NR 2003:16

Scientific Basis for Swedish Occupational Standards XXIV

Ed. Johan Montelius
Criteria Group for Occupational Standards
National Institute for Working Life
S-113 91 Stockholm, Sweden

Translation:
Frances Van Sant

ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE
ISBN 91-7045-697-6 ISSN 0346-7821

Arbetslivsinstitutet
National Institute for Working Life

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by the National Institute for Working Life. The series presents research by the Institute's own researchers as well as by others, both within and outside of Sweden. The series publishes scientific original works, dissertations, criteria documents and literature surveys.

Arbete och Hälsa has a broad target-group and welcomes articles in different areas. The language is most often English, but also Swedish manuscripts are welcome.

Summaries in Swedish and English as well as the complete original text are available at www.arbetslivsinstitutet.se/ as from 1997.

ARBETE OCH HÄLSA
Editor-in-chief: Staffan Marklund
Co-editors: Marita Christmansson, Birgitta Meding, Bo Melin and Ewa Wigaeus Tornqvist

National Institute for Working Life
S-113 91 Stockholm
Sweden

ISBN 91–7045–697–6
ISSN 0346–7821
http://www.arbetslivsinstitutet.se/
Printed at Elanders Gotab, Stockholm

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 Swedish Work Environment Authority (SWEA). In most cases a scientific basis is written on request from the SWEA. 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 databases 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 secretariat or by a scientist appointed by the secretariat. The author of the draft is indicated under Contents. 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 the SWEA.

This is the 24th volume that is published and it contains consensus reports approved by the Criteria Group during the period July 2002 to June 2003. These and previously published consensus reports are listed in the Appendix (p 67).

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of June, 2003)

Maria Albin		Dept Environ Occup Medicine, University Hospital, Lund
Olav Axelson		Dept Environ Occup Medicine, University Hospital, Linköping
Anders Boman		Dept Environ Occup Dermatology, Norrbacka, Stockholm
Christer Edling		Dept Environ Occup Medicine, University Hospital, Uppsala
Sten Flodström		National Chemicals Inspectorate
Lars Erik Folkesson		Swedish Metal Workers' Union
Sten Gellerstedt		Swedish Trade Union Confederation
Johan Högberg	chairman	Inst Environmental Medicine, Karolinska Institutet and Natl Inst for Working Life
Anders Iregren		Dept for Work and Health, Natl Inst for Working Life
Gunnar Johanson	v. chairman	Inst Environmental Medicine, Karolinska Institutet and Natl Inst for Working Life
Bengt Järvholm		Occupational Medicine, University Hospital, Umeå
Kjell Larsson		Inst Environmental Medicine, Karolinska Institutet
Carola Lidén		Dept Environ Occup Dermatology, Norrbacka, Stockholm
Johan Montelius	secretary	Dept for Work and Health, Natl Inst for Working Life
Göran Pettersson		Swedish Industrial Workers Union
Bengt Sjögren		Inst Environmental Medicine, Karolinska Institutet
Kerstin Wahlberg	observer	Swedish Work Environment Authority
Olof Vesterberg		Natl Inst for Working Life

Contents

[1] Drafted by Birgitta Lindell, Department for Work and Health, National Institute for Working Life, Sweden.

[2] Drafted by Bengt Järvholm, Occupational Medicine, Dept. of Public Health and Clinical Medicine. Umeå University, Sweden;
Anders Blomberg, Respiratory Medicine and Allergy, Dept. of Public Health and Clinical Medicine. Umeå University, Sweden;
Thomas Sandström, Respiratory Medicine and Allergy, Dept. of Public Health and Clinical Medicine. Umeå University, Sweden;
Anna-Lena Sunesson, Dept. of Work and the Physical Environment, National Inst. for Working Life, Sweden.

[3] Drafted by Lars Järup, The Small Area Health Statistics Unit (SAHSU), Department of Epidemiology and Public Health, Imperial College, London, England.

[4] Drafted by Ulla Stenius, Institute of Environmental Medicine, Karolinska Institutet, Sweden.

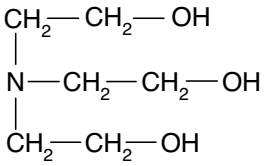
[5] Drafted by Birgitta Lindell, Department for Work and Health, National Institute for Working Life, Sweden.

Consensus Report for Triethanolamine

October 23, 2002

This document is an update of the Consensus Report published in 1983 (46).

Chemical and physical data. Uses

CAS No.:	102-71-6
Synonyms:	2,2´,2´´-nitrilotriethanol nitrilo-2,2´,2´´-(2-hydroxyethyl)amine tris (2-hydroxyethyl) amine 2,2´,2´´-trihydroxytriethylamine triethylolamine TEA
Formula:	$C_6H_{15}NO_3$
Structure:	
Molecular weight:	149.19
Boiling point:	335.4 °C
Melting point:	20.5 °C
Density:	1.12 g/cm^3 (20 °C)
Vapor pressure:	<0.001 kPa (20 °C)
Saturation concentration:	<10 ppm
Conversion factors:	1 ppm = 6.19 mg/m^3 (20 °C) 1 mg/m^3 = 0.162 ppm (20 °C)

Triethanolamine (TEA) at room temperature occurs either as hygroscopic crystals or as a viscous, clear to yellowish, hygroscopic liquid with a weak odor of ammonia (19, 25, 28). It is a moderately strong base and mixes with water, methanol and acetone (19, 21). TEA may contain diethanol amine and monoethanol amine as impurities (6). In the presence of nitrite or nitrous oxides TEA can form N-nitroso diethanolamine (19). Endogenous nitrosation of TEA is presumed to be of negligible extent, however (25).

TEA is an ingredient in printing inks (product register, Swedish National Chemicals Inspectorate). It is also used as a corrosion inhibitor in cutting fluids, as a detergent, as an absorbent for acidic gases, as an additive in concrete/cement,

in the textile industry, and as an intermediate in the production of anionic surfactants. TEA is also an ingredient in various cosmetics and medicines (19, 27, 29).

Uptake, biotransformation, excretion

Absorption of TEA by the skin and digestive tract is both rapid and high. A Japanese study (Kohri *et al*. 1982, cited in References 19 and 25) reports that 53 – 63% of an oral dose given to rats disappeared from the digestive tract within about 30 to 60 minutes. In experiments in which ^{14}C-labeled TEA, either undiluted or blended in acetone or water, was applied to the skin of mice and rats (1000 - 2000 mg/kg b.w., 1.8 - 2 cm^2) either with or without occlusion, uptake was over 70% within a period of 24 to 48 hours (most of it within 24 hours). Uptake was calculated from excretion data and the amount of radioactivity remaining in internal organs. The highest radioactivity level in blood was noted 2 to 3 hours after the treatment (mice, 2000 mg/kg b.w., unoccluded). For undiluted TEA (occlusion, 48 hours), the calculated absorption rates were 500 mg/cm^2/hour for mice and 2000 mg/cm^2/hour for rats. Uptake was calculated by subtracting the amount of radioactivity remaining at the site of application (44). It is clear that skin absorption of TEA can result in significant systemic exposure.

Mice were given intravenous injections (1 mg/kg b.w.) or dermal applications (2000 mg/kg b.w., unoccluded) of ^{14}C-labeled TEA, and it could be shown that TEA was eliminated from blood in two phases (i.v. 24 h: $t_{1/2a}$ = 0.3 h, $t_{1/2b}$ = 10 h; dermal 48h: $t_{1/2a}$ = 1.9 h, $t_{1/2b\_}$ = 31 h) (44). In the same study it was found that TEA is excreted primarily in urine in unmetabolized form (no metabolites were found in analysis of mouse urine). Mice and rats given either intravenous injections (1 mg/kg b.w.) or dermal applications (1000-2000 mg/kg b.w.) of TEA excreted 50 - 70% of the dose in urine (most of it during the first 24 hours) and about 10 - 30% in feces (44). A Japanese study (Kohri *et al*. 1982, cited in References 19 and 25) reports that rats given a single oral dose of TEA (2 - 3 mg/kg b.w.) excreted 53% unchanged in urine and 20% in feces within 24 hours.

Toxic effects

Human data

In an irritation test, pure TEA or a 1:1 solution of TEA in water was applied to human skin under occlusion for 24 hours. The treatment resulted in little or no erythema, and it was concluded that TEA was not irritating to skin (36). It should be pointed out, however, that TEA tested with other vehicles or other exposure times may cause skin irritation (see below).

Several cases of contact allergy to TEA have been reported in people exposed to TEA in cutting fluids, cosmetics or medicines. In most of the earlier studies, however, subjects were tested with concentration that are irritating to skin, and in the light of present knowledge those test results are open to question. The test

concentration now recommended is 2 to 2.5% in vaseline, although 2.5% in vaseline is known to be slightly irritating (41). Evaluating the results of studies (1, 3, 4, 5, 8, 10, 12, 13, 16, 18, 32, 34, 35, 38, 40, 45) in which higher test concentrations and/or other vehicles were used is therefore difficult. Considering the large number of people exposed to TEA in shampoos, cosmetics and other skin preparations, contact allergy to TEA is fairly unusual (22).

There are some acceptably designed studies of contact allergy due to occupational exposure (Table 1). In a large German study of eczema patients who were metalworkers, it is reported that of 295 subjects patch-tested with 2.5% TEA in vaseline, one had a positive reaction (48). There are also a few case reports describing cases of contact allergy to TEA among metalworkers, which were diagnosed with acceptable tests (6, 37). There is also a study reporting that the incidence of contact eczema on the hands and lower arms of workers increased after a synthetic coolant containing TEA was introduced into the production process. Patch tests with TEA (2.5% in vaseline) were given to 52 subjects with contact eczema, and 3 had positive reactions (2).

Positive reactions to acceptable patch tests of TEA have also been reported in contexts other than occupational exposure (Table 1). Data on 475 cases of contact allergy to ingredients in cosmetics were reviewed in a large European retrospective study: 3 patients had a positive reaction to TEA (concentration and vehicle not reported) (20). In a large German study, 14 of 2054 eczema patients patch-tested with 2.5% TEA in vaseline had a positive reaction (41). The patients were tested because of suspected allergy to various topical preparations. In another study over 700 patients with suspected cosmetic or medicine-related contact dermatitis (topical substances) were patch-tested with 2.5% TEA in vaseline, and 20 had a positive reaction (47). There are also a few case reports of contact allergy to TEA diagnosed by patch tests with acceptable concentrations of TEA in vaseline (see Table 1).

In summary, it can be concluded from these studies that, considering its widespread use, TEA rarely causes contact allergy.

There is a study (39) describing occupational asthma in two metalworkers whose exposures included a cutting fluid containing TEA. One of them reported coughing and shortness of breath during the workday, growing more severe toward the end of the workweek. This patient was using a cutting fluid containing 85% TEA, and had been exposed to several substances including oil mist for over 10 years before the symptoms appeared. His spirometry values were normal, but there was bronchial hyperreactivity. A provocation test with heated cutting fluid containing TEA elicited a prompt reaction (within 1 hour), with a maximum drop of 21% in PEF and a 13% reduction of FEV_1. Tests with the same cutting fluid, used cold, yielded an immediate drop of 18% in PEF. The other patient, whose exposures included mists of turning and cooling fluids, reported coughing, shortness of breath, chest tightness, rhinitis and eye irritation in connection with work, and later on also coughing at night and noisy breathing. His spirometry

Table 1. Reactions to TEA in patch tests given to eczema patients seen at dermatology clinics.

Concentration	Vehicle	No. Positive/ No. Tested	Occupation/ Exposure	Ref.
2.5%	Vaseline	3/52	Metalworkers	2
2% & 5%	Vaseline	1/2, 2/2	Cosmetics	26
2.5%	Vaseline	20/737	Cosmetics/medicine	47
2.5%	Vaseline	1/295	Metalworkers	48
2.5%	Vaseline	14/2054	Ointment base	41
0.5% & 5%	Vaseline	1/1	Metalworker	37
2.5%	Vaseline	1/1	Cosmetics/medicine	22
1.25% & 2.5%	Vaseline	1/1	Grinder	6
Not given	Not given	3/475	Cosmetics	20
1% & 5%	Vaseline	1/1	Sunscreen	11

values were normal and he had no bronchial hyperreactivity. Provocation tests with heated turning fluid containing 14% TEA caused an immediate drop of 17% in PEF accompanied by wheezing, and provocation with cold "pure" TEA caused an immediate drop of 21% in PEF. Two asthmatic control patients, one with mild and one with moderate hyperreactivity, were exposed to heated TEA and to a TEA aerosol without developing respiratory symptoms, and their PEF was unaffected. According to the data in this study, there are two reported cases of TEA-related asthma.

There is a report of an 8-year-old girl who sneezed uncontrollably upon exposure to clothing and towels washed in a detergent containing 5% TEA. The sneezing fits gradually disappeared after use of the detergent was stopped, but resumed when the detergent was again used. Sneezing was also triggered by TEA powder/solutions. A prick test was positive for TEA (10^{-7} – 10^{-4} M) but not for any other ingredient in the detergent. A positive result was also obtained with the Passive Cutaneous Anaphylaxis (PCA) test, and TEA-specific IgE was identified in the serum of the patient. TEA induced dose-dependent histamine liberation from the patient's white blood cells. PCA tests given to controls were negative for both specific IgE and histamine liberation (23).

Animal data

TEA given orally has low acute toxicity. The reported LD_{50} for experimental animals is in the range 5.2 - 11.3 g/kg b.w. The reported LD_{50} for skin application (rabbits, 24 hours, occlusion) is >20 g/kg b.w. (29).

Oral administration of 60 or 120 doses of 200, 400, 800 or 1600 mg TEA/kg b.w. to guinea pigs (5 days/week by pipette) or rats (7 days/week in feed) resulted in small, partially reversible histopathological changes in liver and kidneys (Table 2). The highest dose resulted in inflammation of renal tubuli but had no effect on glomeruli. These changes were partially reversible. The animals given the lower doses usually had smaller changes in their kidneys. Some fatty changes of the

liver were observed in the guinea pigs at the two highest dose levels, but histological examination 2 to 3 months after the final dose revealed no changes in their livers. The lowest dose level had only slight effects on the kidneys ("slight swelling with increased secretion"). According to the authors, in no case were the observed kidney and liver changes severe enough to have any effect on function (28). Dose-dependent growth inhibition and increased kidney weights were reported in a cancer study (Table 2) in which rats were given 0, 1, or 2% TEA in drinking water for 2 years (because of high mortality, the dose for females in both dose groups was halved as of week 69). Histological examinations revealed chronic nephropathy and other changes in kidneys, especially in the females. There was no observed increase in the incidence of liver damage or pre-neoplastic changes in the livers in any treated group, but there was a dose-dependent increase in the occurrence of neoplastic nodules in the livers of the males (33). A sketchily described study reports that deaths and histopathological changes in liver, kidneys, spleen or testes were seen in rats given 730 mg TEA/kg b.w./day in feed for 90 days (Table 2). Changes in liver or kidney weights were observed at a dose level of 170 mg/kg b.w./day, but 80 mg/kg b.w./day was reported to have no effect (42).

In a study in which 8 g TEA/kg b.w. was applied to the skin of guinea pigs 5 days/week (occlusion) the animals died after 2 to 17 applications. Changes in liver, kidneys, lungs and adrenals were observed (28). When TEA was painted onto the skin of mice (10, 33 or 100%, acetone vehicle; equivalent to about 150, 500 or 2150 mg/kg b.w.) 3 days/week for 13 weeks, males in the high-dose group had lower lymphocyte counts and lower levels of alkaline phosphatases in serum ($p<0.05$), but no other indications of systemic toxicity were noted in histopathological, hematological or clinical-chemical examination. The authors consider these changes to be of uncertain biological relevance (14). In an unpublished cancer study (NTP 1994, cited in Reference 29; NTP 1999, cited in Reference 25) in which TEA in acetone was applied to the skin of rats 5 days/week for 2 years (males: 32 – 125 mg/kg b.w./day, females: 63 - 250 mg/kg b.w./day), observed effects included elevated kidney weights and, toward the end of the exposure period, lower body weights in females in the high-dose group. In a parallel cancer study with mice (NTP 1994, cited in Reference 29; NTP 1999, cited in Reference 25), skin applications of TEA in acetone (males: 200 – 2000 mg/kg b.w; females:100 – 1000 mg/kg b.w.) 5 days/week for 2 years resulted in elevated kidney weights in males at dose levels of 630 mg/kg b.w/day and higher.

In an unpublished study (cited in References 25 and 29) in which rats and mice were exposed by inhalation to 125 - 2000 mg/m^3 TEA in aerosol form 6 hours/day, 5 days/week for a 16-day period, reported effects include reduced body weights at the highest exposure level, and in rats elevated kidney weights at exposures of 500 mg/m^3 and higher. There were no observed histopathological changes in kidneys. Effects on the mice included changes in some hematological parameters (dose levels not given), and females exposed to 1000 mg/m^3 or more had lower thymus and heart weights.

Various degrees of irritation have been reported after skin application of TEA. TEA was reported to be non-irritating or mildly irritating in different skin irritation tests with rabbits (15, 49). Guinea pigs developed skin inflammation after 2 to 17 skin applications of 8 g undiluted TEA/kg b.w./day (5 days/week, occlusion) (28). Mice given repeated skin applications for up to 20 weeks, however, showed no serious indications of chronic irritation (14, 43). In an unpublished long-term study, TEA in acetone was painted on the skin of mice and rats (concentrations not given). For the mice (high-dose group), the treatment resulted in acanthosis and chronic skin inflammation, but not necrosis; and for the rats, inflammation and sores at the site of application (NTP 1994, cited in Reference 29; NTP 1999, cited in Reference 25).

TEA has also been tested on animals for allergenic effect on skin. It caused no sensitization in the Guinea Pig Maximization Test (0/20 animals) and was classified as a weak allergen (Grade 1) (7).

Several studies have reported that TEA is slightly irritating to the eyes of rabbits (15, 21, 49). An older study, however, reports that undiluted TEA caused relatively severe damage to the eyes of rabbits (Grade 5 on a scale of 1 to 10) 18 to 24 hours after application (9).

Mutagenicity

TEA has been tested for mutagenicity/genotoxicity in several short-term tests both with and without metabolic activation (25). TEA alone yielded negative results in tests with various strains of bacteria and yeast (*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538; *E. coli* WP2, WP2*try*$^-$, WP2*uvr*A; *B. subtilis* TKJ5211*uvr*A$^-$, H17 *rec*$^+$/M45*rec*$^-$; *S. cerevisiae* JD1). TEA mixed with sodium nitrite yielded mutagenic effects in test systems with various strains of *B. subtilis* without metabolic activation, but negative results when metabolizing systems were added. TEA without metabolic activation was also negative in *in vitro* test systems measuring DNA repair (rat liver cells), sister chromatid exchanges (CHO cells), chromosome aberrations (rat liver cells, CHO cells, CHL cells) and cell transformation (hamster embryo cells). TEA induced no sister chromatid exchanges or chromosome aberrations in CHO cells when metabolizing systems were added. There are also a few *in vivo* tests of TEA. Gene mutations were not induced by up to 30,000 ppm (equivalent to 30,000 mg/kg) TEA given to *Drosophila* either orally or by injection (sex-linked recessive lethal test). Chromosome damage, expressed as an elevated frequency of micronuclei in red blood cells, was not observed in mice after skin application of TEA for 13 weeks (25).

Carcinogenicity

According to the IARC, it is not possible to determine whether TEA is carcinogenic to either man or experimental animals (25). In its summary assessment TEA

is placed in Group 3: "not classifiable as to its carcinogenicity to humans." This conclusion is based on the following studies:

In a cancer study, mice were given feed pellets containing 0, 0.03% or 0.3% TEA for their entire lives. There was a significant ($p<0.05$) increase of lymphomas in females (control 1/36; low-dose group 7/37; high-dose group 9/36), but no observed increase in males (24). The report contains no information on lymphoma incidence in historic controls, but Knaak *et al*. (29) state that the lymphoma incidence in controls in this study is extremely low. It is also unclear whether breakdown products were formed when the TEA was heated for pellet production. In another mouse study, drinking water containing 0, 1% or 2% (maximum tolerable dose) TEA was given to animals of both sexes for 82 weeks, and the animals were killed immediately thereafter. No increase in tumor incidence is reported (30). A study in which rats were given TEA in drinking water for 2 years also reports no significant increase in tumor incidence (33). In this study, 0, 1%, or 2% TEA (≈ 525 or 1100 mg/kg b.w./day) was given to males for 2 years; these concentrations were halved for females from week 69 onward because of a dose-dependent increase in mortality (≈ 910 or 1970 mg/kg b.w./day initially; ≈ 455 or 985 mg/kg b.w./day after reduction). A positive trend ($p<0.05$) was seen for neoplastic nodules/carcinomas in the livers of males and for sarcomas in the mucous membranes of the uterus and adenomas in the kidneys of females, when the statistics were adjusted for age. The incidence in the control group, however, was lower than that in historic controls, and the authors concluded that TEA was not carcinogenic (29, 33).

In a cancer study in which TEA in acetone was applied to the skin of mice (males: 0, 200, 630, 2000 mg/kg b.w.; females: 0, 100, 300, 1000 mg/kg b.w.) 5 days/week for 103 weeks, tumors were seen in the livers of both sexes. No conclusions can be drawn from this observation, however, since the animals had been infected with *Helicobacter hepaticus*, a bacterium associated with hepatitis and in some cases also with higher incidences of liver tumors (17; NTP 1999, cited in Reference 25; NTP 1994, cited in Reference 29). TEA in acetone applied to the skin of rats (males: 0, 32, 63 or 125 mg/kg b.w.; females: 0, 63, 125, 250 mg/kg b.w.) 5 days/week for 103 weeks caused no significant increase in tumor incidence. Males treated with TEA had more severe renal hyperplasias (and adenomas) than controls, however (NTP 1999, cited in Reference 25; NTP 1994, cited in Reference 29). In a study with transgenic mice (Tg.AC), no increase of skin tumors was seen in animals given dermal applications of TEA in acetone (3, 10 or 30 mg per animal per application, ≈120, 400 or 1200 mg/kg b.w.) 5 days/week for 20 weeks. The animals were killed 6 weeks after the final treatment (43).

No cancer studies of persons exposed only to TEA were found in the literature. However, there are several epidemiological studies of workers exposed to metal-working fluids containing ethanol amines either with or without sodium nitrite. A slight increase of cancers, especially in stomach, esophagus and larynx, has been discovered in these studies, but since exposures were always mixed it is hardly

possible to draw from the presented data any conclusions about the carcinogenicity of TEA (25).

Effects on reproduction

Injection of 1.3 - 10.5 mmol TEA in acetone into chicken eggs had an embryotoxic effect (ED_{50} 2.6 mmol/egg), but no significant teratogenic effect (3/110 anomalies vs. 1/100 in acetone-treated control eggs) (31).

Unpublished studies (cited in References 25 and 29) report no effects on mating, fertility, growth or survival of offspring in rats given daily skin applications of 500 mg TEA (in acetone) /kg b.w., and no effects on reproduction in mice given skin applications of 2 g TEA/kg b.w./day. No significant effects on sperm (motility, morphology, number) or changes in duration of estrus cycle were reported in another unpublished study (NTP 1999, cited in Reference 25) in which rats and mice received skin application of up to 2 (rats) or 4 (mice) g TEA/kg b.w./day for 13 weeks.

