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Scientific Basis for Swedish Occupational Standards XXXII

Swedish Criteria Group for Occupational Standards
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Translation:
Språkservice Sverige AB (Carbon dioxide) and Space 360 AB (Ethylamine and Diethylamine, n-Butyl acrylate, Ethanolamine), and Johan Montelius at the Swedish Work Environment Authority.
The consensus reports in this volume are translated from Swedish. If there is any doubt as to the understanding or interpretation of the English version, the Swedish version shall prevail.

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Preface

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

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

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

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

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

This publication is the 32nd in the series, and contains consensus reports approved by the Criteria Group from October, 2010 through May, 2012. The consensus reports in this and previous publications in the series are listed in the Appendix (page 76).

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Contents

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Consensus Report for Ethylamine and Diethylamine

February 16, 2011

Data search was performed in Toxline, including PubMed, in November 2010. This report updates a previous Consensus Report published in *Arbete och Hälsa* 1983 (27).

Chemical and physical data. Use

Ethylamine

CAS No.	75-04-7
Synonyms	monoethylamine, ethanamine, aminoethane, 1-aminoethane, MEA, EA
Structural formula	CH_3-CH_2-NH_2
Molecular weight	45.08
Melting point	-81 °C
Boiling point	16.6 °C
Vapour pressure	113 kPa (20 °C), 116 kPa (20 °C)
Density	0.6829 (20 °C)
Conversion factors	1 ppm = 1.87 mg/m^3, 1 mg/m^3 = 0.53 ppm (20 °C)
Other data	May be sold as a 70% aqueous solution.

Ethylamine is a colourless, flammable gas or liquid that evaporates at room temperature. The odour is described as being sharp, ammonia-like, and fishy (7, 8, 27). The odour threshold was indicated in one study as 0.95 ppm (geometric mean, standard error = 2.6) (2). The substance is miscible with water, ethanol, and ether, and is strongly basic in an aqueous solution (pK_b = 3.29) (7). Ethylamine is primarily used as an intermediate within the chemical and pharmaceutical industries. It is used as an intermediate for dyestuff, as a stabiliser for rubber latex, in the manufacture of emulsifiers and detergents, and in oil refining (1, 7, 8). No registered use, however, was listed in Sweden in 2008 (SPIN database, KemI 2010-11-16, http://www.kemi.se/sv/Innehall/Databaser/). Ethylamine occurs naturally in various foodstuffs, e.g. oysters, fish, radishes, spinach, lettuce, cheese (camembert) and wine (8, 33, 54). Consumption of 400 g dried oysters (average concentration 122 ppm) and 0.5 l wine has been estimated to yield a maximum intake of 50 mg ethylamine (8).

Diethylamine

CAS No.	109-89-7
Synonyms	N,N-diethylamine, diethamine, N-ethylethanamine, DEA
Structural formula	CH_3-CH_2-NH-CH_2-CH_3
Molecular weight	73.14
Melting point	-38.9 °C, -48 °C, -50 °C
Boiling point	56.3 °C, 55.5 °C
Vapour pressure	25.9 kPa (20 °C)
Saturation concentration	255,700 ppm (20 °C)
Density	0.7074
Conversion factors	1 ppm = 3.03 mg/m^3, 1 mg/m^3 = 0.33 ppm (20 °C)

Diethylamine is a colourless, strongly basic (pK_b = 3) and flammable liquid at room temperature, and is miscible with water, alcohol and most organic solvents. Its odour is fishy and ammonia-like (3, 7, 27, 53). The odour threshold was indicated in one study as 0.13 ppm (geometric mean, standard error = 2.9) (2). In the presence of nitrogen oxides, it can form N-nitrosodiethyl-amine (11). Diethylamine is used in synthesis of resins, colours, pesticides and medicines, and in electroplating. It can be used as a solvent, as a rubber accelerator, as a polymerisation inhibitor/catalyst and a corrosion inhibitor (3, 7). Total use in Sweden in 2008 was reported as 15 tons (5 products) (SPIN database, KemI 2010-11-16, http://www.kemi.se/sv/Innehall/Databaser/). The substance occurs naturally in various foodstuffs, e.g. spinach, smoked herring, and apples (33).

Uptake, biotransformation, excretion

The absorption of simple aliphatic amines via the skin, the lungs, and the gastrointestinal tract has been reported as high, but quantitative data on ethylamine and diethylamine is largely absent (7, 22). Fiserova-Bergerova *et al.* (15) indicates a theoretically estimated value of 3.36 mg/cm^2/hr for the dermal penetration rate of ethylamine. The calculations, however, have been questioned and criticised as drastically overestimating skin absorption (5). Data on acute toxicity (LD_{50}) in research animals indicate high toxicity for ethylamine and medium to high toxicity for diethylamine, both in peroral and dermal administration (see below).

Few metabolism studies of ethylamine and diethylamine have been found. It has, however, been reported that lower aliphatic amines (primary and secondary amines) are primarily metabolised into carboxylic acid and urea, which are excreted in the urine (3, 7). Intermediate substances such as aldehydes and ammonia, for example, are also formed during metabolism (7, 8). The secondary amine diethylamine is more resistant to metabolism than the primary amine ethylamine, and is largely excreted in an unaltered form. In an older study (38) it was reported that 32% was excreted in unaltered form in the urine over one day in a test subject

who had received 2g ethylamine hydrochloride perorally, while 86% was excreted in unaltered form in a person who received 5g diethylamine hydrochloride perorally (38). Excretion of ethylamine in 200 test subjects who ate normal foodstuffs was reported to be 7.8 mg/day on average with large variations (0.2-35.3 mg) (31).

