M Tesarz, T Lindh, F Gamberale och A Kjellberg. Buller – exponering och hälsoeffekter inom kraftindustrin.

13 G Lidén, L Kenny, D Mark och C Chalmers. Provtagningseffektivitet för den svenska metoden för mätning av totaldamm.

14 B Lindell. DECOS and NEG Basis for an Occupational Standard. Platinum.

15 A Iregren, B Sjögren, M Andersson, W Frech, M Hagman, L Johansson och A Wennberg. Exponering för aluminium i smältverk. Effekter på nervsystemet.

16 L Punnett and U Bergqvist. National Institute for Working Life – Ergonomic Expert Committee Document No 1. Visual Display Unit Work and Upper Extremity Musculoskeletal Disorders. A Review of Epidemiological Findings.

17 M Sundström. Arbetsskadeförsäkringen – bedömningen i domstol av belastningsskador hos kontorister och sjuksköterskor.

18 E Åhsberg. Upplevd trötthet efter mentalt arbete – en fältstudie.

19 U Bergqvist and E Vogel (eds), L Aringer, J Cunningham, F Gobba, N Leitgeb, L Miro, G Neubauer, I Ruppe, P Vecchia and C Wadman. Possible health implications of subjective symptoms and electromagnetic fields. A report prepared by a European group of experts for the European Commission, DG V.

20 B Beije and P Lundberg. DECOS and NEG Basis for an Occupational Standard. Glutaraldehyde.

21 G Aronsson och L Svensson. Nedvarvning, återhämtning och hälsa bland lärare i grund- och gymnasieskolan.

23 Z Wang. Acute Cytokine Responses to Inhaled Swine Confinement Building Dust.

24 Kriteriegruppen för hygieniska gränsvärden. Ed. P Lundberg. Vetenskapligt Underlag för Hygieniska Gränsvärden 18.

25 Criteria Group for Occupational Standards. Ed. P Lundberg. Scientific Basis for Swedish Occupational Standards XVIII.