Dose-effect / dose-response relationships

There are no data on which to base a dose-effect or dose-response relationship for occupational exposure to TEA. Dose-effect relationships observed in animal experiments are summarized in Table 2. A brief review mentions some unpublished data indicating an effect on kidney weight after inhalation exposure at doses that may possibly be lower than those in Table 2.

Conclusions

In general, there are little or no data on health effects of inhalation exposure to TEA, for either humans or animals. However, two cases of asthma, diagnosed as work-related and caused by TEA, have been reported.

The critical effect in animal studies with repeated oral administration of TEA is effects on the kidneys. A few cases of allergic contact eczema due to skin contact with TEA have been reported, but the allergenic potency of TEA is probably low. Animal studies have shown that skin uptake can be quite high.

Table 2. Dose-effect relationships observed in laboratory animals exposed to TEA.

Exposure	Species	Effects	Ref.
2150 mg/kg b.w./day dermal 3 days/week 13 weeks	Mouse	Mild skin irritation, significant reduction ($p<0.05$) in lymphocyte counts (males), significant reduction ($p<0.05$) of alkaline phosphatases in serum (males)	14
2% in drinking water, 2 years (≈ males 1100 mg/kg b.w./day; females: 1970 and later 985 mg/kg b.w./day)***	Rat	Females: increased mortality, pyelonephritis, hydronephrosis Both sexes: impaired growth, elevated kidney weights, chronic nephropathy, mineralization of renal papillae and "nodular hyperplasia of the pelvic mucosa"	29, 33
800 mg/kg b.w./day per os 60 or 120 days	Rat, Guinea pig	Rat: histopathological changes in kidneys* and liver Guinea pig: histopathological changes in kidneys and liver**	28
730 mg/kg b.w./day per os 90 days	Rat	Deaths; histopathological changes in liver, kidneys, spleen and/or testes	42
1% in drinking water 2 years (≈ males: 525 mg/kg b.w./day; females: 910 and later 455 mg/kg b.w./day)***	Rat	Females: Increased mortality, pyelonephritis, hydronephrosis, chronic nephropathy Both sexes: Poor growth, elevated kidney weights, mineralization of renal papillae	29, 33
400 mg/kg b.w./day per os 60 or 120 days	Rat, Guinea pig	Rat: histopathological changes in kidneys* and liver* Guinea pig: histopathological changes in kidneys*	28
200 mg/kg b.w./day per os 60 or 120 days	Rat, Guinea pig	Histopathological changes in kidneys**	28
170 mg/kg b.w./day per os 90 days	Rat	Changes in liver or kidney weights	42

* observed after 60 days
**observed after 120 days
*** due to high mortality the dose for females in both dose groups was halved from week 69 onward

References

1. Alomar A, Conde-Salazar L, Romaguera C. Occupational dermatoses from cutting oils. *Contact Dermatitis* 1985;12:129-138.
2. Angelini G, Meneghini CL. Dermatitis in engineers due to synthetic coolants. *Contact Dermatitis* 1977;3:219-220.

3. Angelini G, Rantuccio F, Meneghini CL. Contact dermatitis in patients with leg ulcers. *Contact Dermatitis* 1975;1:81-87.
4. Angelini G, Vena GA, Meneghini CL. Allergic contact dermatitis to some medicaments. *Contact Dermatitis* 1985;12:263-269.
5. Batten TL, Wakeel RA, Douglas WS, Evans C, White MI, Moody R, Ormerod AD. Contact dermatitis from the old formula E45 cream. *Contact Dermatitis* 1994;30:159-161.
6. Blum A, Lischka G. Allergic contact dermatitis from mono-, di- and triethanolamine. *Contact Dermatitis* 1997;36:166.
7. Boman A, Wahlberg JE, Fregert S. Sensitizing potential of triethanolamine studied with the guinea pig maximization test method. *Dermatosen* 1993;41:58-59.
8. Calas E, Castelain PY, Piriou A. Epidemiology of contact dermatitis in Marseilles. *Ann Dermatol Venereol* 1978;105:345-347. (in French, English abstract)
9. Carpenter CP, Smyth HF. Chemical burns of the rabbit cornea. *Am J Ophthalmol* 1946;29:1363-1372.
10. Castelain MPY. Eczéma généralisé diffus par sensibilisation à la triéthanolamine. *Bull Soc Fr Dermatol Syphiligr* 1967;74:562. (in French)
11. Chu CY, Sun CC. Allergic contact dermatitis from triethanolamine in a sunscreen. *Contact Dermatitis* 2001;44:41-42.
12. Conde-Salazar L, Guimaraens D, Romero LV, Harto A, Gonzalez M. Occupational dermatitis from glass fiber. *Contact Dermatitis* 1985;13:195-196.
13. Curtis GH, Netherton EW. Cutaneous hypersensitivity to triethanolamine. *Arch Dermatol* 1940;41:729-731.
14. DePass LR, Fowler EH, Leung HW. Subchronic dermal toxicity study of triethanolamine in C3H/HeJ mice. *Food Chem Toxicol* 1995;33:675-680.
15. Dutertre-Catella H, Lich NP, Huyen VN, Truhaut R. Comparative study of skin and eye irritation by ethanolamines (mono, di, tri and poly). *Arch Mal Prof* 1982;43:455-460. (in French, English abstract)
16. Fisher AA, Pascher F, Kanof NB. Allergic contact dermatitis due to ingredients of vehicles. *Arch Derm* 1971;104:286-290.
17. Fox JG, MacGregor JA, Shen Z, Li X, Lewis R, Dangler CA. Comparison of methods of identifying *Helicobacter hepaticus* in B6C3F$_1$ mice used in a carcinogenesis bioassay. *J Clin Microbiol* 1998;36:1382-1387.
18. Fräki JE, Peltonen L, Hopsu-Havu VK. Allergy to various components of topical preparations in stasis dermatitis and leg ulcer. *Contact Dermatitis* 1979;5:97-100.
19. Gillner M, Loeper I. Health effects of selected chemicals. Triethanolamine. *Nord* 1993:29:235-260.
20. Goossens A, Beck MH, Haneke E, McFadden JP, Nolting S, Durupt G, Ries G. Adverse cutaneous reactions to cosmetic allergens. *Contact Dermatitis* 1999;40:112-113.
21. Griffith JF, Nixon GA, Bruce RD, Reer PJ, Bannan EA. Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. *Toxicol Appl Pharmacol* 1980;55:501-513.
22. Hamilton TK, Zug KA. Triethanolamine allergy inadvertently discovered from a fluorescent marking pen. *Am J Contact Derm* 1996;7:164-165.
23. Herman JJ. Intractable sneezing due to IgE-mediated triethanolamine sensitivity. *J Allergy Clin Immunol* 1983;71:339-344.
24. Hoshino H, Tanooka H. Carcinogenicity of triethanolamine in mice and its mutagenicity after reaction with sodium nitrite in bacteria. *Cancer Res* 1978;38:3918-3921.
25. IARC. Some industrial chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon: International Agency for Research on Cancer, 2000;77:381-401.

26. Jones SK, Kennedy CTC. Contact dermatitis from triethanolamine in E45 cream. *Contact Dermatitis* 1988;19:230.

27. Järvholm B. *Criteria Document for Swedish Occupational Standards. Amines*. Arbete och Hälsa 1982;30:1-33. National Board of Occupational Safety and Health, Solna, Sweden. (in Swedish, English abstract)

28. Kindsvatter VH. Acute and chronic toxicity of triethanolamine. *J Ind Hyg Toxicol* 1940;22:206-212.

29. Knaak JB, Leung HW, Stott WT, Busch J, Bilsky J. Toxicology of mono-, di-, and triethanolamine. *Rev Environ Contam Toxicol* 1997;149:1-86.

30. Konishi Y, Denda A, Uchida K, Emi Y, Ura H, Yokose Y, Shiraiwa K, Tsutsumi M. Chronic toxicity carcinogenicity studies of triethanolamine in B6C3F1 mice. *Fundam Appl Toxicol* 1992;18:25-29.

31. Korhonen A, Hemminki K, Vainio H. Embryotoxicity of sixteen industrial amines to the chicken embryo. *J Appl Toxicol* 1983;3:112-117.

32. Lindemayr H, Drobil M. Eczema of the lower leg and contact allergy. *Der Hautarzt* 1985;36:227-231. (in German, English abstract)

33. Maekawa A, Onodera H, Tanigawa H, Furuta K, Kanno J, Matsuoka C, Ogiu T, Hayashi Y. Lack of carcinogenicity of triethanolamine in F344 rats. *J Toxicol Environm Health* 1986;19:345-357.

34. Meneghini CL, Angelini G. Behaviour of contact allergy and new sensitivities on subsequent patch tests. *Contact Dermatitis* 1977;3:138-142.

35. Meneghini CL, Rantuccio F, Lomuto M. Additives, vehicles and active drugs of topical medicaments as causes of delayed-type allergic dermatitis. *Dermatologica* 1971;143:137-147.

36. Müller-Decker K, Heinzelmann T, Fürstenberger G, Kecskes A, Lehmann WD, Marks F. Arachidonic acid metabolism in primary irritant dermatitis produced by patch testing of human skin with surfactants. *Toxicol Appl Pharmacol* 1998;153:59-67.

37. Niklasson B, Björkner B, Sundberg K. Contact allergy to a fatty acid ester component of cutting fluids. *Contact Dermatitis* 1993;28:265-267.

38. Samsoen M, Jelen G. Allergy to Daktarin gel. *Contact Dermatitis* 1977;3:351-352.

39. Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational asthma caused by ethanolamines. *Allergy* 1994;49:877-881.

40. Scheuer B. Contact allergy caused by triethanolamine. *Der Hautarzt* 1983;34:126-129. (in German, English abstract)

41. Schnuch A, Arnold R, Bahmer F, Brasch J, Diepgen TL, Enders F, Frosch PJ, Fuchs T, Geier J, Henseler T, Müller S, Peters KP, Schulze-Dirks A, Stary A, Uter W, Zimmermann J. Epicutaneous patch testing with an emulsifier, additive and vehicle series. Results of the Information Network of Dermatological Clinics (IVDK). *Dermatosen* 1993;41:176-183. (in German, English abstract)

42. Smyth HF, Carpenter CP, Weil CS. Range-finding toxicity data: list IV. *Arch Ind Hyg Occup Med* 1951;4:119-122.

43. Spalding JW, French JE, Stasiewicz S, Furedi-Machacek M, Conner F, Tice RR, Tennant RW. Responses of transgenic mouse lines $p53^{+/-}$ and Tg.AC to agents tested in conventional carcinogenicity bioassays. *Toxicol Sci* 2000;53:213-223.

44. Stott WT, Waechter JM, Rick DL, Mendrala AL. Absorption, distribution, metabolism and excretion of intravenously and dermally administered triethanolamine in mice. *Food Chem Toxicol* 2000;38:1043-1051.

45. Suurmond D. Patch test reactions to phenergan cream, promethazine and triethanolamine. *Dermatologica* 1966;133:503-506.

46. Swedish Criteria Group for Occupational Standards. Some aliphatic amines. *Scientific Basis for Swedish Occupational Standards IV*. Arbete och Hälsa 1983;36:19-34. National Board of Occupational Safety and Health, Solna, Sweden.
47. Tosti A, Guerra L, Morelli R, Bardazzi F. Prevalence and sources of sensitization to emulsifiers: a clinical study. *Contact Dermatitis* 1990;23:68-72.
48. Uter W, Schaller S, Bahmer FA, Brasch J, Diepgen TL, Enders F, Frosch PJ, Fuchs T, Henseler T, Müller S, Peters KP, Przybilla B, Schaller J, Schnuch A, Schulze-Dirks A, Stary A. Contact allergy in metal workers. *Dermatosen* 1993;41:220-227.
49. Weil CS, Scala RA. Study of intra- and interlaboratory variability in the results of rabbit eye and skin irritation tests. *Toxicol Appl Pharmacol* 1971;19:276-360.

Consensus Report for Diesel Exhaust

December 4, 2002

This Report is a review of the risks of occupational exposure to diesel exhaust, with emphasis on those identified in studies with human subjects. Diesel exhaust also occurs in the general environment as a component of a complex mixture of air pollutants of diverse origin (combustion products from heating, particles and gases from remote sources, dust etc.). There are several studies on the health effects of air pollutants in the general environment, but these studies are given cursory attention in this document since diesel exhaust is only a part of general air pollution.

Diesel exhausts are extremely complex mixtures of substances, some of which – especially nitrogen dioxide and elemental carbon – have been used as indicators of exposure to diesel exhaust. In this report we have paid particular attention to the degree of association between indicator substances and effects on health. The Report is based on a survey published in 1993 (4) and on subsequently published literature. In many cases reference is made primarily to critical reviews judged to cover the relevant literature.

Physical and chemical characteristics

Diesel exhaust is produced by the combustion of diesel oil, which yields a complex mixture of compounds in both gas and particle form. The exact composition varies with fuel type, engine model and tuning, driving conditions, load, exhaust cleaning methods etc. The gas phase includes carbon dioxide, carbon monoxide, nitrous oxides, sulfur oxides, aldehydes and hydrocarbons – both volatile hydrocarbons such as methane and ethylene and heavier poly-aromatic hydrocarbons (PAH). The composition of some types of diesel fuel and examples of the variation in composition of the exhausts from these fuels are tabulated in Beije (4).

Both density and volatility affect the relationship between the composition of the diesel fuel and that of the exhaust. The relationship between aromatic and polyaromatic hydrocarbons and sulfur in the fuel and the chemical composition of the exhaust has been explored in a large number of studies. The importance of sulfur in particle formation has led to the introduction of MK1 (= *miljöklass 1,* environmental class 1), a diesel fuel with low sulfur content. Aromatic hydrocarbons in the diesel fuel also make a large contribution to particle formation. Today nearly all diesel fuel used in Sweden is MK1. In 2001, 98% of all diesel fuel sold was MK1, and only 2% was MK3. This can be compared with 1993, when only 20% of all diesel fuel sold was MK1, 57% was MK2 and 23% MK3 (56). Some of the requirements for these fuel classes are listed in Table 1.

Table 1. Swedish standards for environmental classification (MK) of diesel fuel (chemical content) (56).

Component	Measure	MK1	MK2	MK3
Aromatic hydrocarbons (max. volume)	%	5	20	-
PAH (max. volume)	%	Not detectable	0.1	-
PAH (max. mass)	%	-	-	11
Sulfur	mg/kg	10	50	350

The composition of diesel exhaust is closely related to the type of engine. Regulations in many countries stipulate that vehicle manufacturers must have at least one vehicle of each engine and model type emission-tested. The emissions covered by regulations are usually nitrous oxides (NO_X), carbon monoxide (CO), total hydrocarbons (THC) and particles. The tests are made under a number of specified driving conditions known to affect emission levels. Different protocols have been used in different countries and for different types of vehicles, which makes it difficult to compare data from different studies. There is little information on emissions from vehicles that have been in use for several years. Moreover, the vehicles that are tested are not always representative – for example, about a third of the heavy vehicles tested in the USA are mass-transit buses, which in 1998 accounted for only about 5% of the heavy vehicles on the road (63).

Yanowitz *et al*. (63) tracked changes in emissions from diesel vehicles tested during the 1976 – 1998 period. There were clear reductions in particles (PM), carbon monoxide and hydrocarbons, whereas NO_X levels declined very little. The authors also point out that some manufacturers design their engines to produce low emissions under the test conditions, which means that during actual use the vehicle's emissions might be higher than they would have been if the engines had been designed for optimum performance under driving conditions.

Particle emissions can be greatly reduced (at least in terms of total mass) by various exhaust purification systems, most commonly catalytic treatment and various types of particle filters. A general problem with engine tuning, fuel modifications and other measures taken to reduce particles in diesel exhaust is that they often increase the emission of NO_X and vice versa.

Indicators and their measurement

Particles

Particles that can be inhaled are usually < 10 μm in diameter. These particles, often called PM_{10}, can be divided by size into three groups:

1. Ultra-fine particles smaller than 0.1 μm. Formed during combustion (e.g. in diesel engines) and from chemical substances in the gas phase.

2. Particles 0.1 - 2.5 μm. Formed by coagulation of ultra-fine particles and by adsorption of gas-phase material onto existing particles. These particles can remain suspended in the air for a long time.
3. Particles larger than 2.5 μm. Includes airborne dust and dirt. Though relatively few in number, these account for a large amount of the total PM_{10} mass.

Categories 1 and 2 are sometimes referred to together as $PM_{2.5}$.

Ultra-fine particles with diameters of 5 to 50 nm account for 50 - 90% of the total number of particles in diesel exhaust, but only 1 – 20% of the total mass (16). However, small particles often join together to form larger ones, which means that the size distribution in a sample may depend partly on when the sample is taken (in the exhaust pipe or after the exhaust has been in the air for a few minutes). The size distribution of particles in diesel exhaust may thus vary somewhat because of differences in sampling conditions.

A problem that has increasingly come into focus with regard to measuring particle emissions from diesel engines is the difficulty of differentiating diesel particles from other particles.

Many publications in recent years have presented studies of elemental carbon (EC) as a measure of particle emissions from diesel vehicles and thus as an indicator of diesel exhaust. Of other methods used for determination of particles in diesel exhaust the most common are gravimetric, for determination of the mass of sub-micrometer particles and respirable combustible dust (RCD). In mines in the USA, diesel particles have usually been measured as diesel particulate matter (DPM), separated by size during sampling and analyzed with gravimetric methods, while in Canada particles are usually measured as RCD. Both of these methods, however, are vulnerable to interference from particles produced by other forms of combustion, and neither method is sensitive enough to measure personal exposures unless concentrations are high.

Elemental carbon (EC) is determined by collecting diesel exhaust particles on a quartz filter, followed by a two-step analysis in which organic carbon (OC) is first removed and the amount of elemental carbon is then determined (40).

The EC method, unlike other methods used for particles, is said to be specific for diesel exhaust. However, the proportion of elemental carbon in diesel particles can vary, which makes it difficult to directly extrapolate the amount of EC to a measure of the total mass of particles smaller than 1 μm (40). Studies have shown that interference from tobacco smoke is negligible (5, 64), as is interference from spores, pollen and other particles from plants (5). In coal mines there is a risk of interference from the coal being mined, although Birch and Cary (5) maintain that the EC method can be used in this environment also, provided that a suitable impacter is used in sampling. In an inter-laboratory calibration study in which ten laboratories analyzed EC, there was a pooled relative standard deviation of 52.3% (5).

NO_X

NO_X is by tradition the primary indicator for diesel exhaust. Although it is often measured as NO_2, it is emitted primarily as NO. In oxidative environments NO is oxidated to NO_2 , and in environments such as mines and bus garages where emissions remain in the air and mix with substances such as ozone, a large part of the total amount of NO_X is NO_2. In other environments such as tunnels for vehicle traffic, where most of the emissions in the air are of recent origin, much of the NO_X occurs as NO (18).

Some comparative studies of air concentrations of EC, RCD and NO_X (or NO_2) in environments exposed to diesel exhaust have been published. The studies show a correlation between EC and RCD, although the proportions may vary (RCD is 10 to 50 times higher than EC). Correlations between nitrous oxides and EC or RCD have been weak in these studies (61), which means that a measure of EC can not be translated to a measure of NO_X (and vice versa). In some studies, however, several indicator substances have been measured simultaneously.

There has been some interest in profiling the polyaromatic hydrocarbons (PAH) associated with particles in diesel exhaust, since biological experiments have shown effects of these substances (55, 62). In environmental monitoring there is also an interest in using PAH patterns to differentiate emission sources such as biofuel and diesel fuel.

Occurrence and exposure

In 2001, refineries in Sweden produced/sold 3,556,000 m^3 of diesel fuel. This is 19% more than in 1992. Comparable figures from other Nordic countries are 3,015,000 m^3 for Denmark, a 37% increase over 1992; 3,642,000 m^3 for Norway, more than twice as much as in 1992; and 2,159,000 m^3 for Finland, 48% more than in 1993.

Results of monitoring for various diesel exhaust components and/or exposure indicators have been reported for railroad workers, vehicle mechanics, forklift operators, miners, tunnel repairmen and workers on ro-ro freighters and in bus garages, vehicle inspection stations etc. The highest concentrations are reported in mines that use diesel equipment (Table 2).

Interest in particles as indicators of exposure is clearly reflected in the literature giving exposure data for diesel exhausts. Most of the articles published in the past decade report only particle measurements of various types. A few of these studies, published in the past six years, are summarized in Table 2.

Occupational exposure should be regarded in the perspective of exposure of the general public. In the USA, the EPA has estimated the average exposure to diesel particles (measured as DPM) to be 0.6 $\mu g/m^3$ for the entire population: 0.3 $\mu g/m^3$ in the country and 0.8 $\mu g/m^3$ in cities (figures are from 1996) (16). The EPA document also cites several studies in which elemental carbon was measured. Concentrations as high as 40 $\mu g/m^3$ have been measured on automobile freeways

Table 2. Exposure to diesel exhaust at various workplaces.

Workplace/occupation	Country	Monitored component	Concentration (range)	Ref.
Ambulance depot	USA	Respirable dust EC	118 (70-180) μg/m^3 33 (18-42) μg/m^3	19
Ro-ro freighters	USA	Respirable dust EC	198 (32-920) μg/m^3 37 (7-111) μg/m^3	19
Railroad worker	USA	Respirable dust EC	190 (32-902) μg/m^3 17 (7-50) μg/m^3	19
	Canada	EC	7 (2-14) μg/m^3	61
Bus garage	USA	Respirable dust EC	224 (70-980) μg/m^3 31 (7-217) μg/m^3	19
Firefighter	USA	EC	20-79 μg/m^3	5
Firehouse employee	USA	EC	4-52 μg/m^3	5
Airport personnel	USA	EC	7-15 μg/m^3	5
Public transportation worker	USA	EC	15-98 μg/m^3	5
Vehicle inspection	USA	Respirable dust EC	149 (90-220) μg/m^3 11 (7-31) μg/m^3	19
Truck driver	USA	Respirable dust EC	369 (79-1356) μg/m^3 66 (7-403) μg/m^3	19
Tunnel excavator	Norway	Total dust Respirable dust EC NO_2	5.5 (0.2-56) mg/m^3 1.7 (0.03-9.3) mg/m^3 220 (63-580) μg/m^3 1.5 (0.06-5.5) mg/m^3	1
Coal mines, diesel equipment without exhaust treatment	USA	DPM	Mine A 0.85 mg/m^3 Mine B 2.1 mg/m^3 Mine C 1.3 mg/m^3	21
Coal mines, diesel equipment with exhaust treatment	USA	DPM	Mine A 0.2 mg/m^3 Mine B 1.2 mg/m^3 Mine C 0.1 mg/m^3 Mine D 0.1 mg/m^3	21
Coal mines, exhaust treatment not reported	Australia	DPM	0.01-0.64 mg/m^3	44
Other mines, exhaust treatment not reported	USA	DPM	Salt 0.4-0.7 mg/m^3 Lead/zinc 0.3-1.1 mg/m^3 Limestone 0.3 mg/m^3 Potash 0.6-1.6 mg/m^3	21
	USA	DPM EC	Potash 0.1-1.0 mg/m^3 Potash 190 (17-606) μg/m^3	57
	Germany	Respirable dust	Potash 0.038-1.28 mg/m^3	59
Iron mine, diesel equipment with exhaust treatment	Sweden	EC	29 (5-81) μg/m^3	31

in the USA. In a study of EC concentrations in Dutch schools, levels of 1.1 – 6.3 μg/m^3 (n = 23) were measured in schools near highways, whereas in schools over 400 meters from highways the levels were 0.8 – 2.1 μg/m^3 (n = 8) (16). Kinney *et al*. (30) used personal monitors to measure EC levels on the sidewalks in Harlem (USA), and obtained values in the range 1.5 – 6 μg/m^3. Zaebst *et al*. (64) measured elemental carbon in urban environments in the USA. On highways the average was 2.5 μg/m^3 (n = 21) and in residential areas 1.1 μg/m^3 (n = 23).

Uptake, biotransformation, excretion

Diesel exhaust is a complex mixture of gases and particles. For nitrogen dioxide, for example, calculated uptake is 80 to 90 % (33). In an experiment with healthy subjects it was found that 23% of the particles from diesel exhaust were deposited in the lungs, but there is reason to believe that deposition rates vary considerably (4). Liberation of substances bound to the particles in the lungs is probably also subject to large variation, depending on what substances are involved and where the particle is deposited. A major subject of study has been benzo-a-pyrene (BaP). Theoretical calculations indicate that retention of BaP might be lower in the bronchi than in the more peripheral parts of the lungs (4). BaP disappears from the lungs of laboratory animals in a fast phase (<1 hour) and a slow phase (18 days). The metabolism of BaP has been extensively studied (35).

The biotransformation and excretion of BaP from diesel exhaust have been studied in animal experiments. In human studies, non-smoking subjects who work in garages and vehicle repair shops have higher excretion of 1-hydroxy-pyrene in urine and a greater amount of DNA adducts (both total and aromatic) than controls (24, 26, 37).

A problem with these studies is determining the extent to which excretion of 1-hydroxypyrene is also due to skin uptake. Persons exposed to diesel exhaust while working in garages and repair shops can be expected to get motor oil and other substances containing PAH on their hands.

Toxic effects

The toxic effects of diesel exhaust that have received the most attention are its effects on the lungs and respiratory passages, both acute and chronic, and the increased risk of various forms of cancer. Although is not clear just what substances (or substance) in diesel exhaust are responsible for its toxic effects, particles or NO_2 are often used as indicators. Diesel exhaust comprises a not insignificant proportion of air pollutants in urban areas. Studies from several parts of the world, including Sweden, have shown that variations in the airborne particle concentration in urban areas not only affect the health of asthmatics (frequency and severity of symptoms) but also are correlated to variations in mortality (16). Mortality from heart disease has also been shown to increase. Other studies have shown that this type of pollution affects heart rhythm in

patients with severe heart disease. Further, some studies have demonstrated a correlation between air pollutants and indicators of inflammation such as acute-phase proteins and fibrinogen. Since it is known that persons with higher levels of such indicators have an elevated risk of developing heart/circulatory diseases, it has been proposed that some health effects of air pollution are caused via an inflammatory reaction. Studies from the USA have also demonstrated correlations between the average levels of air pollutants in urban areas and mortality and occurrence of cancer (16). In these studies, particles (e.g. PM_{10} or $PM_{2.5}$, defined above under Indicators) or NO_2 are often used as exposure indicators. Since both particles and NO_2 also have sources other than diesel exhaust, it is not possible to determine the degree to which diesel exhaust is implicated in these health effects. Studies that specifically attempt to connect diesel exhaust with effects on health are described below.

Human studies – controlled exposure

Effects of diesel exhaust

The cellular and biochemical effects on respiratory passages of short-term exposure to diesel exhaust have been studied in exposure experiments. These are made possible by accurate exposure and monitoring equipment that can show that the levels of particles and soluble components are the same as those in the exhaust pipe (47).

One study describes symptoms affecting the eyes and nose, as well as increased airway resistance, after 1 hour of exposure to diesel exhaust at a particle concentration of 300 $\mu g/m^3$ (PM_{10}) and an NO_2 concentration of 2.9 mg/m^3 (46).

Several studies have been made using bronchoalveolar lavage (BAL) and analysis of tissue samples from respiratory passages. BAL showed elevated numbers of neutrophilic granulocytes in healthy persons 6 to 24 hours after 1 hour of exposure to diesel exhaust with a particle concentration of 300 $\mu g/m^3$ (PM_{10}) and an NO_2 concentration of 2.9 mg/m^3 (45, 48, 49). Reduced phagocyte activity was also noted in alveolar macrophages (45, 48). Tissue samples taken from mucous membranes in the airways of healthy subjects six hours after exposure to diesel exhaust (300 $\mu g/m^3$, PM_{10}) showed clear inflammatory changes, with elevated levels of adhesion molecules, inflammatory cells and cytokines (49, 50). There were also systemic effects, including higher numbers of neutrophilic granulocytes and thrombocytes in peripheral blood.

In a recent study, both healthy subjects and subjects with mild asthma were exposed to a low concentration of diesel exhaust (PM_{10} 108 $\mu g/m^3$, NO_2 0.36 mg/m^3) for 2 hours. In the healthy subjects the effects were very small – only an increase in the number of neutrophilic granulocytes – and the only significant effect in the asthmatics was an increase in bronchial epithelium of IL-10, a cytokine often associated with bronchial reactivity (25).

A primary indication of asthma is that inhalation of irritants causes the airways to contract. In asthmatics this reaction, called bronchial reactivity, is seen at much

lower doses than in healthy subjects. This is the characteristic symptom of asthma. In a recently published study, increased bronchial reactivity was seen in a group of asthmatics 24 hours after one hour of exposure to diesel exhaust (PM_{10}, 300 $\mu g/m^3$) (41). These asthmatics had moderately severe asthma that required treatment with inhalation steroids (800-1200 μg/day). These observations of increased bronchial reactivity may help to explain epidemiological data indicating that air pollution with higher particulate content results in more severe symptoms in asthmatics.

In another study, subjects with mild allergic asthma were exposed for 30 minutes to exhaust in a highway tunnel. Since the exposure came from traffic, the air also contained other pollutants such as dust from road and tire wear. No attempt was made to identify the origin of the particles. The average concentration of NO_2 was 313 $\mu g/m^3$, PM_{10} was 170 $\mu g/m^3$, and $PM_{2.5}$ was 95 $\mu g/m^3$. Four hours later a provocation test was made with a low dose of an inhaled allergen (birch pollen). After the allergen exposure, the subjects exposed to the tunnel concentrations of NO_2 (300 $\mu g/m^3$ or higher) developed both significantly higher early reaction (measured as increased airway resistance) and late reaction, with lower FEV_1 3 to 10 hours after the allergen inhalation. Moreover, subjects exposed to $PM_{2.5}$ in concentration > 100 $\mu g/m^3$ had slightly greater early reactions than controls (58). This study showed that exposure to environments containing exhaust and dust from road traffic significantly enhances the asthmatic reaction to allergen inhalation.

Effects of NO_2

Several studies have been made in which subjects in an exposure chamber were exposed to NO_2 alone in concentrations ranging from 1.1 to 9 mg/m^3, after which BAL and mucous membrane biopsies were used to quantify inflammation indicators (7, 8, 22, 23, 51, 52, 53, 54). The heaviest exposure was 3.6 mg/m^3 for 4 hours on 4 consecutive days (8). It is interesting to note that these inflammatory changes were much smaller than those caused by diesel exhaust, even when the exposure dose of NO_2 was many times higher. NO_2 is therefore assumed to play a subordinate role in inflammatory reactions to diesel exhaust exposure.

Effects of particles

A number of studies have been made to assess the allergenic potential of the particles in diesel exhaust. When 0.30 mg of diesel exhaust particles were deposited in the noses of healthy subjects, levels of IgE and IgE-secreting cells were higher 1 to 4 days after the treatment. This dose was estimated to be equivalent to 24 hours of inhaling outdoor air in Los Angeles, California (14). Amounts of mRNA, including mRNA coding for cytokines that stimulate IgE production, increased in cells from nasal lavage after 0.15 mg diesel exhaust particles had been deposited in the noses of healthy subjects (12). This can contribute to increased local IgE production. The role of diesel particles as adjuvants to allergens has also been examined. An allergen in combination with

diesel particles significantly increased the expression of mRNA for TH_2 cytokines and inhibited the formation of γ-interferon, and also increased the production of antigen-specific IgE (13).These data indicate that diesel exhaust particles can increase B-cell differentiation and raise IgE production. Diesel exhaust particles have also been found to enhance sensitization on exposure to new allergens. When an antigen from keyhole limpets (a mollusk) was used in sensitization tests together with either diesel exhaust particles or a placebo, the exhaust particles caused a much stronger sensitization and allergic reaction (15). The allergen was placed on the nasal mucosa of healthy, previously unsensitized subjects with or without simultaneous exposure to diesel exhaust particles.

Animal studies

In general, it is difficult to extrapolate these data to human exposures because much higher concentrations of diesel exhaust are used in animal experiments. In long-term studies, rats exposed to a particle concentration of 1000 $\mu g/m^3$ for 6 months had indications of local inflammation, epithelium proliferation, fibrosis and emphysema development (29). No changes were seen in the lungs of cats exposed to 6000 $\mu g/m^3$ diesel particles for more than a year, although at higher concentrations (6340-11,700 $\mu g/m^3$) and NO_2 (4.9-5.2 mg/m^3) there were morphological changes in the form of peribronchial fibrosis and elevated numbers of inflammatory cells and fibroblasts, indicating a pro-fibrotic effect of long-term exposure to diesel exhaust (27). In a comparative study, cynomolgus monkeys and rats were exposed to 2000 $\mu g/m^3$ diesel exhaust particles for 2 years: it was found that the monkeys retained more particles but, unlike the rats, showed no indications of inflammation or fibrosis (38, 39).

In vitro studies

Studies have been made with transformed cell lines developed from human bronchial epithelium, and the results generally confirm the results of the *in vivo* studies. Increased synthesis and liberation of inflammation-generating cytokines such as IL-1, IL-6, IL-8, GM-CSF, as well as increased liberation of the adhesion molecule s-ICAM-1, have been reported (2, 9, 11). Cells from asthmatics are reported to be more sensitive to low concentrations of particles from diesel exhaust than cells from healthy persons with regard to production of IL-8, GM-CSF and sICAM-1 (3). It has also been noted that a high dose of DEP reduces the production of cytokines IL-8 and RANTES in cells from asthmatics *in vitro* (3). Human epithelial cells have been found to produce cytokines involved in allergic reactions and allergy development after they have been exposed to DEP (43), which is in accord with the above-described reaction to experimental instillation of DEP in the nose (12, 13, 14). Further, isolated human B-cells can increase their production of IgE after exposure to particles from diesel exhaust (60).

Mutagenicity, carcinogenicity

Mutagenicity

Diesel exhaust contains many substances, including several with known mutagenic effect, such as various PAHs and nitro-PAH. Many mutagenicity tests have been made with diesel exhaust or particles from diesel exhaust, with positive results. Filtered diesel exhaust has also shown mutagenic activity *in vitro*.

When mice and rats were exposed to diesel exhaust in long-term studies, the mice developed more micronuclei but not in the rats. No dominant-lethal effect was seen in rats exposed to diesel exhaust. Sex-linked recessive lethal mutations were not found in *Drosophila* exposed to diesel exhaust for 8 hours (concentration expressed as 2.2 mg soot/m^3). Elevated levels of DNA adducts have been observed in laboratory animals exposed to diesel exhaust (4).

In a small Swedish study a non-significant increase of chromosome aberrations (CA), but no increase of sister chromatid exchanges (SCE), was found in truck drivers (N = 12) (17). In another Swedish study, no increase of CA was seen among miners exposed to diesel exhaust when they were compared to controls (42). Studies of persons occupationally exposed to diesel exhaust have revealed no increase in urine mutagenicity (4).

Carcinogenicity

Animal data

Different species have shown different responses in cancer tests with diesel exhaust.

Studies with mice have had varying results, and do not clearly indicate a carcinogenic response. Studies with hamsters have been negative (16). Studies with rats have clearly shown a dose-dependent carcinogenic response (4). A study with CD-1 mice, under experimental conditions known to cause a dose-dependent increase of lung tumors in rats, yielded no lung tumor increase in the mice (34). In the rat studies, however, the tumor increase occurred only at such high doses that the normal clearing system in the lungs was overloaded. In general, the rats that developed tumors were exposed to particle concentrations around 2.5 mg/m^3 (16). Rats exposed to similar particle concentrations of soot or titanium dioxide also have elevated incidences of lung tumors. Rats exposed to filtered (particle-free) diesel exhaust under the same conditions showed no statistically significant increase in lung tumors (16).

Human data

There are many epidemiological studies in which the possibility of a connection between cancer and occupational exposure to diesel exhaust has been explored. Groups commonly studied are drivers – especially drivers of trucks, construction equipment or diesel locomotives – and miners. There are several compilations and meta-analyses of these studies. In these analyses, the relative cancer risk for

drivers of trucks and diesel locomotives has been around 1.5; the results vary somewhat depending on the studies included and the treatment of confounding factors. The confounding factor receiving by far the most attention is smoking, but few studies provide adequate information on smoking habits. Other confounding factors are possible simultaneous exposure to other carcinogens such as asbestos. Estimates of exposure to diesel exhaust are also a weakness of most of the studies. Occupation is frequently used, and sometimes there are exposure estimates based on job category. The greatest hope of obtaining reliable exposure data is in studies of miners, especially those who work in mines where there is little radon or quartz. The levels of diesel exhaust are relatively high in mines (compared to city traffic, for example). The inadequacy of data in these studies is due mostly to the fact that diesel equipment was introduced fairly recently (often during the 1960s) and there has not been enough time to reveal a low increase in statistical risk.

Common to all the compilations of epidemiological studies on the risk of lung cancer due to exposure to diesel exhaust is that they support the suspicion that there is a connection. Most, however, express some reservation due to the occurrence of confounding factors. Other forms of cancer that have been tentatively connected to exposure to diesel exhaust are bladder cancer, cancer in lymphoid tissue and blood-forming organs, and prostate cancer (16). These connections, however, are not unequivocally supported in the literature and are not reviewed more fully here. A compilation of the conclusions in surveys of a connection between lung cancer and exposure to diesel exhaust is given in Table 3.

Table 3. Assessments of relationships between exposure to diesel exhaust and lung cancer given in meta-analyses and surveys of epidemiological studies.

Reference	Conclusion
IARC 1989 (28)	"limited "
California EPA 1998 (10)	"consistent evidence for a causal association"
Bhatia *et al*. 1998 (6)	"This meta-analysis supports a causal association between increased risks for lung cancer and exposure to diesel exhaust."
Lipsett & Campleman 1999 (32)	"This meta-analysis provides quantitative evidence consistent with several prior reviews, which have concluded that the epidemiological evidence supports a causal relationship between occupational exposure to diesel exhaust and lung cancer."
NTP 2000 (36)	"elevated lung cancer in occupationally exposed groups."
EPA 2002 (16)	"judged to be strong but less than sufficient to satisfy the criteria for a "known" human carcinogen"

Indicators of cancer risk

The epidemiological studies do not contain exposure data that is good enough to allow identification of the component or components in diesel exhaust that would be the best indicator(s) of risk (NO_2, certain types of particles, etc.).

Swedish conditions are reflected in a case-control study from Stockholm county, in which the risk of lung cancer was examined for 1042 cases and 2364 controls (20). Exposure to diesel exhaust and other substances was based on information on occupation, which was then classified blind by an occupational hygienist for case/control status: 180 of the cases and 312 controls were judged to have occupational exposure to diesel exhaust. There was no clear connection to intensity of exposure to diesel exhaust, defined as the highest exposure ever during a year. However, there was a statistically significant correlation between estimated cumulative dose and risk of lung cancer when data were adjusted for tobacco smoking, exposure to radon in the home, asbestos exposure and environmental exposure to nitrogen dioxide and other combustion products. The relative risk for an increase of the cumulative dose with 1 mg/year/m^3 of diesel fumes measured as NO_2 was 1.09 (95% CI: 1.02 – 1.16).

Animal studies have shown that both "pure" carbon particles and mixtures of polyaromatic hydrocarbons can increase the incidence of lung cancer in rats (16).

Reproductive effects

Studies with monkeys have not shown effects on spermatogenesis even at relatively high concentrations (2.0 mg/m^3 DEP measured as soot) (4). No studies on teratogenicity were found.

Dose-effect / dose-response relationships

Controlled experiments with human subjects indicate that effects of short-term exposure to diesel exhaust appear in the airways when the particle content is about 0.1 mg/m^3 and the NO_2 level is about 0.4 mg/m^3 (see Table 4). With one hour of exposure to exhaust at an NO_2 level of 2 to 3 mg/m^3, healthy subjects developed symptoms involving the mucous membranes of eyes and respiratory passages. In persons with asthma severe enough to require treatment with steroids, bronchial reactions (measured as bronchial hyperreactivity) appeared at about 2 mg/m^3 nitrogen dioxide. In these studies the exposure to elemental carbon was not measured, and there are no similar studies in which carbon was used as an indicator of exposure to diesel exhaust.

Experimental studies with rats and other small rodents indicate that there are large inter-species differences in susceptibility to lung cancer from diesel exhaust. Studies with rats indicate also that there is probably a threshold dose below which there is no risk. No animal study, however, has been judged by the EPA to be strong enough to determine whether there is a threshold for animals (16).

Table 4. Dose-response relationships observed in people experimentally exposed to diesel exhaust for brief periods.

Exposed group	Particle concentration	NO_2 (mg/m^3)	Time	Result	Ref.
Healthy n=8	$4.3x10^6/cm^3$ (≈300 $\mu g/m^3$)	2.7	1 hour	Symptoms in mucous membranes of eyes and nose	47
Healthy n=8	$4.3x10^6/cm^3$ (≈300 $\mu g/m^3$)	2.7	1 hour	Inflammation, inhibition of macrophage phagocytosis in BAL	48
Healthy n=12	$2.6 x10^6/cm^3$	3.4	1 hour	Increased bronchial resistance, symptoms involving eyes and nose	46
Healthy n=10	$2.6 x10^6/cm^3$	2.3	1 hour	Inflammation, inhibition of macrophage phagocytosis in BAL	45
Healthy n=15	300 $\mu g/m^3$ ($4.3x10^6/cm^3$)	2.9	1 hour	Indications of inflammation in BAL and biopsies of bronchial mucosa. Systemic effects with increased neutrophils and thrombocytosis in peripheral blood	49
Heallthy n=15	300 $\mu g/m^3$ ($4.3x10^6/cm^3$)	2.9	1 hour	Elevated mRNA expression for IL-8 in BAL and biopsies of bronchial mucosa. Increase of cytokines in bronchial mucosa	50
Asthmatics treated with steroid inhalation, 800-1200 μg/day. n=14	300 $\mu g/m^3$	2.2	1 hour	Doubling of bronchial hyperreactivity	41
Healthy n=25 Asthmatics with mild asthma, treated only with bronchodilators n=15	108 $\mu g/m^3$	0.36	2 hours	Healthy: Slight indications of inflammation in BAL and biopsies of bronchial mucosa. Asthmatic: No acute inflammation, but increase of cytokine (IL-10), which may eventually make the asthma more severe	25

In addition, epidemiological studies of persons who are probably exposed to considerably lower levels than laboratory rats raise strong suspicions of a correlation between lung cancer and exposure to diesel exhaust.

Conclusions

The critical effect of exposure to diesel exhaust is irritation and inflammation of respiratory passages. Slight inflammatory reactions in respiratory passages have been observed after brief (2-hour) exposure to exhaust levels at which the measured amount of nitrogen dioxide was about 0.4 mg/m^3 and particle content about 0.1 mg/m^3. Clinical effects such as irritation in healthy subjects and increased bronchial reactivity in asthmatics appeared under similar exposure conditions at an NO_2 level of about 2 mg/m^3 and a particle level of 0.3 mg/m^3 (measured as PM_{10}). There are no studies indicating whether elemental carbon can be used as an exposure indicator for such health effects of diesel exhaust.

Occupational exposure to diesel exhaust can increase the risk of lung cancer. This statement is based primarily on epidemiological studies, which, however, are unable to clarify the size of the risk in relation to amount of exposure. It is possible that the increase in risk that has been observed is due to other factors. Neither epidemiological studies nor animal experiments have been able to determine which components in diesel exhaust are the best indicators to use for estimating such risks.

References

1. Bakke B, Stewart P, Ulvestad B, Eduard W. Dust and gas exposure in tunnel construction work. *Am Ind Hyg Assoc J* 2001;62:457-465.
2. Bayram H, Devalia JL, Khair OA, Abdelaziz MM, Sapsford RJ, Sagai M, Davies RJ. Comparison of ciliary activity and inflammatory mediator release from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients and the effect of diesel exhaust particles in vitro. *J Allergy Clin Immunol* 1998;102:771-782.
3. Bayram H, Devalia JL, Sapsford RJ, Ohtoshi T, Miyabara Y, Sagai M, Davies RJ. The effect of diesel exhaust particles on cell function and release of inflammatory mediators from human bronchial epithelial cells in vitro. *Am J Respir Cell Mol Biol* 1998;18:441-448.
4. Beije B. *Criteria Documents from the Nordic Expert Group 1993*. Diesel exhaust. Arbete och Hälsa 1993;35:83-156. National Institute of Occupational Health, Solna, Sweden.
5. Birch ME, Cary RA. Elemental carbon-based method for occupational monitoring of particulate diesel exhaust: methodology and exposure issues. *Analyst* 1996;121:1183-1190.
6. Bhatia R, Lopipero P, Smith AH. Diesel exhaust exposure and lung cancer. *Epidemiology* 1998;9:84-91.
7. Blomberg A, Krishna MT, Bocchino V, Biscione GL, Shute JK, Kelly FJ, Frew AJ, Holgate ST, Sandström T. The inflammatory effects of 2 ppm NO_2 on the airways of healthy subjects. *Am J Respir Crit Care Med* 1997;156:418-424.
8. Blomberg A, Krishna MT, Helleday R, Söderberg M, Ledin M-C, Kelly FJ, Frew AJ, Holgate ST, Sandström T. Persistent airway inflammation but accommodated antioxidant and lung function responses after repeated daily exposure to nitrogen dioxide. *Am J Respir Crit Care Med* 1999;159:536-543.

9. Boland S, Baeza-Squiban A, Fournier T, Houcine O, Gendron MC, Chevrier M, Jouvenot G, Coste A, Aubier M, Marano F. Diesel exhaust particles are taken up by human airway epithelial cells in vitro and alter cytokine production. *Am J Physiol* 1999;276 (4 Pt 1):L604-613.
10. California Environmental Protection Agency. (CAL EPA OEHHA). *Health risk assessment for diesel exhaust*. Public and Scientific Review Draft. February 1998 (cited in EPA 2002).
11. Devalia JL, Bayram H, Rusznak C, Calderon M, Sapsford RJ, Abdelaziz MA, Wang J, Davies RJ. Mechanisms of pollution-induced airway disease: In vitro studies in the upper and lower airways. *Allergy* 1997;52:45-51.
12. Diaz-Sanchez D, Tsien A, Casillas A, Dotson AR, Saxon A. Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. *J Allergy Clin Immunol* 1996;98:114-123.
13. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. *J Immunol* 1997;158:2406-2413.
14. Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest* 1994;94:1417-1425.
15. Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *J Allergy Clin Immunol* 1999;104:1183-1188.
16. EPA. *Health assessment document for diesel exhaust*. USEPA EPA/600/8-90/057F.01 May 2002. U.S. Environmental Protection Agency, Washington, D.C. (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=29060)
17. Fredga K, Davring L, Sunner M, Bengtsson BO, Elinder CG, Sigtryggsson P, Berlin M. Chromosome changes in workers (smokers and nonsmokers) exposed to automobile fuels and exhaust gases. *Scand J Work Environ Health* 1982;8:209-221.
18. Funasaka K, Miyazaki T, Kawaraya T, Tsuruho K, Mizuno T. Characteristics of particulates and gaseous pollutants in a highway tunnel. *Environ Pollution* 1998;102:171-176.
19. Groves J, Cain JR. A survey of exposure to diesel engine exhaust emissions in the workplace. *Ann Occup Hyg* 2000;44:435-447.
20. Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Jarup L, Scheele P. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol* 2000;152:32-40.
21. Haney RA, Saseen GP, Waytulonis RW. An overview of diesel particulate exposures and control technology in the U.S. mining industry. *Appl Occup Environ Hyg* 1997;12:1013-1018.
22. Helleday R, Huberman D, Blomberg A, Stjernberg N, Sandström T. Nitrogen dioxide exposure impairs the frequency of the mucociliary activity in healthy subjects. *Eur Respir J* 1995;8:1664-1668.
23. Helleday R, Sandström T, Stjernberg N. Differences in bronchoalveolar cell response to nitrogen dioxide exposure between smokers and nonsmokers. *Eur Respir J* 1994;7:1213-1220.
24. Hemminki K, Soderling J, Ericson P, Norbeck HE, Segerback D. DNA adducts among personnel servicing and loading diesel vehicles. *Carcinogenesis* 1994;15:767-769.
25. Holgate ST, Sandström T, Frew AJ, Stenfors N, Nordenhäll C, Salvi S, Blomberg A, Helleday R, Söderberg M. Health effects of acute exposure to air pollution. Part I: healthy and asthmatic subjects exposed to diesel exhaust. *Res Rep Health Eff Inst* 2002;112:1-30.

26. Hou SM, Lambert B, Hemminki K. Relationship between hprt mutant frequency, aromatic DNA adducts and genotypes for GSTMI and NAT2 in bus maintenance workers. *Carcinogenesis* 1995;16:1913-1917.
27. Hyde DM, Plopper CG, Peplko WE, Mattox J. Peribronchial fibrosis in lungs of cats chronically exposed to diesel exhaust. *Lab Invest* 1985;52:192-206.
28. IARC. Diesel and gasoline engine exhaust and some nitroarenes. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 46. Lyon: International Agency for Research on Cancer. 1989;46:41-185.
29. Kato A, Lyono H, Kuwabara N. Electron-microscopic observations on rat lungs after long term inhalation of diesel emissions – non-neoplastic lesions. *Japanese J Thoracic Dis* 1992;30:238-247.
30. Kinney PL, Aggarwal M, Northridge ME, Janssen NAH, Shepard P. Airborne concentrations of PM2.5 and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. *Environ Health Perspect* 2000;108:213-218.
31. Lidén G, Figler B, Wahler J. Measurements of diesel particles in an iron ore mine. In: Hagberg M, Knave B, Lillenberg L, Westberg H, eds. *X2001 – Exposure Assessment in Epidemiology and Practice*. Arbete och Hälsa 2001;10:347-349. National Institute for Working Life, Solna, Sweden.
32. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. *Am J Public Health* 1999;89:1009-1017.
33. Lundberg P, ed. *Scientific Basis for Swedish Occupational Standards VII*. Arbete och Hälsa 1986;35:30-41. Swedish National Board of Occupational Safety and Health, Solna.
34. Mauderly JL, Banas DA, Griffith W, Hahn FF, Henderson RF, McClellan RO. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundam Appl Toxicol* 1996;30:233-242.
35. Miller KP, Ramos KS. Impact of cellular metabolism on the biological effects of benzo(a)pyrene and related hydrocarbons. *Drug Metab Rev* 2001;33:1-35.
36. National Toxicology Program (NTP). *Ninth Report on Carcinogens*. Public Health Service, U.S Department of Health and Human Services, Research Triangle Park, N.C., 2000. (http://ntp-server.niehs.nih.gov/)
37. Nielsen PS, Andreassen A, Farmer PB, Ovrebo S, Autrup H. Biomonitoring of diesel exhaust-exposed workers. DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. *Toxicol Lett* 1996;86:27-37.
38. Nikula KJ, Avila KJ, Griffith WC, Mauderly JL. Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. *Fundam Appl Toxicol* 1997;37:37-53.
39. Nikula KJ, Avila KJ, Griffith WC, Mauderly JL. Sites of particle retention and lung tissue responses to chronically inhaled diesel exhaust and coal dust in rats and cynomolgus monkeys. *Environ Health Perspect* 1997;105 Suppl 5:1231-1234.
40. NIOSH. National Institute for Occupational Safety and Health. Elemental Carbon (diesel particulate): Method 5040. *NIOSH Manual of Analytical Methods* 4th ed., 1999. (http://www.cdc.gov/niosh/nmam/pdfs/5040.pdf)
41. Nordenhäll C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. *Eur Respir J* 2001;17:909-915.
42. Nordenson I, Sweins A, Dahlgren E, Beckman L. A study of chromosomal aberrations in miners exposed to diesel exhausts. *Scand J Work Environ Health* 1981;7:14-17.
43. Ohtoshi T, Takizawa H, Okazaki H, Kawasaki S, Takeuchi N, Ohta K, Ito K. Diesel exhaust particles stimulate human airway epithelial cells to produce cytokines relevant to airway inflammation in vitro. *J Allergy Clin Immunol* 1998;101:778-785.
44. Rogers A, Whelan B. Exposures in Australian mines. *Health Effects Institute* 1999, No 7, March 7-9, Stone Mountain, GA, pp 147-156.

45. Rudell B, Blomberg A, Helleday R, Ledin MC, Lundbäck B, Stjernberg N, Hörstedt P, Sandström T. Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. *Occup Environ Med* 1999;56:527-534.
46. Rudell B, Ledin M-C, Hammarström U, Stjernberg N, Lundbäck B, Sandström T. Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. *Occup Environ Med* 1996;53:658-662.
47. Rudell B, Sandström T, Hammarström U, Ledin ML, Hörstedt P, Stjernberg N. Evaluation of an exposure setup for studying effects of diesel exhaust in humans. *Int Arch Occup Environ Health* 1994;66:77-83.
48. Rudell B, Sandström T, Stjernberg N, Kolmodin-Hedman B. Controlled diesel exhaust exposure in an exposure chamber: Pulmonary effects investigated with bronchoalveolar lavage. *J Aerosol Sci* 1990;21:411-414.
49. Salvi S, Blomberg A, Rudell B, Kelly FJ, Sandström T, Holgate ST, Frew AJ. Acute inflammatory response in the airways and peripheral blood following short term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999;159:702-709.
50. Salvi SS, Nordenhäll C, Blomberg A, Rudell B, Pourazar J, Kelly FJ, Sandström T, Holgate ST, Frew AJ. Acute exposure to diesel exhaust increases IL-8 and GRO-a production in healthy human airways. *Am J Respir Crit Care Med* 2000;161-550-557.
51. Sandström T, Andersson MC, Kolmodin-Hedman B, Stjernberg N, Ångström T. Bronchoalveolar mastocytosis and lymphocytosis after nitrogen dioxide exposure in man: a time-kinetic study. *Eur Respir J* 1990;3:138-143.
52. Sandström T, Helleday R, Bjermer L, Stjernberg N. Effects of repeated exposure to 4 ppm nitrogen dioxide on bronchoalveolar lymphocyte subsets and macrophages in healthy men. *Eur Respir J* 1992;5:1092-1096.
53. Sandström T, Ledin M-C, Thomasson L, Helleday R, Stjernberg N. Reductions in lymphocyte subpopulations after repeated exposure to 1.5 ppm nitrogen dioxide. *Br J Ind Med* 1992;49:850-854.
54. Sandström T, Stjernberg N, Eklund A, Ledin MC, Bjermer L, Kolmodin-Hedman B, Lindström K, Rosenhall L, Ångström T. Inflammatory cell response in bronchoalveolar lavage fluid after nitrogen dioxide exposure of healthy subjects: a dose-response study. *Eur Respir J* 1991;3:332-339.
55. Sjögren M, Li H, Banner C, Rafter J, Westerholm R, Rannug U. Influence of physical and chemical characteristics of diesel fuels and exhaust emissions on biological effects of particle extracts: a multivariate statistical analysis of ten diesel fuels. *Chem Res Toxicol* 1996;9:197-207.
56. SPI, Swedish Petroleum Institute, statistics 2002 (http://www.spi.se)
57. Stanevich RS, Hintz P, Yereb D, Dosemeci M, Silverman DT. Elemental carbon levels at a potash mine. *Appl Occup Environ Hyg* 1997;12:1009-1012.
58. Svartengren M, Strand V, Bylin G, Jarup L, Pershagen G. Short-term exposure to air pollution in a road tunnel enhances the asthmatic response to allergen. *Eur Respir J* 2000;15:716-724.
59. Säverin R. German potash miners: cancer mortality. *Health Effects Institute* 1999, No 7, March 7-9, Stone Mountain, GA, pp 220-229.
60. Takenaka H, Zhang K, Diaz-Sanchez D, Tsien A, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. *J Allergy Clin Immunol* 1995;95:103-115.
61. Verma DK, Shaw L, Julian J, Smolynec K, Wood C, Shaw D. A comparison of sampling and analytical methods for assessing occupational exposure to diesel exhaust in a railroad work environment. *Appl Occup Environ Hyg* 1999;14:701-714.

62. Westerholm R, Egebäck KE. Exhaust emissions from light- and heavy-duty vehicles: chemical composition, impact of exhaust after treatment, and fuel parameters. *Env Health Perspect* 1994;102 Suppl 4:13-23.

63. Yanowitz J, McCormick RL, Graboski MS. In-use emissions from heavy-duty diesel vehicles. *Env Sci Tech* 2000;34:729-740.

64. Zaebst DD, Clapp DE, Blade LM, Marlow DA, Steenland K, Hornung RW, Scheutzle D, Butler J. Quantitative determination of trucking industry workers' exposures to diesel exhaust particles. *Am Ind Hyg Assoc J* 1991;52:529-541.

Consensus Report for Cadmium

February 5, 2003

This Report is based primarily on a recently published critical review of the literature (30) and subsequently published articles, but some data have also been drawn from earlier surveys (44, 70). The Criteria Group has previously published Consensus Reports for cadmium, most recently in 1992 (36); this document will therefore focus primarily on the subsequently published material.

Chemical and physical data. Occurrence

Formula:	Cd
CAS No.:	7440-43-9
Atomic weight:	112.4
Atomic number:	48
Density:	8.6 g/cm^3
Melting point:	321 °C
Boiling point:	765 °C
Conversion factors:	1 μg/l = 8.9 nmol/l
	1 μmol/l = 112 μg/l
	1μg/g creatinine = 1μmol/mol creatinine = 1 nmol/mmol creatinine
	1 mmol/kg = 112 mg/kg

Cadmium is one of the heavy metals (usually defined as metals with a density higher than 5 g/cm^3). It occurs naturally in ores together with zinc, lead and copper. Cadmium compounds are used as pigments (830 tons/year), in alloys and batteries (about 4200 tons/year), and as stabilizers in plastics (mostly stearate in PVC products); annual use within the EU dropped from about 270 tons in 1997 to 30 tons in 2000 (12). Over 90% of the cadmium used in Sweden is in rechargeable nickel-cadmium (NiCd) batteries (Swedish National Chemicals Inspectorate, 1996). The National Swedish Environment Protection Board estimates that 143 tons of NiCd batteries were collected for recycling in the year 2000. Metallic cadmium has been used mostly as a corrosion inhibitor (cadmium plating). Cadmium also occurs as a contaminant in phosphate fertilizers. Cadmium in cadmium compounds has the oxidation state +II. Of the cadmium compounds, acetate, chloride and sulfate are readily soluble in water and oxide and sulfide much less soluble. Organic salts of cadmium (e.g. stearate) have fairly low solubility.

In Sweden, occupational exposure to cadmium occurs almost exclusively in battery production. Handling and recycling of scrap metal containing cadmium may also involve some exposure, but the extent of any such exposure would be extremely difficult to estimate. Silver solder containing cadmium is probably still used to a small extent. Air concentrations in Swedish workplaces are probably almost always below the limit set by the National Board of Occupational Safety and Health (50 μg/m^3 total dust; AFS 2000:3).

Uptake, biotransformation, excretion

Occupational exposure to cadmium is primarily via inhalation, although there may also be some uptake via the digestive tract (e.g. if lunch is eaten at the work station) (1). It should be mentioned that cigarette smoke is the primary source of cadmium exposure for smokers who are not occupationally exposed, and that tobacco smoke in ambient air may be a source of some cadmium exposure (18). For non-smokers, most environmental exposure is via the digestive tract.

Uptake of inhaled cadmium is between 10 and 50 percent, depending mostly on particle size (respirable particles < 5 μm) and solubility (chemical form) (70). Absorption from the digestive tract is much lower, on the order of a few percent (5, 70).

Experimental studies have shown that cadmium absorbed after relatively high single doses binds to high-molecular proteins in the blood (such as albumin) and is transported to the liver, where it is bound to metallothioneine (MT) and then re-distributed to other tissues and organs (44). In contrast to albumin-bound cadmium, the Cd-MT complex is filtered through the renal glomeruli and resorbed in the tubuli. The resorbed cadmium accumulates in the renal cortex, where it has a half time of over 10 years. Several studies have indicated that cadmium kinetics may be dose-dependent, and possibly also dependent on exposure path (30). Much of the cadmium taken up by the mucous cells in the digestive tract (long-term, low-level exposure) is bound directly to MT in the cells. Some of this cadmium can be excreted in feces when these cells are sloughed off, whereas the absorbed Cd-MT complex is transported in the blood, mostly to the kidneys.

The half time for cadmium in blood has two phases – a short phase of 75 to 128 days and a longer phase of 7.4 to 16 years – that reflect the body burden (24). Cadmium is excreted slowly in urine, with a half time of about 10 to 15 years (equivalent to a daily excretion of about 0.01 percent of the body burden).

Biological markers for exposure and dose

Routine exposure control is traditionally based on determination of cadmium in blood and urine. The cadmium content in blood reflects primarily current exposure (but can also be used as a measure of body burden a few years after occupational exposure has stopped; see above), whereas the cadmium content in urine is related primarily to the body burden. Cumulative blood cadmium (blood cadmium content multiplied by years of exposure, expressed in nmol/l x years)

can also be used as a measure of body burden (23, 25). However, cadmium in urine rises if there is kidney damage – no matter what the cause (30). Refinements in analysis methods over recent years have made it possible to lower the detection limits. At present Inductively Coupled Plasma Mass Spectrometry (ICP-MS) has largely replaced atomic absorption (AAS) for determination of cadmium in blood and urine. To compensate for the inconsistent water content in urine, cadmium in urine is usually given in relation to the amount of excreted creatinine.

In vivo methods – neutron activation (NA) and x-ray fluorescence (XRF) – have been developed to determine cadmium in kidneys and liver. These methods allow direct determination of cadmium in these organs, but are still far too complicated and uncertain to provide a feasible alternative to cadmium in blood or urine as a measure of dose (9, 10, 30).

Biological markers for kidney damage

Tubular damage

There are several sensitive methods for assessing the function of renal tubuli (13). Low-molecular proteins such as $ß_2$-microglobulin, retinol-binding protein (RBP) and Human Complex-forming glycoprotein (Protein HC = α_1-microglobulin), as well as tubular intracellular enzymes (e.g. N-acetyl-ß-D-glucosaminidase, NAG), have all been used to detect early damage to renal tubuli. It is important to bear in mind, however, that increased excretion of such proteins or enzymes is not necessarily caused by cadmium or other heavy metals. Urinary excretion of $ß_2$-microglobulin may increase with fever or urinary infections, for example. A major disadvantage of $ß_2$-microgobulin is that the protein is unstable at low pH (<5.6) in urine. Other alternatives (such as α_1-microglobulin) may therefore be preferable for epidemiological studies of cadmium exposure and early kidney damage.

Glomerular damage

The function of the renal glomeruli, GFR (Glomerular Filtration Rate), is usually determined with methods that measure how fast an injected foreign substance – often a very small amount of radioactively labeled CrEDTA or the contrast medium Iohexol™ – is eliminated from the blood via the kidneys. A commonly used method for rough determination of GFR is to measure creatinine in serum; however, this usually does not rise until the GFR has dropped to about half the normal value, i.e. with considerably reduced renal function. S-Cystatin C has recently come into use as a marker for glomerular damage (59). Increased glomerular permeability results in a rise in the content of large proteins (albumin) and/or blood cells in the urine. Analysis for these is often used in occupational medicine to detect early glomerular damage (69).

Toxic effects

Acute effects

Inhalation of high concentrations of cadmium (1 mg/m^3 or higher) can be lethal (45). Acute pulmonary effects and deaths are rare, but still occur occasionally (4, 53).

Kidney damage

Tubular damage

It is well documented that long-term exposure to cadmium causes kidney damage (30). The damage is usually to the renal tubuli, and is characterized by increased excretion of low-molecular proteins (see above under Biological markers for kidney damage). Most of the kidney damage is probably localized in the proximal tubuli. It has sometimes been argued that the tubular damage is reversible, but the evidence is weak (19, 64). On the other hand, there is convincing evidence that the tubular damage caused by cadmium is not reversible (30, 50).

In a summary of the situation in 1992, WHO stated that excretion in urine of 10 nmol Cd/mmol creatinine (corresponding to about 200 mg Cd/kg renal cortex) was a "critical limit" below which kidney damage could not occur (70). However, WHO also estimated that about 10 percent of individuals with this much cadmium in their kidneys would suffer tubular damage. Several reports published since then have indicated that the "critical concentration" of cadmium in urine and kidney tissue is probably much lower. In other words, early kidney damage and/or skeletal effects probably occur at levels below the critical limit published by WHO.

In a study of occupationally exposed workers (76 men) in the United States it was found that a U-Cd content of 6.8 nmol/mmol creatinine was associated with a 10% prevalence of tubular proteinuria (39), and a study from Singapore reported a significantly elevated age-standardized prevalence of two sensitive markers for tubular damage (U-α_1-microglobulin and U-NAG) at U-Cd levels exceeding 5 nmol/mmol creatinine in a group of workers (45 men and 52 women) in a nickel-cadmium battery factory (11).

In a frequently cited Belgian study (Cadmibel) of cadmium's effects in the general population (n = 2327), indications of cadmium-induced kidney damage were found in about 10% of subjects with urine concentrations of about 2 to 3 nmol Cd/mmol creatinine (adjusted for other significant variables) (8). It should be noted that this figure includes a "background prevalence" of 5%, since "elevated values" were defined as those lying above the 95th percentile in a reference population. This method of calculating, however, is usual in studies of kidney damage caused by cadmium. The authors observed that, despite the fact that the body burden of cadmium increases with age, the effects of cadmium on the studied markers for kidney damage were independent of age and gender. Diabetics were reported to be particularly sensitive. A more recent Belgian study

(57) confirms these earlier results (8). It was found that people living in cadmium-contaminated areas had elevated excretion of several markers for tubular damage.

A Japanese study of the population in a cadmium-contaminated area (1403 men and 1716 women; 478 men and 696 women in a reference population) showed dose-response relationships between urine cadmium, age and $ß_2$-microglobulinuria (15). The prevalence of tubular proteinuria was 14.3 for men and 18.7 for women in the exposed group, with an odds ratio of 4.1[1] (no confidence interval was given) for tubular proteinuria among the exposed subjects (average U-Cd = 5 nmol/mmol creatinine) compared with unexposed subjects (average U-Cd = 2 nmol/mmol creatinine). It should be mentioned that the limit for tubular damage was set at 1000 μg $ß_2$-microglobulin/g creatinine (= 113 μg/mmol creatinine), which is quite a bit higher than limits usually applied outside Japan (e.g. 34 μg/mmol creatinine). It was calculated that a 10% prevalence of tubular proteinuria corresponded to a U-Cd excretion of 1.6 – 4.6 nmol/mmol creatinine, which is similar to the results from Belgium.

A recently published Swedish study including both occupationally exposed workers and an environmentally exposed population showed a clear dose-response relationship between cadmium in urine and damage to renal tubuli (see also Table 1), with a prevalence of 10% at a U-Cd content of 1.0 nmol Cd/mmol creatinine, adjusted for the average age of the subjects (53 years) (33).

Yet another newly published study (151 women, 159 men) reports a dose-effect relationship between markers for kidney damage (NAG, alanine-amino peptidase (AAP)) and cadmium in urine at very low concentrations: < 0.25 to ≥ 1 nmol/mmol creatinine; at ≥ 1 the markers were significantly higher than at < 0.25 (43). However, it is difficult to interpret these findings in terms of damage.

Although the subjects of occupational exposure studies are usually young or middle-aged men, there are also high-risk groups in the general population. For example, women are more likely than men to suffer from iron deficiency, a condition facilitating the absorption of cadmium. Old people are another high-risk group. It is therefore not surprising that tubular damage was observed in the general population at lower cadmium levels than in the occupationally exposed subjects. Kidney function normally declines with advancing age, most notably GFR but also to some extent tubular function. It should be mentioned that most of the earlier studies do not take the effect of age into the calculations; however, it is judged to be rather small (30).

Correlations between exposure (air), dose (blood, urine) and prevalence of damage to renal tubuli have thus been demonstrated in several studies, a few of which are presented in Table 1. Cadmium oxide is the compound most common in occupational exposures (in Sweden), although a few studies have addressed other compounds (e.g. sulfide) and environments (e.g. zinc smelters). The studies shown in Tables 1a and 1b are of exposure to cadmium oxide (CdO).

---

[1] It should be mentioned that prevalence odds ratios tend to overestimate the actual risk – and the higher the prevalence the higher the overestimate.

Table 1a. Correlations between exposure to CdO and prevalence of damage to renal tubuli. Marker for tubular damage: $ß_2$-microglobulin. Cutoff level: 34 µg/mmol creatinine, corresponding to a background prevalence of 2.5%.

Exposure/dose/exposure measure Interval (arithmetic mean)	Number of persons	Prevalence (%)	Ref.
Cumulative air concentration $\mu g/m^3$ *x years*			25
<359	264	1.1	
359-<1710	76	9.2	
1710-<4578	43	23	
4578-<9458	31	32	
9458-<15,000	16	31	
≥15,000	10	50	
Cumulative blood concentration nmol/l x months			25
<5,000	221	1.4	
5,000-<10,000	87	4.6	
10,000-<15,000	38	16	
15,000-<30,000	48	23	
30,000-<60,000	27	30	
≥60,000	16	50	
Cadmium in urine nmol/mmol creatinine			28
<1 (0.45)	248	0.8	
1-<3 (1.67)	165	2.4	
3-<5 (3.98)	63	14	
5-<10 (7.04)	57	28	
≥10 (15.07)	28	46	

Table 1b. Correlations between exposure to CdO and prevalence of damage to renal tubuli. Marker for tubular damage: protein HC (α_1-microglobulin). Cutoff levels: 0.6 mg/mmol creatinine for women, 0.8 mg/mmol creatinine for men, corresponding to a background prevalence of 5%. (from Reference 33)

Measure of exposure Interval (arithmetic mean)	Number of persons		Prevalence (%)	
	Total	Occupationally exposed	Total	Occupationally exposed
Cadmium in urine nmol/mmol creatinine				
<0.3 (0.21)	265	13	4.9	7.7
0.3-<0.5 (0.38)	273	30	14	13
0.5-<1 (0.69)	298	66	23	12
1-<2 (1.4)	108	55	30	18
2-<3 (2.5)	24	23	33	30
3-<5 (3.8)	21	20	33	35
≥5 (6.8)	12	12	50	50

Other effects on kidneys

As early as 1950 it was noticed that cadmium-exposed workers could have low GFR in addition to proteinuria (14). This was subsequently confirmed in several studies of occupationally exposed workers (30). Järup *et al*. (29) examined cadmium-exposed solderers, and found correlations between cadmium dose, degree of tubular damage (measured as $ß_2$-microglobulin clearance) and declining age-adjusted GFR. At a blood cadmium level of 100 nmol/l GFR had dropped to 80% of the reference level, and an elevated prevalence of reduced GFR was seen at levels as low as 50 to 75 nmol/l. Other studies have shown that glomerular damage can be independent of tubular damage (6).

An elevated incidence of kidney stones among workers occupationally exposed to cadmium has been found in several studies (30). The kidney stones were usually associated with tubular proteinuria, and may possibly be related to increased excretion of calcium in urine due to the tubular damage. A dose-response relationship between cumulative exposure to airborne cadmium and age-adjusted cumulative incidence of kidney stones has been reported (27). The median cadmium content in the urine of worker with kidney stones was 3.7 (95% Confidence Interval (CI): 2.4 – 6.4) nmol/mmol creatinine.

A relation between cadmium exposure and kidney failure has also been reported in a recent ecological study (17). The study reviewed records of patients treated for chronic uremia, and found a nearly doubled risk for persons living less than 2 km from the source of exposure (SRR = 1.9; 95% CI: 1.3 – 2.5) and for those occupationally exposed (SRR = 2.3; 95% CI 0.6 – 6.0) when these groups were compared to unexposed subjects in the same district (Kalmar county).

Skeletal damage (effects)

Long-term exposure to cadmium can cause bone disease, which was first reported from Japan, where *itai-itai* (it hurts-it hurts) (a combination of osteomalacia and osteoporosis) was first diagnosed in the 1950s. The source of exposure was cadmium-contaminated water that was being used to irrigate the local rice fields. The cadmium content in the bones of *itai-itai* patients was found to be several times as high as that in unexposed persons. There are also a few reports of similar skeletal effects from sources outside Japan (30).

Reduced bone density after exposure to cadmium is described in a few animal studies. An American study of beagles showed that bone loss could appear at fairly low blood cadmium levels (27 - 71 nmol/l) (7). The results indicated that cadmium affects the bones directly.

Some data published in the past few years indicate that even relatively low exposure to cadmium can cause skeletal damage in the form of reduced bone density and fractures. A Belgian study of persons living in cadmium-contaminated areas showed a relationship between elevated excretion of cadmium in urine and reduced bone density/fractures (58). A doubling of the urine cadmium level was associated with a significant elevation in relative risk for fractures (RR = 1.73; 95% CI: 1.16 –2.57). In a Swedish study of occupationally exposed brazers (hard

solder) it was found that reduced bone density was positively correlated to age and to blood cadmium (which in this group of workers was found to be a relevant measure of the body burden) (31). Brazers with tubular damage had lower bone density than the others. These results were later confirmed in a study of 1064 persons occupationally or environmentally exposed to cadmium (2). This study reports both dose-effect and dose-response relationships between urine cadmium and reduced bone density (osteoporosis), with odds ratios of 2.2 (95% CI: 1.0 – 4.8) for men 60 or older in the dose group 0.5 – 3 nmol Cd/mmol creatinine, and 5.3 (95% CI: 2.0 – 14) for those in the highest dose category (3 nmol Cd/mmol creatinine or higher) compared with the lowest group (< 0.5 nmol Cd/mmol creatinine). For women aged 60 or older the odds ratio was 1.8 (95% CI: 0.65 – 5.3) in the dose group 0.5 – 3 nmol Cd/mmol creatinine; there were no women in the high-dose group.

These reports indicate that bone damage associated with cadmium can occur at much lower cadmium concentrations than was earlier believed.

Neurological effects

Animal studies have shown that cadmium can be neurotoxic, but few studies have found neural damage in human subjects. Slightly reduced functional ability on psychological tests has been reported in occupationally exposed subjects (45). In one study, effects on the central nervous system (e.g. longer reaction times) were seen in neuropsychological tests given to a group of workers with various degrees of cadmium exposure (average value in urine = 12.6 nmol Cd /mmol creatinine; range 0.4 – 38.4) (66). This group also had a higher (dose-dependent) incidence of peripheral neuropathy than a control group. In a study of retired workers, the cadmium-exposed group had a much higher risk of polyneuropathy than a control group (odds ratio = 9.92; 95% CI: 1.60 – 61.6) (65). The prevalence of poly-neuropathy was related to the body burden of cadmium.

Effects on the heart and circulatory system

Data from animal experiments have suggested that cadmium might be a risk factor for cardiovascular disease, but this has not been confirmed in studies of humans (30, 35, 70). Data from the previously mentioned Cadmibel study gave no support to the hypothesis that cadmium exposure would lead to a heightened prevalence of hypertonia or cardiovascular disease (8). On the other hand, a Japanese study showed an elevated risk of mortality due to cardiovascular disease in cadmium-exposed subjects with indications of damage to renal tubuli (65 men and 113 women) when they were compared to persons without kidney damage (1014 men and 1216 women) (41). In a follow-up study of a Swedish cohort of nickel-cadmium battery workers, no increase in risk of mortality due to cardiovascular disease was found when they were compared with a regional (Kalmar county) reference population (32).

Mortality

Studies of persons from cadmium-contaminated areas in Japan who have cadmium-induced kidney damage ($ß_2$-microglobulin ≥ 1000 μg/g creatinine) have shown a clear connection between degree of kidney damage and elevation in mortality (3, 40). Similar findings were made earlier in other cadmium-contaminated areas in Japan (21, 22). Although it is not clear from the Japanese studies, there is reason to believe that much of the increased mortality can be ascribed to chronic kidney failure. In this context it can be mentioned that the prevalence of active uremia care in Japan is two to four times as high as it is in Europe (62).

Mutagenicity

Mutagenicity tests with bacteria have generally been negative, and studies of chromosome aberrations in persons occupationally exposed to cadmium have been inconclusive (45). It has been proposed that cadmium might inhibit DNA repair and thus have a synergistic effect with some mutagens and carcinogens (51). One review article concludes that cadmium is probably not mutagenic and that its possible carcinogenic qualities seem to be due to indirect, thus far unknown, mechanisms (68).

Carcinogenicity

Human data

Lung cancer

In its most recent carcinogenicity assessment of cadmium, the IARC stated that there was "sufficient evidence" for classifying cadmium as a human carcinogen (Group 1) (20). However, the IARC pointed out that the assessment was based on only a few studies of occupationally exposed persons and that there were often shortcomings in the exposure data. As a rule, possible confounding factors such as smoking and simultaneous exposure to other substances such as nickel and arsenic could not be included. The IARC assessment was based largely on studies from the U.S. with few cases of lung cancer (63). Statistically significant dose-response relationships were shown with several different regression models (60). From this analysis it was estimated that exposure to cadmium (smoke) at 100 $\mu g/m^3$ should give rise to about 50 - 111 lung cancer cases in 1000 workers exposed to cadmium for 45 years. The American studies have been criticized, mostly on the basis of inadequate control for confounding factors – especially arsenic (30). Sorahan and Lancashire re-analyzed the American cohort, including in their analysis data on arsenic exposure (56). They found that there was still a dose-response relationship between cumulative cadmium exposure and lung cancer, but only in combination with arsenic exposure. The increase in lung cancer risk may also be due to the arsenic exposure alone. No risk increase for lung cancer was found in an English

study; there was a negative correlation between cumulative cadmium exposure and lung cancer risk (55). These findings are supported by a Swedish study in which, although the most recent follow-up (to 1992) of a cohort of nickel-cadmium battery workers revealed a statistically significant increase in the risk of death due to lung cancer (SMR = 176; 95% CI: 101 – 287), and a nearly significant risk increase for lung cancer incidence (SMR = 173; 95% CI 97 – 285), there was a negative dose-response relationship between cumulative cadmium exposure and lung cancer risk (32). The same results were obtained when smoking habits were included in the analysis. It should be observed, however, that a negative trend based on SMR values can be false due to problems in comparing SMRs for sub-groups with different age structures (38). Further, a negative trend may be due to the "healthy worker" effect, which is often more pronounced in sub-groups with many years of employment (46).

Prostate cancer

It has long been suspected that cadmium might cause prostate cancer (48), but this has not been confirmed in recent studies. Studies that show somewhat higher risks have been published, as have studies that are negative (30). This inconsistency has also been commented by the IARC (20).

Renal cancer

Some early data indicated a connection between cadmium exposure and renal cancer (34). Later studies have been unable to clearly confirm this, though a large multi-center study showed a (nearly) significant increase in relative risk of renal cancer (RR = 2.0; 95% CI 1.0 – 3.9), but with a negative dose-response relationship arguing against a causal relationship (37). A population-based multi-center study with 935 cases of renal cancer found an elevated risk associated with occupational exposure to cadmium (OR = 1.4, 95% CI: 1.1 – 1.8 for men; OR = 2.5, 95% CI: 1.2 – 5.3 for women) (47).

Other forms of cancer

It has been suggested that cadmium increases the risk of testicular cancer (49), bladder cancer (54) and pancreatic cancer (52), but the evidence is weak.

Animal data

It has been shown in several laboratory studies that cadmium can cause tumors in animals (30). The IARC, in its most recent assessment, concluded that there is "sufficient evidence" that cadmium is carcinogenic, but also pointed out that the evidence that cadmium is carcinogenic when given orally to experimental animals is limited (20). The carcinogenic effects on laboratory animals have usually been observed after inhalation or injection of cadmium compounds.

The mechanisms behind cadmium's ability to induce prostate cancer have been discussed (67). The authors observed in summary that, in long-term studies with rats, the cadmium-induced tumors occur mainly in the ventral prostata regardless

of whether the exposure was oral, parenteral or by direct injection. It should be mentioned that cadmium treatment can induce several different types of tumors in prostata, including invasive adenocarcinoma. According to the authors these results with rats support the hypothesis that cadmium may have a role in causing prostate cancer in humans.

International classifications

The IARC has classified cadmium as a human carcinogen (Group 1), meaning that there is adequate evidence of carcinogenicity from studies of both humans and experimental animals. However, recent epidemiological studies (reviewed above) do not support this assessment – notwithstanding the data indicating that cadmium can be carcinogenic to laboratory animals. The evidence that cadmium is a human carcinogen is rather weak, especially for oral exposure. A classification of cadmium as "probably carcinogenic to humans" (IARC Group 2A) would probably be more reasonable (30). This conclusion is in accord with the EU classification of some cadmium compounds (Carcinogen Category 2 with inhalation; Annex 1 to the directive 67/548/EEC).

Effects on reproduction

Teratogenic effects have been observed in experimental animals exposed to cadmium (usually after injection of high doses), whereas the few studies made of humans have been inconclusive (16, 30, 45). A study of 149 industrial workers exposed to lead at work and cadmium via smoking indicated that moderate blood levels of lead (< 400 μg/l = 2 μmol/l) and cadmium (< 10 μg/l = 90 nmol/l) can lower semen quality (61).

In summary, there is no conclusive evidence that cadmium has effects on reproduction, although the question remains open (16, 30).

Dose-effect / dose-response relationships

Exposure to cadmium concentrations exceeding 1 mg Cd/m^3 can result in acute, severe effects on the lungs (edema, pneumonitis) (45).

Relationships between cadmium dose and effects on kidneys are illustrated in Table 2. NAG and AAP in urine were measured in one study and were significantly higher at ≥ 1 than at < 0.25 nmol Cd/mmol creatinine (43).

Present Swedish regulations for biological control of occupational exposure to cadmium, with reference to the threshold values recommended by WHO, define persons "who do not run a substantial risk of kidney damage (i.e. Cd in blood < 200 nmol/l and Cd in urine < 10 nmol/mmol creatinine)" (National Swedish Board of Occupational Safety and Health, AFS 2000:7). Table 1 shows that there are clear relationships between exposure to airborne cadmium, absorbed dose (blood, urine) and tubular proteinuria, and that damage to renal tubuli can develop at cadmium concentrations much lower than those previously considered safe.

Table 2. Dose-effect relationships between cadmium dose (measured in urine and/or blood) and effects on kidneys.

Dose measure		Effect	Ref.
U-Cd (nmol/mmol creatinine)	B-Cd (nmol/l)		
<0.25 – ≥1		Increasing NAG and AAP with increasing U-Cd, significantly higher at U-Cd ≥ 1 nmol/mmol than at < 0.25.	43
1 - 3		Damage to renal tubuli (proteinuria)	8, 33
	50 - 75	Glomerular damage (reduced GFR)	29
> 4	> 60	Kidney stones	27

Studies of Swedish battery workers show an elevated risk for damage to renal tubuli at about 3 nmol Cd/mmol creatinine. U-Cd above 3 nmol/mmol creatinine was associated with a 5 to 15 percent prevalence of $ß_2$-microglobulinuria (depending on age) (26). The correlation between cadmium in urine (at levels above 3 nmol/mmol creatinine) and cumulative exposure to airborne cadmium is described by the following equation (26, 28):

$$\text{Ln(U-Cd, nmol/mmol creatinine)} = -1.7 + 0.38 \times \ln(\text{cumulative air Cd}, \mu g/m^3 \times \text{years})$$

Thus a U-Cd value of 3 nmol/mmol creatinine is approximately equal to 1500 $\mu g/m^3$ x years of exposure, or in other words about 30 years of exposure to air concentrations corresponding to the exposure limits now in force in Sweden (50 $\mu g/m^3$ total dust). An air concentration calculated from U-Cd ≤ 3 nmol mmol creatinine would be altogether too uncertain. A 10% prevalence of proteinuria was found in workers aged 60 or more at levels as low as 1.5 nmol/mmol creatinine, whereas in younger workers this prevalence was seen at 5 nmol/mmol. The higher prevalence in older workers may be due to degenerative changes in the renal tubuli, since aging is associated with increasing sensitivity to cadmium and consequent acceleration of cadmium-induced tubular damage.

Studies published so far indicate that damage to renal glomeruli seldom occurs below the levels at which tubular damage occurs, but the Japanese studies have shown dose-response relationships between cadmium dose and mortality (42).

Both animal studies and human data indicate that bone damage (osteoporosis) can be a critical effect of cadmium exposure, but it is still too early to draw definite conclusions regarding the relevance of these findings to human health. It should, however, be emphasized that osteoporosis is a major public health problem and that further studies are planned to clarify the role of cadmium in development of osteoporosis. When the results of these studies are known, it may be necessary to re-evaluate the critical effect of cadmium exposure.

Conclusions

The critical effect of exposure to cadmium is probably the damage to renal tubuli, but data from two large European studies indicate that bone damage can occur at equally low levels. New data indicate an elevated risk of tubular damage at urine levels around 1 nmol Cd/mmol creatinine. The studies are based mainly on environmental exposures and air concentrations are not given. Calculation of air concentration based on such a low U-Cd level would be altogether too uncertain to provide a meaningful value.

Cadmium has been judged by the IARC to be carcinogenic to humans, but recently published data do not support this assessment.

References

1. Adamsson E, Piscator M, Nogawa K. Pulmonary and gastrointestinal exposure to cadmium oxide dust in a battery factory. *Environ Health Perspect* 1979;28:219-222.
2. Alfven T, Elinder CG, Carlsson MD, Grubb A, Hellström L, Persson B, Pettersson C, Spång G, Schutz A, Järup L. Low-level cadmium exposure and osteoporosis. *J Bone Miner Res* 2000;15:1579-1586.
3. Arisawa K, Nakano A, Saito H, Liu XJ, Yokoo M, Soda M, Koba T, Takahashi T, Kinoshita K. Mortality and cancer incidence among a population previously exposed to environmental cadmium. *Int Arch Occup Environ Health* 2001;74:255-262.
4. Barbee JY Jr, Prince TS. Acute respiratory distress syndrome in a welder exposed to metal fumes. *South Med J* 1999;92:510-512.
5. Berglund M, Åkesson A, Nermell B, Vahter M. Intestinal absorption of dietary cadmium in women is dependent on body iron stores and fiber intake. *Environ Health Perspec* 1994;102:1058-1066.
6. Bernard A, Roels H, Buchet JP, Cardenas A, Lauwerys R. Cadmium and health: the Belgian experience. *IARC Scientific Publications* 1992;118:15-33. Lyon: International Agency for Research on Cancer.
7. Bhattacharyya MH, Sacco-Gibson NA, Peterson DP. Cadmium-induced bone loss: increased susceptibility in female beagles after ovariectomy. *IARC Scientific Publications* 1992;118:279-286. Lyon: International Agency for Research on Cancer.
8. Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, DePlaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L. Renal effects of cadmium body burden of the general population. *Lancet* 1990;336:699-702.
9. Börjesson J, Bellander T, Järup L, Elinder CG, Mattsson S. In vivo analysis of cadmium in battery workers versus measurements of blood, urine and workplace air. *Occup Environ Med* 1997;54:424-431.
10. Börjesson J, Gerhardsson L, Schutz A, Perfekt R, Mattsson S, Skerfving S. Kidney cadmium as compared to other markers of cadmium exposure in workers at a secondary metal smelter. *Am J Ind Med* 2001;39:19-28.
11. Chia KS, Tan AL, Chia SE, Ong CN, Jeyaratnam J. Renal tubular function of cadmium exposed workers. *Ann Acad Med Singapore* 1992;21:756-759.
12. Corden C, Floyd P, Brooke D, Crookes M, MacCrae S, Moore L. *The Risks to Health and Environment by Cadmium used as a Colouring Agent or a Stabiliser in Polymers and for Metal Plating*. Risk & Policy Analysts Limited, J316/Cadmium, 2000.
13. Fels LM, Bundschuh I, Gwinner W, Jung K, Pergande M, Graubaum HJ, Price RG, Taylor SA, De Broe ME, Nuyts GD, Mutti A, Franchini I, Lauwerys R, Roels H, Bernard A, Gelpi

E, Rosello J, Hotter G, Stolte H. Early urinary markers of target nephron segments as studied in cadmium toxicity. *Kidney Int* 1994;46 Suppl 47:81-88.

14. Friberg L. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. *Acta Med Scand* 1950;Suppl 240:1-124.
15. Hayano M, Nogawa K, Kido T, Kobayashi E, Honda R, Turitani I. Dose-response relationship between urinary cadmium concentration and $ß_2$-microglobulinuria using logistic regression analysis. *Arch Environ Health* 1996;51:162-167.
16. Health Council of the Netherlands. *Evaluation of the effects on reproduction, recommendation for classification. Cadmium and its compounds*. The Hague: Health Council of the Netherlands, Committee for compounds toxic to reproduction 2000; publication no. 2000/04OSH.
17. Hellström L, Elinder CG, Dahlberg B, Lundberg M, Järup L, Persson B, Axelson O. Cadmium exposure and end-stage renal disease. *Am J Kidney Dis* 2001;38:1001-1008.
18. Hossn E, Mokhtar G, El-Awady M, Ali I, Morsy M, Dawood A. Environmental exposure of the pediatric age groups in Cairo City and its suburbs to cadmium pollution. *Sci Total Environ* 2001;273:135-146.
19. Hotz P, Buchet JP, Bernard A, Lison D, Lauwerys R. Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. *Lancet* 1999;354:1508-1513.
20 IARC. Cadmium and cadmium compounds. In: Beryllium, cadmium, mercury and exposure in the glass manufacturing industry. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 58*. Lyon: International Agency for Research on Cancer, 1993;58:119-237.
21. Iwata K, Saito H, Moriyama M, Nakano A. Follow up study of renal tubular dysfunction and mortality in residents of an area polluted with cadmium. *Br J Ind Med* 1992;49:736-737.
22. Iwata K, Saito H, Moriyama M, Nakano A. Association between renal tubular dysfunction and mortality among residents in a cadmium-polluted area, Nagasaki, Japan. *Tohoku J Exp Med* 1991;164:93-102.
23. Jakubowski M, Razniewska G, Halatek T, Trzcinka-Ochocka M. Integrated index of occupational exposure to cadmium as a predictor of kidney dysfunction. *IARC Scientific Publications* 1992;118:319-324. Lyon: International Agency for Research on Cancer.
24. Järup L, Rogenfelt A, Elinder CG, Nogawa K, Kjellström T. Biological half-time of cadmium in the blood of workers after cessation of exposure. *Scand J Work Environ Health* 1983;9:327-331.
25. Järup L, Elinder CG, Spång G. Cumulative blood-cadmium and tubulara proteinuria: a dose-response relationship. *Int Arch Occup Environ Health* 1988;60:223-229.
26. Järup L. *Dose-response Relations for Occupational Exposure to Arsenic and Cadmium*. Doctoral Thesis, Karolinska Institutet. Arbete och Hälsa 1992;38:1-50. National Institute of Occupational Health, Solna, Sweden.
27. Järup L, Elinder C-G. Incidence of renal stones among cadmium exposed bettery workers. *Br J Ind Med* 1993;50:598-602.
28. Järup L, Elinder C-G. Dose-response relations between urinary cadmium and tubular proteinuria in cadmium exposed workers. *Am J Ind Med* 1994;26:759-769.
29. Järup L, Persson B, Elinder C-G. Decreased glomerular filtration rate in cadmium exposed solderers. *Occup Environ Med* 1995;52:818-822.
30. Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure – a review of the literature and a risk estimate. *Scand J Work Environ Health* 1998;24 Suppl 1:1-51.
31. Järup L, Alfven T, Persson B, Toss G, Elinder CG. Cadmium may be a risk factor for osteoporosis. *Occup Environ Med* 1998;55:435-439.

32. Järup L, Bellander T, Hogstedt C, Spång G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup Environ Med* 1998;55:755-759.

33. Järup L, Hellström L, Alfven T, Carlsson MD, Grubb A, Persson B, Pettersson C, Spång G, Schutz A, Elinder CG. Low level exposure to cadmium and early kidney damage: the OSCAR study. *Occup Environ Med* 2000;57:668-672.

34. Kolonel LN. Association of cadmium with renal cancer. *Cancer* 1976;37:1782-1787.

35. Kopp SJ, Glonek T, Perry HM Jr, Erlanger M, Perry EF. Cardiovascular actions of cadmium at environmental exposure levels. *Science* 1982;217:837-839.

36. Lundberg P (ed). *Scientific Basis for Swedish Occupational Standards XIII*. Arbete och Hälsa 1992;47:66-73. National Institute of Occupational Health, Solna, Sweden.

37. Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, McCredie M, Adami HO. International renal-cell cancer study. IV. Occupation. *Int J Cancer* 1995;61:601-605.

38. Miettinen OS. Standardization of risk ratios. *Am J Epidemiol* 1972;96:383-388.

39. Mueller PW, Paschal DC, Hammel RR, Klincewicz SL, MacNeil ML, Spierto B, Steinberg KK. Chronic renal effects in three studies of men and women occupationally exposed to cadmium. *Arch Environ Contam Toxicol* 1992;23:125-136.

40. Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M, Kitagawa Y, Kawano S, Ishizaki M, Sugita N, Nishi M, Kido T, Nogawa K. Prognostic factors of renal dysfunction induced by environmental cadmium pollution. *Environ Res* 1994;64:112-121.

41. Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M, Miura K, Takahara H, Kawano S, Nishi M, Mizukoshi K, Kido T, Nogawa K. Mortality of inhabitants in an area polluted by cadmium: 15 year follow up. *Occup Environ Med* 1995;52:181-184.

42. Nishijo M, Nakagawa H, Morikawa M, Tabata M, Miura T, Yoshita K, Higashiguchi K, Seto T, Kido T, Nogawa K, Mizukoshi K, Nishi M. Relationship between urinary cadmium and mortality among inhabitants living in a cadmium polluted area in Japan. *Toxicol Lett* 1999;108:321-327.

43. Noonan CW, Sarasua SM, Campagna D, Kathman SJ, Lybarger JA, Mueller PW. Effects of exposure to low levels of environmental cadmium on renal biomarkers. *Environ Health Perspect* 2002;110:151-155.

44. Nordberg GF, Kjellström T, Nordberg M. Kinetics and metabolism. In: Friberg L, Elinder C-G, Kjellström T, Nordberg GF, eds. *Cadmium and Health: A Toxicological and Epidemiological Appraisal, Volume I. Exposure, dose and metabolism*. Boca Raton, Florida: CRC Press, Inc 1985.

45. Nordberg GF. *Criteria Documents from the Nordic Expert Group 1992*. Cadmium. Arbete och Hälsa 1993;1:85-124. National Institute of Occupational Health, Solna, Sweden.

46. Pearce N, Checkoway H, Shy C. Time-related factors as potential confounders and effect modifiers in studies based on an occupational cohort. *Scand J Work Environ Health* 1986;12:97-107.

47. Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. *Int J Epidemiol* 2000;29:1014-1024.

48. Potts CL. Cadmium proteinuria. The health of battery workers exposed to cadmium oxide dust. *Ann Occup Hyg* 1965;8:55-61.

49. Rhomberg W, Schmoll HJ, Schneider B. High frequency of metalworkers among patients with seminomatous tumors of the testis: a case-control study. *Am J Ind Med* 1995;28:79-87.

50. Roels H, Djubgang J, Buchet JP, Bernard A, Lauwerys R. Evolution of cadmium-induced renal dysfunction in workers removed from exposure. *Scand J Work Environ Health* 1982;8:191-200.

51. Rossman TG, Roy NK, Lin WC. Is cadmium genotoxic? *IARC Scientific Publications* 1992;118:367-375. Lyon: International Agency for Research on Cancer.

52. Schwartz GG, Reis IM. Is cadmium a cause of human pancreatic cancer? *Cancer Epidemiol Biomarkers Prev* 2000;9:139-145.

53. Seidal K, Jörgensen N, Elinder CG, Sjögren B, Vahter M. Fatal cadmium-induced pneumonitis. *Scand J Work Environ Health* 1993;19:429-431.

54. Siemiatycki J, Dewar R, Nadon L, Gerin M. Occupational risk factors for bladder cancer: results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol* 1994;140:1061-1080.

55. Sorahan T, Lister A, Gilthorpe MS, Harrington JM. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. *Occup Environ Med* 1995;52:804-812.

56. Sorahan T, Lancashire RJ. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. *Occup Environ Med* 1997;54:194-201.

57. Staessen JA, Lauwerys RR, Ide G, Roels HA, Vyncke G, Amery A. Renal function and historical environmental cadmium pollution from zinc smelters. *Lancet* 1994;343:1523-1527.

58. Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, Fagard R. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. *Lancet* 1999;353:1140-1144.

59. Staessen JA, Nawrot T, Hond ED, Thijs L, Fagard R, Hoppenbrouwers K, Koppen G, Nelen V, Schoeters G, Vanderschueren D, Van Hecke E, Verschaeve L, Vlietinck R, Roels HA. Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. *Lancet* 2001;357:1660-1669.

60. Stayner L, Smith R, Thun M, Schnorr T, Lemen R. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann Epidemiol* 1992;2:177-194.

61. Telisman OS, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocic B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. *Environ Health Perspect* 2000;108:45-53.

62. Teraoka S, Toma H, Nihei H, Ota K, Babazono T, Ishikawa I, Shinoda A, Maeda K, Koshikawa S, Takahashi T, Sonoda T. Current status of renal replacement therapy in Japan. *Am J Kidney Dis* 1995;25:151-164.

63. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers – an update. *J Natl Cancer Inst* 1985;74:325-333.

64. Tsuchiya K. Health effects of cadmium with special reference to studies in Japan. *IARC Scientific Publications* 1992;118:35-49.

65. Viaene MK, Roels HA, Leenders J, De Groof M, Swerts LJ, Lison D. Masschelein R. Cadmium: a possible etiological factor in peripheral polyneuropathy. *Neurotoxicology* 1999;20:7-16.

66. Viaene MK, Masschelein R, Leenders J, De Groof M, Swerts LJ, Roels HA. Neurobehavioural effects of occupational exposure to cadmium: a cross sectional epidemiological study. *Occup Environ Med* 2000;57:19-27.

67. Waalkes MP, Rehm S. Cadmium and prostate cancer. *J Toxicol Environ Health* 1994;43:251-269.

68. Waalkes MP. Cadmium carcinogenesis in review. *J Inorg Biochem* 2000;79:241-244.

69. WHO. *Environmental Health Criteria 119*. Principles and Methods for the Assessment of Nephrotoxicity Associated with Exposure to Chemicals. Geneva: International Programme on Chemical Safety, Commission of the European Communities, World Health Organization, 1991.

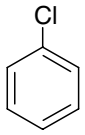
70. WHO. *Environmental Health Criteria 134*. Cadmium. Geneva: International Programme on Chemical Safety, World Health Organization, 1992.

Consensus Report for Chlorobenzene

April 2, 2003

This Consensus Report is based on a criteria document compiled jointly by the National Institute of Occupational Safety and Health (NIOSH) in the USA and the Swedish Criteria Group (5), and on a document from DFG (1). The Criteria Group published a previous Consensus Report on chlorobenzene in 1993 (8).

Physical and chemical data. Uses

CAS No.	108-90-7
Synonyms:	monochlorobenzene, benzene chloride, phenyl chloride
Formula:	C_6H_5Cl
Structure:	
Molecular weight:	112.56
Melting point:	- 45 °C
Density:	1.11 g/ml (20 °C)
Boiling point:	131 - 132 °C
Vapor pressure:	1.58 kPa (25 °C)
Flash point:	28 °C
Saturation concentration:	15,600 ppm
Distribution coefficient: (n-octanol/water)	log P_{ow}: 2.84
Conversion factors (20 °C):	1 ppm = 4.60 mg/m^3 1 mg/m^3 = 0.217 ppm

At room temperature chlorobenzene is a clear liquid with an odor similar to that of benzene. The odor threshold is reported to be between 1 and 3 mg/m^3 (0.21 -- 0.68 ppm). Chlorobenzene is insoluble in water but dissolves readily in oils and mixes with alcohol, chloroform, benzene and other organic solvents. Chlorobenzene is used industrially in chemical syntheses and as a solvent and de-greaser.

Uptake, biotransformation, excretion

Chlorobenzene can be absorbed via the lungs and digestive tract. No data on skin uptake were found (5). When radioactively labeled chlorobenzene was given to rats, the radioactivity was rapidly distributed to body organs: the highest concentration was in fatty tissue, followed by kidney, liver and brain (5).

Chlorobenzene is metabolized primarily by the P-450 system (CYP2E1 and CYP3A) in various organs (mostly the liver) and excreted in urine. Electrophilic epoxides are formed as intermediates and are conjugated to water-soluble metabolites by glutathione transferases. Hydroxylated metabolites such as methachlorophenol are also formed: these are further metabolized to water-soluble compounds, usually via glutathione conjugation. The toxic effects of chlorobenzene are attributed to the formation of epoxides and their ability to bind to macromolecules (3, 5). It has been found that chlorobenzene is metabolized differently by different species and that CYP2E1 plays the largest role in its biotransformation (15). Human liver microsomes have higher transformation activity than liver microsomes from rodents (rats and mice), and are thus more efficient metabolizers of chlorobenzene. The human microsomes produced a smaller amount of covalently bound metabolites, however (15). This study also revealed large individual differences in the amount of CYP2E1 in human liver microsomes, with some containing up to five times as much as others. Epoxides are inactivated by the enzyme epoxide hydrolase, and its activity has been shown to be greater in human liver than in rodent liver (4). This may mean that humans are less sensitive to epoxide-mediated toxicity, but it is possible that the simultaneously formed catechols also have toxic properties (6).

The metabolites 4-chlorocatechol, 2-chlorophenol, 3-chlorophenol, 4-chlorophenol and 4-chlorophenylmercapturic acid have been identified in the urine of humans exposed to chlorobenzene (12). The main metabolite formed in people exposed on the job or in inhalation experiments has been found to be 4-chlorocatechol (75% of the metabolites in urine) (10). In animal studies, 60% of the chlorobenzene dose has been identified in urine as 4-chlorophenylmercapturic acid, regardless of exposure path (1, 11). In an inhalation study, volunteers were exposed to 10 ppm (46 mg/m^3) chlorobenzene 8 hours/day for 5 days: a two-phase elimination of chlorobenzene in blood was reported, with a half time of 53 minutes during the first hour of exposure and 150 minutes thereafter. The half times for metabolites in blood were 6.4 hours for 4-chlorocatechol and 12.4 to 16.5 hours for the chlorophenols (13% of the metabolites in urine). Eighty percent of the total amount of metabolites was excreted in urine within 16 hours. No accumulation of chlorobenzene or its metabolites was registered during the week of exposure (10). No effects on health were mentioned in the article (10). 4-chlorocatechol in urine has been proposed as a biological exposure indicator for chlorobenzene (1, 5).

Toxic effects

Human data

There are a few studies (older case reports of acute poisoning) that describe symptoms in exposed persons. In acute poisoning in cases of attempted suicide the toxic picture is dominated by severe effects on the central nervous system (1, 5). In a Japanese study, 5 volunteers (the authors of the article) were exposed to 275 mg/m^3 chlorobenzene for 7 hours (3 hours in the morning and 4 in the afternoon). The exposure elicited subjective symptoms such as drowsiness (in all five), headache ("75%") and throbbing pain in the eyes ("50%"). Some deterioration in the results of a neuropsychological test (flicker fusion) was noted after the first 3 hours of exposure, but was no longer measurable after the afternoon exposure session (17).

Animal data

The acute toxicity of chlorobenzene is relatively low. The LC_{50} for various laboratory animals has been found to be above 8000 mg/m^3 with at least 6 hours of exposure, and the lowest LD_{50} values are above 1000 mg/kg. Chlorobenzene in high doses has effects on the nervous system: tremor, muscular spasms, breathing difficulty, drowsiness, ataxia and paralysis (5).

Repeated exposure to chlorobenzene, whether in oral doses or by inhalation, has been shown to damage liver and kidneys. Typical indications of liver damage are increase of ALAT and ASAT and effects on liver weights. Increased liver weights are reported after single doses above 200 mg/kg. In an 11-week inhalation study with rats, the LOEL (Lowest Observed Effect Level) for increased liver weight (hypertrophy) was 230 mg/m^3 (the lowest exposure level) (14). In a 13-week study in which rats were given chlorobenzene orally, the LOEL for this effect was 125 mg/kg and the NOEL (No Observed Effect Level) was 60 mg/kg (9).

In a 13-week study with mice (oral administration), the LOEL for dilation of renal tubules and interstitial nephritis (kidney inflammation) was 250 mg/kg/day and the NOEL 125 mg/kg/day (9). In an 11-week inhalation study with rats, the LOEL for this effect was 690 mg/m^3 and the NOEL 230 mg/m^3 (14).

Effects on other organs have also been reported. Mice exposed to 250 mg/kg chlorobenzene daily for 13 weeks had reduced numbers of lymphoid and myeloid cells in the spleen and necroses in the thymus (NOEL 125 mg/kg/day). In the same study, bone marrow depression was seen in rats after 13 weeks of exposure to 500 mg/kg/day chlorobenzene (NOEL 250 mg/kg/day) (9). Elevated lung weights were registered in rabbits that had been exposed to 345 mg/m^3 chlorobenzene for 24 weeks (5). In an inhalation study, mice (5 males and 5 females per group) were exposed to 100 mg/m^3 chlorobenzene 7 days/week for 3 months: the exposure resulted in leucopenia and effects on bone marrow (18). Exposure conditions are poorly described, however, and the concentration in the exposure chamber may have been uneven and dose estimates consequently either too high

or too low. In a more recent study with oral exposures, the reported NOEL for similar effects is 250 mg/kg for rats and 125 mg/kg for mice (9).

Chlorobenzene is moderately irritating to skin and eyes, but showed no sensitizing effect on guinea pigs in the Guinea Pig Maximization Test (1).

Genotoxicity, carcinogenicity

It is suspected that chlorobenzene may be a low-potency genotoxic substance, since some studies indicate that it is genotoxic although most of them do not (1, 5). The question of chlorobenzene's genotoxicity is discussed in greater detail in the Criteria Document (5). Results have been negative in most genotoxicity tests with bacteria (1, 5). However, chlorobenzene was mutagenic in a mouse lymphoma test, both with and without metabolic activation. No DNA-damaging effects have been detected either in bacterial tests or in an "unscheduled DNA synthesis" test with mammalian cells. Chlorobenzene showed no clastogenic activity in Chinese hamster ovary (CHO) cells, but there was an increase in the number of sister chromatid exchanges (SCE) in CHO cells in the absence of metabolizing systems. Most *in vivo* studies have produced negative results. Negative results were obtained in the recessive lethal test with *Drosophila melanogaster*. Tests for chromosome aberrations and micronuclei have also been negative. Positive results were obtained in one *in vivo* test for micronuclei, but the validity of this result has been questioned (1). Weak covalent binding to DNA has been shown both *in vivo* and *in vitro*. Binding to RNA and protein has also been demonstrated *in vivo* after an intraperitoneal injection of chlorobenzene (3). An adduct, N^7-phenylguanine, has been identified in the urine of rats exposed to chlorobenzene (11).

Chlorobenzene was tested for carcinogenic activity in a cancer study (16). Groups of 50 rats and mice were given chlorobenzene orally for 103 weeks. The only significant effect was an increased occurrence of benign neoplastic nodules in the livers of the male rats exposed to the highest dose (120 mg/kg) (untreated controls: 4/50; vehicle (corn oil) only: 2/50; 60 mg/kg: 2/50; 120 mg/kg: 8/49). One female rat in the high-dose group had tubular adenocarcinoma in kidneys. One male in the low-dose group and one in the high-dose group had transitional-cell papillomas in the urinary bladder. This was given specific mention since these tumor forms are extremely rare in rats (0/789 and 0/788 in historic controls). Despite this result, the EPA (2) has stated that for chlorobenzene there is "inadequate evidence of carcinogenicity " (Group D).

Effects on reproduction

An exposure of 2714 mg/m^3 6 hours/day on days 6 - 15 of gestation induced skeletal anomalies in fetuses of rats and rabbits. However, since the exposure was also toxic to the mothers, the authors did not regard this as an indication of teratogenic effect (7). In a two-generation study animals were exposed to up to 2070 mg/m^3 chlorobenzene 6 hours/day, 7 days/week for 11 weeks. The F_1

generation had elevated liver weights (690 mg/m^3 and higher), but no fetotoxic effects or effects on fertility were observed (14). However, there were degenerative changes in germinal cell epithelium in testes (LOEL 690 mg/m^3; NOEL 230 mg/m^3).

Dose-response / dose-effect relationships

There are no data on which to base a dose-response or dose-effect relationship for humans. The five subjects in an exposure-chamber study (275 mg/m^3) reported subjective symptoms such as drowsiness, headache and a throbbing ache in the eyes and had poorer results on a neuropsychological test. As for long-term animal studies, the LOEL and NOEL values and the observed effects are given in Table 1. The LOEL values for effects on the liver are about the same for inhalation and oral administration. There is an inhalation study describing effects on bone marrow at an exposure level of 100 mg/m^3, but the exposure conditions leave room for error and these results are contradicted by a 2-year study in which no similar effects were observed.

Table 1. Effects on laboratory animals exposed to chlorobenzene.

Exposure	Species	Effect	Ref.
Inhalation, 11 weeks 690 mg/m^3 230 mg/m^3	Rat	Degeneration of germinal epithelium in testes LOEL NOEL	14
Inhalation, 11 weeks 690 mg/m^3 230 mg/m^3	Rat	Interstitial nephritis LOEL NOEL	14
Inhalation, 24 weeks 345 mg/m^3	Rabbit	Increased lung weight	5
Inhalation, 11 weeks 230 mg/m^3	Rat	Increased liver weight LOEL	14
Gavage, 5 days/week, 13 weeks 500 mg/kg/day 250 mg/kg/day	Rat	Effects on bone marrow LOEL NOEL	9
Gavage, 5 days/week, 13 weeks 250 mg/kg/day 125 mg/kg/day	Mouse	Interstitial nephritis LOEL NOEL	9
Gavage, 5 days/week, 13 weeks 250 mg/kg/day 125 mg/kg/day	Mouse	Lymphoid and myeloid cell depletion in spleen LOEL NOEL	9
Gavage, 5 days/week, 13 weeks 125 mg/kg/day 60 mg/kg/day	Rat	Higher liver weights LOEL NOEL	9

Conclusions

There are no data that can serve as a basis for establishing a critical effect of occupational exposure to chlorobenzene. The subjects in an exposure chamber study reported CNS effects (subjective symptoms) at a concentration of 275 mg/m^3. In animal experiments, liver enlargement has been observed (LOEL 230 mg/m^3 for 11 weeks), and at high exposure levels effects on kidneys and testes. Chlorobenzene can also affect bone marrow, but it is not clear whether this occurs at the LOEL for effects on the liver. Judging from animal experiments in which chlorobenzene was given by gavage, effects on bone marrow occur at higher exposure levels.

References

1. DFG (Deutsche Forschungsgemeinschaft). *Critical data evaluation for MAK values and classification of carcinogens. Occupational toxicants*. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Weinheim: VCH-Verlagsgesellschaft, 1999.
2. EPA. Health effects assessment of chlorobenzene, (US). Environmental Protection Agency, Chincinnati, OH, EPA/600/8-89/009; National Technical Information Service, PB90-142514, USA.
3. Grilli S, Arfellini G, Colacci A, Mazzullo M, Prodi G. In vivo and in vitro covalent binding of chlorobenzene to nucleic acids. *Jpn J Cancer Res* 1985;76:745-751.
4. Guenther TM, Luo G. Investigation of the role of the 2,3-epoxidation pathway in the bioactivation and genotoxicity of dietary allylbenzene analogs. *Toxicology* 2001;160:47-58.
5. Hellman B. *NIOH and NIOSH Basis for an Occupational Standard*. Chlorobenzene. Arbete och Hälsa 1992;31:1-73. National Institute of Occupational Health, Solna, Sweden.
6. IARC. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol 71. Lyon: International Agency for Research on Cancer 1999;71:433.
7. John JA, Hayes WC, Hanley TR, Johnson KA, Gushow TS, Rao KS. Inhalation teratology study on monochlorobenzene in rats and rabbits. *Toxicol Appl Pharmacol* 1984;76:365-373.
8. Lundberg P (ed). *Scientific Basis for Swedish Occupational Standards*. XIV. Arbete och Hälsa 1993;37:10-20. National Institute of Occupational Health, Solna, Sweden.
9. Kluwe WM, Dill G, Persing R, Peters A. Toxic responses to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. *J Toxicol Environ Health* 1985;15:745-767.
10. Knecht U, Woitowitz H-J. Human toxicokinetics of inhaled monochlorobenzene: latest experimental findings regarding re-evaluation of the biological tolerance value. *Int Arch Environ Health* 2000;73:543-554.
11. Krewet E, Müller G, Norpoth K. The excretion of chlorophenylmercapturic acid, chlorophenols and a guanine adduct in the urine of chlorobenzene-treated rats after phenobarbital treatment. *Toxicology* 1989;59:67-79.
12. Kumagai S, Matsunaga I. Concentrations of urinary metabolites in workers exposed to monochlorobenzene and variation in the concentration during a workshift. *Occup Environ Med* 1994;51:120-124.
13. Kusters E, Lauwerys R. Biological monitoring of exposure to monochlorobenzene. *Int Arch Occup Environ Health* 1990;62:329-331.

14. Nair RS, Bartel JA, Schroeder RE, Knezevich A, Stack CR. A two generation reproduction study with monochlorobenzene vapor in rats. *Fundam Appl Toxicol* 1987;9:678-686.

15. Nedelcheva V, Gut I, Soucek P, Frantik E. Cytochrome P450 catalyzed oxidation of monochlorobenzene, 1,2- and 1,4-dichlorobenzene in rat, mouse, and human liver microsomes. *Chemico-Biol Interact* 1998;115:53-70.

16. NTP. *Toxicology and carcinogenesis studies of chlorobenzene (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). Technical report 261*. Research Triangle Park, NC: National Toxicology Program 1985:1-220.

17. Ogata M, Taguchi T, Hirota N, Shimada Y, Nakae S. Quantitation of urinary chlorobenzene metabolites by HPLC: concentrations of 4-chlorocatechol and chlorophenols in urine and of chlorobenzene in biological specimens of subjects exposed to chlorobenzene. *Int Arch Occup Environ Health* 1991;63:121-128.

18. Zub M. Reactivity of the white blood cell system to toxic action of benzene and its derivatives. *Acta Biol Cracoviencia Ser Zoologica* 1978;21:163-174.

Consensus Report for Lithium and Lithium Compounds

June 4, 2003

This report is based on a criteria document compiled by the Nordic Expert Group (16).

Chemical and physical data

Substance (Synonym)	Chemical formula	Molecular weight	CAS no.
Lithium	Li	6.94	7439-93-2
Lithium hydride	LiH	7.95	7580-67-8
Lithium aluminum hydride (Li-tetrahydroaluminate)	$LiAlH_4$	37.95	16853-85-3
Lithium borohydride (Li-tetrahydroborate)	$LiBH_4$	21.78	16949-15-8
Lithium oxide	Li_2O	29.88	12057-24-8
Lithium hydroxide	LiOH	23.95	1310-65-2
Lithium hydroxide monohydrate	$LiOH{\cdot}H_2O$	41.96	1310-66-3
Lithium nitride	Li_3N	34.83	26134-62-3
Lithium amide	$LiNH_2$	22.95	7782-89-0
Lithium nitrate	$LiNO_3$	68.94	7790-69-4
Lithium carbonate	Li_2CO_3	73.89	554-13-2
Lithium sulfate	Li_2SO_4	109.94	10377-48-7
Lithium fluoride	LiF	25.94	7789-24-4
Lithium chloride	LiCl	42.39	7447-41-8
Lithium bromide	LiBr	86.84	7550-35-8
Lithium acetate	$LiCH_3COO$	65.99	546-89-4
Lithium acetate, dihydrate	$LiCH_3COO{\cdot}2\ H_2O$	102.01	6108-17-4
Lithium citrate	$Li_3C_3H_4(OH)(COO)_3$	209.92	919-16-4
Lithium neodekanoate	$LiC_9H_{19}COO$	178.24	27253-30-1
Lithium stearate	$LiC_{17}H_{35}COO$	290.42	4485-12-5
Lithium 12-hydroxystearate	$LiC_{17}H_{34}(OH)COO$	306.41	7620-77-1

Lithium is a soft, silver-white alkali metal. It oxidizes rapidly on contact with air and develops a coating of gray oxide. Lithium can have an oxidation state of either 0 or +1. On contact with water lithium breaks down the H_2O molecules, releasing hydrogen gas and leaving a strongly alkaline solution of lithium hydroxide. Some other lithium compounds, notably the hydride, nitride, oxide, amide and carbonate, are also alkaline either *per se* or due to their formation of lithium hydroxide. For lithium compounds, solubility in water varies. The

hydroxide dissolves readily in water, as do lithium chloride, lithium bromide and some of the others (12, 16).

Occurrence, use

Lithium occurs naturally in low concentrations, but with considerable geographic variation. Small amounts are in drinking water and various foods: total daily intake of lithium has been estimated to be at most a few mg. Bottled mineral water, however, may contain as much as 5.2 mg Li/liter (0.7 mmol Li/l), and consumption of mineral supplements can add a further 5 – 6 mg (0.7 – 0.9 mmol) Li/day. Lithium oxide is obtained from ore, and other lithium compounds and metallic lithium are produced by further processing. Lithium salts are also extracted from natural salt lakes (16). Lithium and lithium compounds are used in batteries, as catalysts, and as reagents in organic syntheses. Metallic lithium is also used in alloys and in the production of some lithium compounds. Lithium carbonate is the most important compound in industrial use and is the material from which many lithium salts are produced. The substance is also used in aluminum production, as flux in production of glass, glazes and ceramics, and in the construction industry. Another industrially important lithium compound is lithium hydroxide. It is used mostly for production of lithium stearate, an ingredient in e.g. lubricating oils. Lithium salts of fatty acids have uses ranging from vehicle production to cosmetics. Lithium chloride and lithium bromide are used in air conditioning systems to bind moisture. Lithium halides (lithium chloride, lithium fluoride) are also used as fluxes in welding and soldering. Some lithium compounds (the carbonate, citrate, sulfate and acetate) are used medicinally. In Sweden in 2000, the primary consumers of lithium were the glass and engineering industries, motor vehicle production and maintenance, and the pulp and paper industry (16).

Uptake, distribution, excretion

Lithium is absorbed rapidly and completely by the digestive tract, although the exact rate of absorption depends largely on the solubility of the lithium compound in question. One study reports that, after a dilute solution of lithium chloride was given orally to human subjects, maximum serum levels of lithium were reached within 30 to 60 minutes and a plateau was reached after 12 to 24 hours (16). The defined daily dose in Sweden for lithium treatment of affective disorders is 167 mg Li, although the necessary dose varies considerably from patient to patient. The recommended serum level 12 hours after the most recent dose is generally 0.5 to 0.8 mmol Li/l, but in a few cases can be 0.9 to 1.2 mmol Li/l (16).

Human data also indicate that uptake of lithium via respiratory passages can be fairly high, whereas uptake of lithium or lithium compounds via skin is regarded as negligible. Uptake of lithium (dissolved in moisture) has been reported in patients who had used respirators containing a lithium chloride coated heat and moisture exchange unit for at least 5 days. Serum lithium rose from below the

detection limit to 0.01 – 0.05 mmol/l or even as high as 0.1 mmol/l, and dropped back below the detection limit within a few days after use of the respirator was discontinued. A 7-year-old girl on a respirator was observed to have fluctuating levels of lithium in serum, with a peak of 3.9 mmol/l on day 16. The authors estimated that the amount of lithium chloride inhaled daily by adults using a respirator with a new heat and moisture exchange unit (changed daily) amounted to 80% of its lithium content, and was equivalent to a daily oral dose of 100 mg lithium chloride or about 16 mg (2.3 mmol) Li. This is approximately a tenth of the daily dose of lithium carbonate recommended for psychiatric patients. The above data indicate, however, that clinically relevant and even toxic levels can arise in children. Another work reports that more than 90% of the lithium chloride in a new heat and moisture exchange unit had been deposited in a test lung after 20 minutes. However, a much lower inhalation uptake (17%) was measured in rats with normal respiration rate that were exposed for 3 hours to lithium chloride in aerosol form (from a solution containing 1% lithium) (16).

After uptake, lithium is distributed throughout the body, although little of it is metabolized. The amount that binds to proteins in plasma or tissues is probably quite small. At steady state (in human subjects), levels in liver, erythrocytes and brain are lower than in serum, and levels in kidney, thyroid and bone are higher than in serum. In humans, the distribution phase of lithium in serum and plasma has a half time of about 2 to 6 hours. Excretion is primarily via the kidneys: over 95% of a single oral dose is excreted via the kidneys in unchanged form. One-third to two-thirds of the dose is excreted in the first 6 to 12 hours and the rest over the following 14 days. Lithium is freely filtered through the glomeruli, but about 80% of it is resorbed along with sodium and water, mostly in the proximal tubuli. With repeated administration, excretion of lithium rises during the first five or six days until steady state is reached. For a single dose, the half time for the elimination phase is 12 to 27 hours, but it can be as long as 58 hours for older people or with long-term administration. Lithium passes the placental barrier, and blood concentrations in maternal and umbilical blood are about the same. Lithium is also secreted in breast milk. Levels in human breast milk are about 50% of levels in serum (16).

Toxic effects

Human data

Intake of a single dose of lithium can cause acute poisoning. In such cases the symptoms of poisoning are less severe and the poisoning is less dangerous than other types of lithium poisoning, since the half time for elimination of lithium is shorter in previously unexposed persons. The serum lithium level can be high — over 4 mmol/l — without causing clinical symptoms of toxicity. Intake of a single large dose of lithium, however, usually results in vomiting and diarrhea (16).

Poisoning can also appear in patients who have been taking lithium for some time but whose serum levels have risen because of dose increases or deterioration

in kidney function. Serum levels of 1.2 to 1.6 mmol Li/l are commonly associated with a risk of poisoning, but toxic symptoms can also appear at recommended therapeutic doses. The clinical picture of lithium intoxication is only weakly correlated to the concentration of lithium in serum. Side effects are common with therapeutic doses, i.e. with serum or plasma levels around 0.5 to 1.2 mmol Li/l (measured 12 hours after administered dose). Some of the more common side effects at a 12-hour serum lithium level of 0.5 to 0.8 mmol/l are moderate nephrogenic diabetes insipidus, fine hand tremor, weight gain, elevated levels of thyroid-stimulating hormones and hypothyroidism (16).

There are few studies of the effects of occupational exposure to lithium. In a sketchily reported NIOSH study of personnel at a factory producing battery systems, it is stated that workers in departments with higher lithium exposure reported fewer health problems (poorly defined) than workers in a department where lithium exposure was generally lower (17). Air concentrations (whole-shift, personal monitors) were reported to be up to 0.12 mg Li/m^3, and serum levels up to 1.6 μmol Li/l. The authors concluded that, if earlier exposure levels were of the same magnitude as those measured, it was very unlikely that lithium exposure at the factory could cause toxic effects or side effects like those observed in psychiatric patients.

Another NIOSH report (23) gives the frequency of several symptoms (from questionnaires) in workers with various degrees of exposure to alkaline lithium dust in a plant where lithium compounds were produced. In a comparison between 21 workers judged to be "exposed" and 23 workers judged to be "less exposed" (57% and 39% smokers, respectively) it was found that complaints involving the upper respiratory passages were more common among the "exposed" workers. Sinus problems were reported by 43% (vs. 39%), runny noses by 38% (vs. 17%), nosebleeds by 14% (vs. 0%), and dry throats by 52% (vs. 4%). Some other symptoms, notably headaches (38% vs. 9%) and skin irritation (38% vs. 13%), were also more common among the "exposed" workers. Symptoms of irritation, especially sinus problems and runny noses, were reported to be most severe among workers who bagged lithium hydroxide (pH 12.6) and lithium carbonate (pH 11.2), and several workers complained of skin irritation and painful burns from exposure to lithium hydroxide. Both personal and stationary monitors were used to measure total dust and respirable dust, with specific analysis of lithium content. The lithium levels in air (in total dust) registered by personal monitors at these workplaces (bagging areas for lithium hydroxide and lithium carbonate) were 0.02 – 0.05 and 0.54 – 1.84 mg Li/m^3, respectively. In an area where lithium carbonate was ground, the lithium level in air (in total dust) registered by personal monitors was 1.08 – 3.53 mg Li/m^3. Blood samples were taken from 18 "exposed" and 6 "less exposed" workers, and lithium levels in blood were below the detection limit (0.1 mmol/l) in all but two of the samples. These two samples were taken from two workers before a workshift, and contained 0.14 and 0.3 mmol Li/l. There was no measurable increase in blood lithium content during the shift (23).

Pronounced irritation of mucous membranes has also been reported with exposure to 2 mg/m^3 lithium/aluminum dust (lithium content up to 2.5% of the alloy) (4). Further, lithium hydride, lithium tetrahydroaluminate and lithium tetrahydroborate are reported to be both irritating and caustic (5, 7, 8, 18), although there are little data on the air concentrations involved. However, unpublished studies quoted in Patty's (3) and the ACGIH document (1) report symptoms of irritation in workers exposed to very low air concentrations of lithium hydride (no information is given on exposure times or number of workers). Patty's reports the data as follows: no effects observed in the concentration interval 0 – 0.025 mg LiH/m^3; tickling in the nose and sniffles at 0.025 – 0.10 mg LiH/m^3 (but these air concentrations were tolerable for workers accustomed to the exposure); and pronounced nasal irritation and some coughing at concentrations between 0.10 and 0.50 mg LiH/m^3 (this level was not tolerable). At levels between 0.50 and 1.0 mg LiH/m^3 nasal irritation and coughing were pronounced, and some subjects had irritated eyes. At air concentrations between 1 and 5 mg LiH/m^3 all these effects were severe and skin irritation was also seen. Skin irritation also occurred at lower air concentrations during hot weather or in connection with perspiration. The ACGIH document presents the information as follows: the maximum air concentration tolerable for short periods is 0.5 mg LiH/m^3. At 0.05 mg LiH/m^3 workers rapidly become acclimated, but this concentration is unpleasant for individuals who are not accustomed to it. Persons more accustomed to exposure complained of nose and eye irritation at levels above 0.1 mg LiH/m^3 and itching of exposed skin at levels exceeding approximately 0.2 mg LiH/m^3.

Animal data

Single oral doses of various lithium compounds have moderate acute toxicity. The LD_{50} for oral administration of lithium chloride was reported to be 757 mg/kg b.w. for rats and 850 mg/kg b.w. for rabbits, equivalent respectively to 124 and 139 mg (18 and 20 mmol) Li/kg b.w. For oral administration of lithium carbonate, the reported LD_{50} is 500 mg/kg b.w. for dogs and 710 mg/kg b.w. for mice, or respectively 94 and 133 mg (14 and 19 mmol) Li/kg b.w. (16).

In one study with rats, the LC_{50} (death within 14 days) was calculated to be 1800 mg/m^3 for 4 hours of exposure to an aerosol containing 80% lithium carbonate and 20% lithium hydroxide and lithium oxide (aerosol 1) (11). The corresponding LC_{50} (rats, 4 hours, 14 days) was 960 mg/m^3 for an aerosol containing primarily lithium hydroxide with about 23% lithium carbonate (aerosol 2), and 940 mg/m^3 for a mixture of lithium oxide with a small amount of lithium hydroxide and about 12% lithium carbonate (aerosol 3) (22). Four air concentrations of each aerosol were used in the exposures: 620, 1400, 2300 and 2600 mg/m^3 for aerosol 1; 570, 840, 1200 and 1500 mg/m^3 for aerosol 2; and 500, 750, 1000 and 1500 mg/m^3 for aerosol 3. The animals were observed daily, and those that died, as well as those that were killed (14 or 28 days after the exposure), were given histopathological examinations. Dose-dependent effects such as coughing,

breathing difficulty, weight loss, and dried blood and mucus around eyes, nose and mouth, were noted. The most prominent substance-related histopathological changes were the indications of severe irritation in the upper respiratory passages (ulcerative/necrotic laryngitis, erosive/ulcerative rhinitis, squamous metaplasia) and in some cases secondary lung damage. Effects on thymus (atrophy, drastic reduction of lymphocytes) were also observed, but were considered to be a non-specific reaction to systemic stress. For all three aerosols, the irritation effects were observed primarily in the two highest dose groups. The effects of aerosol 1 (containing primarily lithium carbonate) were generally milder and less wide-spread than the effects of the other two mixtures. For example, no rhinitis, laryngitis or alveolitis was seen in any of the 16 animals exposed to 620 mg/m^3 of aerosol 1, whereas these effects were seen in a few animals in the two lowest dose groups exposed to the other two aerosols (11, 22).

When laboratory animals were exposed to 5 – 55 mg LiH/m^3 (4 – 48 mg Li/m^3) for 4 to 7 hours (50% relative humidity), coughing and sneezing were reported at all concentrations. At levels above 10 mg LiH/m^3 corrosion was observed on areas of the fur and skin. Some rats also had severely inflamed and irritated eyes, and in a few rats the nasal septum was destroyed (26). These effects were attributed to the alkalinity of the hydrolysis product lithium hydroxide. In the same study, sores were observed on noses and forepaws, inflammation in eyes, partial sloughing of mucous epithelium in trachea, and in some lungs emphysema (probably secondary damage) after exposure to about 5 mg LiH/m^3, 4 hours/day for 5 days, both when the animals were killed immediately after the exposure and up to 14 days later (Table 2). No exposure-related histopathological changes were seen in lungs, liver, kidneys, trachea or lymph nodes 2 to 5 months after exposure was ended (26). No significant inflammatory changes were observed in the lungs of rabbits exposed to a lithium chloride aerosol containing 0.6 or 1.9 mg Li/m^3, 6 hours/day, 5 days/week for 4 to 8 weeks (optical and electron microscope, bronchial lavage) (14).

Salt balance has a major influence on the toxicity of lithium. In experiments with dogs, it was observed that animals that received daily oral doses of lithium chloride (8.2 mg Li/kg b.w.; 1.2 mmol Li/kg b.w.) and had normal sodium intake survived the entire experiment period of 150 days, whereas the same dose was lethal within 12 to 18 days for animals with low sodium intake (21). When rats were given a diet low in sodium and daily intraperitoneal injections of lithium chloride (3.5 – 69 mg Li/kg b.w./day; 0.5 – 10 mmol Li /kg b.w./day), a daily dose of 6.9 mg (1 mmol) Li/kg b.w. resulted in a temporary increase of serum lithium levels, whereas 21 mg (5 mmol) Li/kg b.w./day yielded a steady increase after a few days. Rats given extra sodium had steadily increasing lithium levels in serum at a dose of 35, but not 21, mg Li/kg b.w./day. Animals with lithium accumulation had deteriorating renal function, leading to death. Histological examination revealed acute degenerative changes in proximal tubuli, but no changes in other examined organs except moderate vacuolization of the adrenal cortex. Lithium-induced polyurea (the initial indication of renal toxicity) was reversible if the

lithium injections were stopped (24). The author concluded from this study that lithium affects primarily renal function.

Mutagenicity, carcinogenicity

Lithium compounds (the chloride, citrate, carbonate, acetate, sulfate and hypochlorite) have been tested for mutagenicity, DNA damage, chromosome aberrations and sister chromatid exchanges in a number of *in vitro* and *in vivo* studies (16). Many of these studies yielded negative results, but positive results were also reported — although usually at high doses (equivalent to therapeutic doses or higher). A possible explanation for the observation of genotoxic effects at higher doses may be increased cell survival, since lithium inhibits apoptosis by inhibiting the enzyme glycogen synthase kinase-3 (16). At low dose levels genotoxic effects (chromosome aberrations) have been reported in only a few, poorly written studies and in a single study of lithium hypochlorite. In this latter study chromosome aberrations were observed in CHO cells *in vitro*, although lithium hypochlorite was negative in other mutagenicity/genotoxicity tests (16). It should be noted that the hypochlorites of calcium and sodium have also been reported to increase chromosome aberrations in mammalian cells, which suggests that the effect can probably be attributed to the hypochlorite ion. The great majority of studies of chromosome damage in leukocytes, lymphocytes and bone marrow cells of patients treated with lithium indicate that lithium therapy does not increase risk of chromosome aberrations or sister chromatid exchanges (16). Weiner (27) concludes that present knowledge, based on all data from human studies, animal studies and genotoxicity studies, indicates that the lithium ion is neither mutagenic nor damaging to DNA, and causes no chromosome aberrations in patients.

There are no available data indicating that lithium has oncogenic effects (18, 20, 27).

Effects on reproduction

Human data

An elevated incidence of a rare heart defect (Epstein's anomaly) in children born to mothers on lithium treatment during their first trimester was reported in the 1970s. The data originated in the Lithium Baby Register, a register containing retrospective, voluntarily submitted data (2, 13). Later studies have indicated that lithium therapy is associated with little or no risk to fetuses (16). In 1994 Cohen *et al*. (6) assessed all the controlled epidemiological studies that had been published after the alarming reports from the Lithium Baby Register and concluded that the risk of teratogenic effects from administration of lithium during the first trimester is lower than initially believed. The question of whether prenatal lithium exposure affects postnatal development has been examined in a few studies. In a follow-up study of 60 children without congenital malformations from the Lithium Baby

Register, no elevation in incidence of physical or mental abnormality was observed when these babies were compared with unexposed siblings (25). In a study in which "milestones in development" (e.g. sitting, crawling, talking, walking) of 22 children of mother treated with lithium were compared with controls, no difference was noted (13). As for possible effects on reproduction in men undergoing lithium treatment, existing data are too scanty to allow a conclusion (16).

Animal data

In animal experiments, teratogenic effects due to administration of lithium have been reported to be dose-related. In one review (15), the NOAEL for effects on fetuses and mothers was given as 10 mg (1.4 mmol) Li/kg b.w./day when lithium was administered during the critical periods for cell differentiation and organogenesis. Defects in the heart/circulatory system have not been observed in animal experiments (16).

Significant inhibition of spermatogenesis has been reported with daily subcutaneous injections of 0.3 mg (0.04 mmol) Li/kg b.w. as lithium chloride for 15 days (10). It was found in this study that lithium affected testicular function by reducing the serum levels of FSH, LH, prolactin and testosterone. Reduced activity of key enzymes in androgen biosyntheses was also observed. Administration of lithium chloride for 20 and 25 days also reduced the weights of testes, prostata and seminal vesicles. Lithium level in serum was reported to be about 0.5 mmol/l (10). The same authors showed that a prolactin injection 8 hours after the treatment with lithium chloride protected against most of these effects (9).

Effects on fertility at doses which seem to have no other effects on the animals were described in an incompletely reported study in which mice of both sexes were given drinking water containing lithium chloride (10 – 200 mmol Li/l; 69 – 1388 mg Li/l). Fewer litters and elevated mortality among the pups during the period between birth and weaning were reported in the group that received 50 mmol (347 mg) Li/l from 2 weeks before mating until the pups were weaned. The plasma level was reported to be about 0.7 mmol Li/l. When the animals received 50 mmol Li/l starting five weeks before mating, postnatal growth and development were also retarded. No reproduction was reported in animals given 100 mmol (694 mg) Li/l (19).

Dose-effect / dose-response relationships

There are little data that can be used to estimate a dose-effect or dose-response relationship for occupational exposure to lithium. Several studies have reported irritation of respiratory passages, eyes and skin, and sometimes skin burns, with exposure to metallic lithium and alkaline lithium compounds. In one study (reviewed in Reference 3) slight nasal irritation is reported at exposure to 0.025 – 0.10 mg LiH/m^3, and pronounced nasal irritation and coughing at 0.10 – 0.50 mg LiH/m^3. Exposure levels of 0.50 – 1.0 mg LiH/m^3 resulted in severe nasal irritation and coughing, and some workers had irritated eyes (Table 1). Lithium

hydroxide seems to be irritating at approximately the same air concentrations. One study of lithium hydroxide exposure (23) reports symptoms of irritation of upper respiratory passages and skin with exposure to about 0.02 – 0.05 mg Li/m^3. For exposure to lithium carbonate, irritation of the upper respiratory passages is reported at levels around 0.5 to 1.8 mg Li/m^3 (23). No effects other than irritation and erosion have been attributed to occupational exposure to lithium or lithium compounds. Available data also indicate that serum levels of lithium in exposed workers are very low compared to levels in psychiatric patients medicated with lithium. A theoretical calculation of daily uptake at an air concentration of 1 mg Li/m^3 yields a value of 10 mg Li (assuming that 10 m^3 air are inhaled in 8 hours and uptake is 100%). This should be compared with the defined daily dose in Sweden — 167 mg Li — when lithium is used to treat psychiatric patients.

Dose-effect relationships observed in laboratory animals exposed by inhalation to lithium hydride are summarized in Table 2.

Table 1. Dose-effect data for occupational exposure to lithium.

Exposure level (mg/m^3)		Effect	Ref.
as Li compound	as Li		
0-0.025 (LiH)	0-0.022	No effect	3
0.069-0.17* (LiOH)	0.02-0.05*	Symptoms of irritation	23
0.025-0.10 (LiH)	0.022-0.09	Tickling in nose, sniffles Tolerable for workers accustomed to it	3
0.05 (LiH)	0.04	Workers acclimate rapidly, unpleasant for people not used to it	1
0.10-0.50 (LiH)	0.09-0.44	Clear nasal irritation, some coughing Not tolerable	3
>0.1 (LiH)	>0.09	Eye and nose irritation in persons somewhat accustomed to exposure	1
>0.2 (LiH)	>0.17	Itching of exposed skin	1
0.5 (LiH)	0.44	Maximum air concentration tolerable for brief periods	1
0.50-1.0 (LiH)	0.44-0.87	Severe nasal irritation, coughing Some workers had irritated eyes	3
2.88-9.8* (Li_2CO_3)	0.54-1.84*	Symptoms of respiratory irritation	23
1.0-5.0 (LiH)	0.87-4.4	Severe respiratory irritation Skin irritation	3

*Amount in total dust as registered by personal monitors.

Table 2. Exposure-effect relationships observed in laboratory animals exposed by inhalation to lithium hydride (from Reference 26).

Exposure (LiH)	Species (number of animals)	Effect
5 mg/m^3, 4 hours/day, 5 days	Rat (10), Guinea pig (3), Mouse (10), Rabbit (3)	Some sores on noses and forepaws, emphysema in a few lungs Guinea pig: eye inflammation Rabbit: eye inflammation Mouse: partial sloughing of mucous epithelium in trachea
45 mg/m^3, 4 hours	Rabbit (2)	Damage to nose and forepaws, acute eye inflammation
49 mg/m^3, 4 hours	Guinea pig (2)	No external damage
55 mg/m^3, 4 hours	Rat (8)	Erosions on noses and forepaws
	Mouse (8)	Erosions on noses and forepaws, Partial sloughing of mucous epithelium in trachea

Conclusions

The critical effect of occupational exposure to lithium and lithium compounds is irritation of the respiratory passages. Exposure to lithium and alkaline lithium compounds can result in irritation of respiratory passages, eyes and skin, and occasionally skin erosion. Irritation of upper respiratory passages has been reported in workers exposed to 0.02 – 0.09 mg Li/m^3 as lithium hydride. Symptoms of irritation have been reported at exposure to about the same air levels of lithium hydroxide.

References

1. ACGIH. *Documentation of the Threshold Limit Values and Biological Exposure Indices*. 7th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists Inc., 2001.
2. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 1996;153:592-606.
3. Beliles RP. Lithium, Li. In: Clayton GD, Clayton FE, eds. *Patty's Industrial Hygiene and Toxicology vol 2*. 4th ed. New York: John Wiley & Sons, 1994:2087-2097.
4. Bencze K, Pelikan C, Bahemann-Hoffmeister A, Kronseder A. Lithium/aluminium alloys. A problem material for biological monitoring. *Sci Total Environ* 1991;101:83-90.
5. Birch NJ. Lithium. In: Seiler HG, Sigel H, Sigel A, eds. *Handbook on the Toxicity of Inorganic Compounds*. New York: Marcel Dekker, 1988:383-393.
6. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994;271:146-150.
7. Cordasco EM, Kosti H, Vance JW, Golden LN. Pulmonary edema of noncardiac origin. *Arch Environ Health* 1965;11:588-596.
8. Cracovaner AJ. Stenosis after explosion of lithium hydride. *Arch Otolaryngol* 1964;80:87-92.

9. Ghosh D, Biswas NM, Ghosh PK. Studies on the effect of prolactin treatment on testicular steroidogenesis and gametogenesis in lithium-treated rats. *Acta Endocrinol* 1991;125:313-318.
10. Ghosh PK, Biswas NM, Ghosh D. Effect of lithium chloride on testicular steroidogenesis and gametogenesis in immature male rats. *Acta Endocrinol* 1991;124:76-82.
11. Greenspan BJ, Allen MD, Rebar AH. Inhalation toxicity of lithium combustion aerosols in rats. *J Toxicol Environ Health* 1986;18:627-637.
12. Hägg G. *Allmän och oorganisk kemi*, 5th ed. Stockholm: Almqvist & Wiksell, 1969:610-619.
13. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, Donnenfeld AE, Rieder M, Santelli R, Smythe J, Pastuszak A, Einarson T, Koren G. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992;339:530-533.
14. Johansson A, Camner P, Curstedt T, Jarstrand C, Robertson B, Urban T. Rabbit lung after inhalation of lithium chloride. *J Appl Toxicol* 1988;8:373-375.
15. Johnson EM. A summary review and human perspective for developmental toxicity evaluations of lithium in laboratory animals. In: Schrauzer GN, Klippel KF, eds. *Lithium in Biology and Medicine*. Weinheim, Germany: VCH Verlagsgesellschaft, 1991:101-112.
16. Json Lagerkvist B, Lindell B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 131. Lithium and lithium compounds*. Arbete och Hälsa 2002;16:1-48. National Institute for Working Life, Solna, Sweden.
17. Kawamoto MM, Echt A, Reh CM. *Health Hazard Evaluation Report*. US Department of Health and Human Services, National Institute for Occupational Safety and Health (NIOSH). Eagle-Picher Industries, Joplin MO, 1999 (HETA 96-0016-2777).
18. Léonard A, Hantson P, Gerber GB. Mutagenicity, carcinogenicity and teratogenicity of lithium compounds. *Mutat Res* 1995;339:131-137.
19. Mroczka DL, Hoff KM, Goodrich CA, Baker PC. Effect of lithium on reproduction and postnatal growth of mice. *Biol Neonate* 1983;43:287-296.
20. Norton B, Whalley LJ. Mortality of a lithium treated population. *Br J Psychiatry* 1984;145:277-282.
21. Radomski JL, Fuyat HN, Nelson AA, Smith PK. The toxic effects, excretion and distribution of lithium chloride. *J Pharmacol Exp Ther* 1950;100:429-444.
22. Rebar AH, Greenspan BJ, Allen MD. Acute inhalation toxicopathology of lithium combustion aerosols in rats. *Fundam Appl Toxicol* 1986;7:58-67.
23. Salisbury S, Keenlyside R. *Health Hazard Evaluation Report*. US Department of Commerce, National Institute for Occupational Safety and Health (NIOSH), The Hazard Evaluations and Technical Assistance Branch. Lithium Corporation of America, Bessemer City, 1981 (HHE 80-036-922).
24. Schou M. Lithium studies. 1. Toxicity. *Acta Pharmacologia et Toxicologia* 1958;15:70-84.
25. Schou M. What happened later to the lithium babies? A follow-up study of children born without malformations. *Acta Psychiatr Scand* 1976;54:193-197.
26. Spiegl CJ, Scott JK, Steinhardt H, Leach LJ, Hodge HC. Acute inhalation toxicity of lithium hydride. *Arch Ind Health* 1956;14:468-470.
27. Weiner ML. Overview of lithium toxicology. In: Schrauzer GN, Klippel KF, eds. *Lithium in Biology and Medicine*. New York: VCH Publishers, Inc., 1991:81-99.

Summary

Montelius J (ed). *Scientific Basis for Swedish Occupational Standards*. XXIV. Arbete och Hälsa 2003:16, pp 1-73. National Institute for Working Life, Stockholm.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish National Institute for Working Life from July, 2002 through June, 2003.

Key Words: Cadmium, Chlorobenzene, Diesel exhaust, Lithium, Litium compounds, Occupational exposure limit (OEL), Risk assessment, Scientific basis, Toxicology, Triethanolamine.

Sammanfattning

Montelius J (ed). *Vetenskapligt underlag för hygieniska gränsvärden*. XXIV. Arbete och Hälsa 2003:16, s 1-73. Arbetslivsinstitutet, Stockholm.

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 2002 - juni 2003.

Nyckelord: Dieselavgaser, Hygieniskt gränsvärde, Kadmium, Klorbensen, Litium, Litiumföreningar, Riskvärdering, Toxikologi, Trietanolamin, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2003:15.

APPENDIX

Consensus reports in this and previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	(No.)
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)
revised	June 14, 2000	2000:22	(XXI)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
Antimony + compounds	December 8, 1999	2000:22	(XXI)
Arsenic, inorganic	December 9, 1980	1982:9	(II)
revised	February 15, 1984	1984:44	(V)
Arsine	October 20, 1987	1988:32	(IX)
Asbestos	October 21, 1981	1982:24	(III)
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)
Butyl acetates	February 11, 1998	1998:25	(XIX)
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)
revised	February 5 2003	2003:16	(XXIV)

Calcium hydroxide	February 24, 1999	1999:26	(XX)
Calcium nitride	January 27, 1993	1993:37	(XIV)
Calcium oxide	February 24, 1999	1999:26	(XX)
Caprolactam	October 31, 1989	1991:8	(XI)
Carbon monoxide	December 9, 1981	1982:24	(III)
Cathecol	September 4, 1991	1992:47	(XIII)
Chlorine	December 9, 1980	1982:9	(II)
Chlorine dioxide	December 9, 1980	1982:9	(II)
Chlorobenzene	September 16 1992	1993:37	(XIV)
revised	April 2 2003	2003:16	(XXIV)
o-Chlorobenzylidene malononitrile	June 1, 1994	1994:30	(XV)
Chlorocresol	December 12, 1990	1992:6	(XII)
Chlorodifluoromethane	June 2, 1982	1982: 24	(III)
Chlorophenols	September 4, 1985	1986:35	(VII)
Chloroprene	April 16, 1986	1986:35	(VII)
Chromium	December 14, 1979	1981:21	(I)
revised	May 26, 1993	1993:37	(XIV)
revised	May 24, 2000	2000:22	(XXI)
Chromium trioxide	May 24, 2000	2000:22	(XXI)
Coal dust	September 9, 1986	1987:39	(VIII)
Cobalt	October 27, 1982	1983:36	(IV)
Copper	October 21, 1981	1982:24	(III)
Cotton dust	February14, 1986	1986:35	(VII)
Creosote	October 26, 1988	1989:32	(X)
Cresols	February 11, 1998	1998:25	(XIX)
Cumene	June 2, 1982	1982:24	(III)
Cyanamid	September 30, 1998	1999:26	(XX)
Cyanoacrylates	March 5, 1997	1997:25	(XVIII)
Cycloalkanes, C_5-C_{15}	April 25, 1984	1984:44	(V)
Cyclohexanone	March 10, 1982	1982:24	(III)
revised	February 24 1999	1999:26	(XX)
Cyclohexanone peroxide	February 13, 1985	1985:32	(VI)
Cyclohexylamine	February 7, 1990	1991:8	(XI)
Desflurane	May 27, 1998	1998:25	(XIX)
Diacetone alcohol	December 14, 1988	1989:32	(X)
Dichlorobenzenes	February 11, 1998	1998:25	(XIX)
1,2-Dibromo-3-chloropropane	May 30, 1979	1981:21	(I)
Dichlorodifluoromethane	June 2, 1982	1982:24	(III)
1,2-Dichloroethane	February 29, 1980	1981:21	(I)
Dichloromethane	February 29, 1980	1981:21	(I)
Dicumyl peroxide	February 13, 1985	1985:32	(VI)
Dicyclopentadiene	March 23, 1994	1994:30	(XV)
Diesel exhaust	December 4 2002	2003:16	(XXIV)
Diethanolamine	September 4, 1991	1992:47	(XIII)
Diethylamine	August 25, 1982	1983:36	(IV)
2-Diethylaminoethanol	January 25, 1995	1995:19	(XVI)
Diethylene glycol	September 16, 1992	1993:37	(XIV)
Diethyleneglycol ethylether + acetate	December 11, 1996	1997:25	(XVIII)
Diethyleneglycol methylether + acetate	March 13, 1996	1996:25	(XVII)
Diethyleneglycol monobutylether	January 25, 1995	1995:19	(XVI)
Diethylenetriamine	August 25, 1982	1983:36	(IV)
revised	January 25, 1995	1995:19	(XVI)
Diisocyanates	April 8, 1981	1982:9	(II)
revised	April 27, 1988	1988:32	(IX)
Diisopropylamine	February 7, 1990	1991:8	(XI)
N,N-Dimethylacetamide	March 23, 1994	1994:30	(XV)
Dimethyl adipate	December 9, 1998	1999:26	(XX)

Dimethylamine	December 10, 1997	1998:25	(XIX)
N,N-Dimethylaniline	December 12, 1989	1991:8	(XI)
Dimethyldisulfide	September 9, 1986	1987:39	(VIII)
Dimethylether	September 14, 1994	1995:19	(XVI)
Dimethylethylamine	June 12, 1991	1992:6	(XII)
Dimethylformamide	March 23, 1983	1983:36	(IV)
Dimethyl glutarate	December 9, 1998	1999:26	(XX)
Dimethylhydrazine	January 27, 1993	1993:37	(XIV)
Dimethyl succinate	December 9, 1998	1999:26	(XX)
Dimethylsulfide	September 9, 1986	1987:39	(VIII)
Dimethylsulfoxide, DMSO	December 11, 1991	1992:47	(XIII)
Dioxane	August 25, 1982	1983:36	(IV)
revised	March 4, 1992	1992:47	(XIII)
Diphenylamine	January 25, 1995	1995:19	(XVI)
4,4'-Diphenylmethanediisocyanate (MDI)	April 8, 1981	1982:9	(II)
reviderat	May 30 2001	2001:20	(XXII)
Dipropylene glycol	May 26, 1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12, 1990	1992:6	(XII)
Disulfiram	October 31, 1989	1991:8	(XI)
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	December 11, 1996	1997:25	(XVIII)
Ethylene chloride	February 29, 1980	1981:21	(I)
Ethylene diamine	August 25, 1982	1983:36	(IV)
Ethylene glycol	October 21, 1981	1982:24	(III)
Ethylene glycol methylether + acetate	June 2, 1999	1999:26	(XX)
Ethyleneglycol monoisopropylether	November 16, 1994	1995:19	(XVI)
Ethyleneglycol monopropylether + acetate	September 15, 1993	1994:30	(XV)
Ethylene oxide	December 9, 1981	1982:24	(III)
Ethylenethiourea	September 27, 2000	2001:20	(XXII)
Ethylether	January 27, 1993	1993:37	(XIV)
Ethylglycol	October 6, 1982	1983:36	(IV)
Ferbam	September 12, 1989	1991:8	(XI)
Ferric dimethyldithiocarbamate	September 12, 1989	1991:8	(XI)
Flour dust	December 10, 1997	1998:25	(XIX)
Formaldehyde	June 30, 1979	1981:21	(I)
revised	August 25, 1982	1983:36	(IV)
Formamide	December 12, 1989	1991:8	(XI)
Formic acid	June 15, 1988	1988:32	(IX)
Furfural	April 25, 1984	1984:44	(V)
Furfuryl alcohol	February 13, 1985	1985:32	(VI)
Gallium + Gallium compounds	January 25, 1995	1995:19	(XVI)
Glutaraldehyde	September 30 1998	1999:26	(XX)
Glycol ethers	October 6, 1982	1983:36	(IV)
Glyoxal	September 13, 1996	1996:25	(XVII)
Grain dust	December 14, 1988	1989:32	(X)
Graphite	December 10, 1997	1998:25	(XIX)
Halothane	April 25, 1985	1985:32	(VI)

2-Heptanone	September 5, 1990	1992:6	(XII)
3-Heptanone	September 5, 1990	1992:6	(XII)
Hexachloroethane	September 15, 1993	1994:30	(XV)
Hexamethylenediisocyanate (HDI)	April 8, 1981	1982:9	(II)
revised	May 30, 2001	2001:20	(XXII)
Hexamethylenetetramine	August 25, 1982	1983:36	(IV)
n-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 bromide	February 11, 1998	1998:25	(XIX)
Hydrogen cyanide	February 7 2001	2001:20	(XXII)
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)
Industrial enzymes	June 5, 1996	1996:25	(XVII)
Isocyanic Acid (ICA)	December 5 2001	2002:19	(XXIII)
Isophorone	February 20, 1991	1992:6	(XII)
Isopropanol	December 9, 1981	1982:24	(III)
Isopropylamine	February 7, 1990	1991:8	(XI)
Isopropylbenzene	June 2, 1982	1982:24	(III)
Lactates	March 29, 1995	1995:19	(XVI)
Lactate esters	June 2, 1999	1999:26	(XX)
Lead, inorganic	February 29, 1980	1981:21	(I)
revised	September 5, 1990	1992:6	(XII)
Lithium and lithium compounds	June 4 2003	2003:16	(XXIV)
Lithium boron nitride	January 27, 1993	1993:37	(XIV)
Lithium nitride	January 27, 1993	1993:37	(XIV)
Maleic anhydride	September 12, 1989	1991:8	(XI)
Manganese	February 15, 1983	1983:36	(IV)
revised	April 17, 1991	1992:6	(XII)
revised	June 4, 1997	1997:25	(XVIII)
Man made mineral fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Mercury, inorganic	April 25, 1984	1984:44	(V)
Mesityl oxide	May 4, 1983	1983:36	(IV)
Metal stearates, some	September 15, 1993	1994:30	(XV)
Methacrylates	September 12, 1984	1985:32	(VI)
Methanol	April 25, 1985	1985:32	(VI)
Methyl acetate	March 28 1990	1991:8	(XI)
Methylamine	August 25, 1982	1983:36	(IV)
Methylamyl alcohol	March 17, 1993	1993:37	(XIV)
Methyl bromide	April 27, 1988	1988:32	(IX)
Methyl chloride	March 4, 1992	1992:47	(XIII)
Methyl chloroform	March 4, 1981	1982:9	(II)
Methylene chloride	February 29, 1980	1981:21	(I)
4,4'-Methylene dianiline	June 16, 1987	1987:39	(VIII)
revised	October 3 2001	2002:19	(XXIII)
Methyl ethyl ketone	February 13, 1985	1985:32	(VI)
Methyl ethyl ketone peroxide	February 13, 1985	1985:32	(VI)
Methyl formate	December 12, 1989	1991:8	(XI)
Methyl glycol	October 6, 1982	1983:36	(IV)
Methyl iodide	June 30, 1979	1981:21	(I)

Methylisoamylamine	September 5, 1990	1992:6	(XII)
Methylisoamylketone	February 6 2002	2002:19	(XXIII)
Methylisocyanate (MIC)	December 5 2001	2002:19	(XXIII)
Methyl mercaptane	September 9, 1986	1987:39	(VIII)
Methyl methacrylate	March 17, 1993	1993:37	(XIV)
Methyl pyrrolidone	June 16, 1987	1987:39	(VIII)
α-Methylstyrene	November 1 2000	2001:20	(XXII)
Methyl-t-butyl ether	November 26, 1987	1988:32	(IX)
revised	September 30, 1998	1999:26	(XX)
Mixed solvents, neurotoxicity	April 25, 1985	1985:32	(VI)
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)
Naphthalene	May 27, 1998	1998:25	(XIX)
Natural crystallinic fibers (except asbestos)	June 12, 1991	1992:6	(XII)
Nickel	April 21, 1982	1982:24	(III)
Nitroethane	April 4, 1989	1989:32	(X)
Nitrogen oxides	December 11, 1985	1986:35	(VII)
Nitroglycerin	February 13, 1985	1985:32	(VI)
Nitroglycol	February 13, 1985	1985:32	(VI)
Nitromethane	January 6, 1989	1989:32	(X)
Nitropropane	October 28, 1986	1987:39	(VIII)
2-Nitropropane	March 29, 1995	1995:19	(XVI)
Nitroso compounds	December 12, 1990	1992:6	(XII)
Nitrosomorpholine	December 8, 1982	1983:36	(IV)
Nitrotoluene	February 20, 1991	1992:6	(XII)
Nitrous oxide	December 9, 1981	1982:24	(III)
Oil mist	April 8, 1981	1982:9	(II)
Organic acid anhydrides, some	September 12, 1989	1991:8	(XI)
Oxalic acid	February 24, 1988	1988:32	(IX)
Ozone	April 28, 1987	1987:39	(VIII)
Paper dust	February 7, 1990	1991:8	(XI)
Pentaerythritol	November 16, 1994	1995:19	(XVI)
1,1,1,2,2-Pentafluoroethane	February 24, 1999	1999:26	(XX)
Pentyl acetate	June 14, 2000	2000:22	(XXI)
Peroxides, organic	February 13, 1985	1985:32	(VI)
Phenol	February 13, 1985	1985:32	(VI)
Phosphorous chlorides	September 30, 1998	1999:26	(XX)
Phosphorous oxides	February 11, 1998	1998:25	(XIX)
Phthalates	December 8, 1982	1983:36	(IV)
Phthalic anhydride	September 12, 1989	1991:8	(XI)
Piperazine	September 12, 1984	1985:32	(VI)
Plastic dusts	December 16, 1986	1987:39	(VIII)
Platinum	June 4, 1997	1997:25	(XVIII)
Polyaromatic hydrocarbons	February 15, 1984	1984:44	(V)
Polyisocyanates	April 27, 1988	1988:32	(IX)
Potassium aluminium fluoride	June 4, 1997	1997:25	(XVIII)
Potassium cyanide	February 7 2001	2001:20	(XXII)
Potassium dichromate	May 24, 2000	2000:22	(XXI)
Potassium hydroxide	Marsh 15, 2000	2000:22	(XXI)

2-Propanol	December 9, 1981	1982:24	(III)
Propene	September 13, 1996	1996:25	(XVII)
Propionic acid	November 26, 1987	1988:32	(IX)
Propylacetate	September 14, 1994	1995:19	(XVI)
Propylene glycol	June 6, 1984	1984:44	(V)
Propylene glycol-1,2-dinitrate	May 4, 1983	1983:36	(IV)
Propylene glycol monomethylether	October 28, 1986	1987:39	(VIII)
Propylene oxide	June 11, 1986	1986:35	(VII)
Pyridine	May 13, 1992	1992:47	(XIII)
Quartz	March 13, 1996	1996:25	(XVII)
Resorcinol	September 4, 1991	1992:47	(XIII)
Selenium	December 11, 1985	1986:35	(VII)
revised	February 22, 1993	1993:37	(XIV)
Sevoflurane	May 27, 1998	1998:25	(XIX)
Silica	March 13, 1996	1996:25	(XVII)
Silver	October 28, 1986	1987:39	(VIII)
Sodium cyanide	February 7 2001	2001:20	(XXII)
Sodium hydroxide	August 24, 2000	2000:22	(XXI)
Stearates, metallic, some	September 15, 1993	1994:30	(XV)
Stearates, non-metallic, some	November 17, 1993	1994:30	(XV)
Strontium	January 26, 1994	1994:30	(XV)
Styrene	February 29, 1980	1981:21	(I)
revised	October 31, 1989	1991:8	(XI)
Sulfur dioxide	April 25, 1985	1985:32	(VI)
Sulfur fluorides	March 28, 1990	1991:8	(XI)
Synthetic inorganic fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Synthetic organic and inorganic fibers	May 30, 1990	1991:8	(XI)
Talc dust	June 12, 1991	1992:6	(XII)
Terpenes, mono-	February 17, 1987	1987:39	(VIII)
Tetrabromoethane	May 30, 1990	1991:8	(XI)
Tetrachloroethane	June 4, 1997	1997:25	(XVIII)
Tetrachloroethylene	February 29, 1980	1981:21	(I)
1,1,1,2-Tetrafluoroethane	March 29, 1995	1995:19	(XVI)
Tetrahydrofuran	October 31, 1989	1991:8	(XI)
Tetranitromethane	April 4, 1989	1989:32	(X)
Thioglycolic acid	June 1, 1994	1994:30	(XV)
Thiourea	December 1, 1987	1988:32	(IX)
revised	June 2, 1999	1999:26	(XX)
Thiram	October 31, 1989	1991:8	(XI)
Thiurams, some	October 31, 1989	1991:8	(XI)
Titanium dioxide	February 21, 1989	1989:32	(X)
Toluene	February 29, 1980	1981:21	(I)
revised	February 6 2002	2002:19	(XXIII)
Toluene-2,4-diamine	November 1, 2000	2001:20	(XXII)
Toluene-2,6-diamine	November 1, 2000	2001:20	(XXII)
Toluene-2,4-diisocyanate	April 8, 1981	1982:9	(II)
revised	May 30, 2001	2001:20	(XXII)
Toluene-2,6-diisocyanate	April 8, 1981	1982:9	(II)
revised	May 30, 2001	2001:20	(XXII)
1,1,1-Trifluoroethane	February 24, 1999	1999:26	(XX)
Trichlorobenzene	September 16, 1993	1993:37	(XIV)
1,1,1-Trichloroethane	March 4, 1981	1982:9	(II)
Trichloroethylene	December 14, 1979	1981:21	(I)

Trichlorofluoromethane	June 2,	1982	1982:24	(III)
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2,	1982	1982:24	(III)
Triethanolamine	August 25,	1982	1983:36	(IV)
revised	October 23	2002	2003:16	(XXIV)
Triethylamine	December 5,	1984	1985:32	(VI)
Trimellitic anhydride	September 12,	1989	1991:8	(XI)
Trimethylolpropane	November 16,	1994	1995:19	(XVI)
Trinitrotoluene	April 17,	1991	1992:6	(XII)
Vanadium	March 15,	1983	1983:36	(IV)
Vinyl acetate	June 6,	1989	1989:32	(X)
Vinyl toluene	December 12,	1990	1992:6	(XII)
White spirit	December 16,	1986	1987:39	(VIII)
Wood dust	June 17,	1981	1982:9	(II)
revised	June 25,	2000	2000:22	(XXI)
Xylene	February 29,	1980	1981:21	(I)
Zinc	April 21,	1982	1982:24	(III)
Zinc chromate	May 24,	2000	2000:22	(XXI)
Zinc dimethyl dithiocarbamate	September 12,	1989	1991:8	(XI)
Ziram	September 12,	1989	1991:8	(XI)

Sent for publication December 2003