Nitrosation

Formation of nitrosamines is of interest, as this type of compound can cause cancer, e.g. liver carcinomas. See also the section on carcinogenicity. Nitrosamine formation in the gaseous phase (air) occurs through a reaction between nitrogen oxides and certain amines in the presence of water. It has been reported that secondary and tertiary amines react rapidly with nitrogen oxides in the dark (nitrosamines break down in sunlight) and that up to 3% nitrosamines can be formed in 20-50% relative atmospheric humidity. In dry air, on the other hand, the reaction between nitrogen oxide or nitrogen dioxide and amines is negligible (11, 46). Pitts *et al.* (37) showed, for example, that 0.5 ppm diethylamine, 0.08 ppm nitrogen oxide, and 0.17 ppm nitrogen dioxide in an outdoor chamber (50 m^3) yielded maximal concentration of diethylnitrosamine, 0.014 ppm (0.06 mg/m^3), within 10 minutes in the dark (30-50% relative atmospheric humidity, temperature 22-31°C) (37). Based on kinetic models, it has been estimated that 0.67 ppm (2.84 mg/m^3) diethylnitrosamine can be formed in a well-ventilated room with 16.5 ppm diethylamine, 5.2 ppm nitrogen dioxide and 16 ppm nitrogen oxide, assuming 50% relative atmospheric humidity and a temperature of 20°C (11). Sources of increased nitrogen oxide levels in the air (and a potential risk for nitrosamine formation) can be exhaust from gasoline and diesel engines, as well as chemicals that decompose and give off nitrogen oxides. Nitrosamines can also be formed in industrial environments from secondary amines and other nitrosation agents than nitrogen oxides, for example nitrite salts (within the rubber industry) (23, 46).

Furthermore, nitrosamines can be formed from secondary amines in acidic environments, for example in the stomach in the presence of nitrite or other nitrosation agents. Small amounts of diethylnitrosamine (rabbits: 100-200 µg and 2000 µg respectively, cats: 60-70 µg) were detected in stomach extracts after peroral administration of 450 mg diethylamine hydrochloride and 300 mg sodium nitrite (rabbits, cats) and 1000 mg diethylamine hydrochloride and 1000 mg sodium nitrite respectively (rabbits). Diethylnitrosamine was also formed *in vitro* during incubation of gastric juices, from humans and other species, with diethylamine hydrochloride and sodium nitrite (10, 40).

Toxic effects

Animal data

Ethylamine

LD_{50} in rats after peroral administration has been reported to be 400 mg/kg body weight (44). LD_{50} in rabbits after application to the skin over approximately 1/10

of the body's surface (24 hours under plastic film) was 266 mg/kg (0.39 ml/kg) (44). In experiments with inhalation exposure of 8000 ppm over 4 hours, 2 of 6 rats died (within 14 days) (44). An LC_{50} value (rats, 4 hours) between 4400 and 6800 ppm has been reported in unpublished experiments (12).

RD_{50} – the dose that yields a 50% reduction in respiratory frequency (an expression of sensory irritation) – was 151 ppm (282 mg/m^3) in experiments on mice with 15 minutes' exposure (16). During inhalation exposure at 49 ppm, 7 hours/day, 5 days/week for 6 weeks (6 animals), irritation effects were observed in the respiratory tract (peribronchitis, pneumonitis, thickening of vessel walls in the lungs) and the eyes (oedema, multiple corneal erosions) of rabbits (Table 1). Corneal injuries were not observed until after 2 weeks of exposure. Focal muscular degeneration in the heart was also noted in some of the animals, but the findings were judged to be uncertain. In similar exposures at 100 ppm (6 animals), irritation effects in the respiratory tract and light to moderate degenerative changes in the renal parenchyma were observed. Effects on heart muscle were not reported at 100 ppm. No control group was used in the study (4).

In an abstract for a conference (30), damage to the nasal cavity, including necrosis, was reported in rats at an exposure of 500 ppm, 6 hours/day, 5 days/week for 120 days, while no such effects were demonstrated in similar exposures of 10 or 100 ppm. Impaired growth (reduced body weight gain) were seen in the high-dosage group, while no treatment-related effects in haematological or clinico-chemical examinations, or signs of cardiotoxicity were reported to have occurred in any dosage group (no details were reported in the summary).

An older Russian study describes the effects on experimental animals after continual inhalation exposure to ethylamine at exposure levels under the current Swedish occupational exposure limit value (10 ppm). Among the effects described were changes to chronaxy (measured in time required for nerve reactions) in muscles, changes in the lungs and neurons in the cerebral cortex in histochemical and pathological examinations, increased excretion of urinary coproporphyrins and increased cholinesterase activity in the blood (8, 12). The study was reported to lack the relevant methodological descriptions (12) and has not been taken into consideration in the previous consensus report (27).

Ulceration of the duodenum (4 of 8 animals) and necrosis in the adrenal glands (3 of 8 animals) were observed in rats when injected subcutaneously with ethylamine 3 times/day for 4 days (does 600 mg/kg body weight). All the experimental animals died (47). In a similar experiment on rats, the effect on the duodenum was estimated as moderate (superficial erosions). The effect on the adrenal cortex was milder. The total dose was stated to be 240 mmol/kg ethylamine (10.8 g/kg body weight) (48).

The application of ethylamine to the eyes of rabbits was reported to produce serious eye damage. It was indicated as 9 on a scale of 10 (10 indicates serious burn injuries from 0.5 ml of a 1% aqueous or propylene glycol solution) (44). In an older study, primary dermal irritation within 24 hours was judged to be very mild (1 out of 10) when applying 0.01 ml undiluted ethylamine to rabbits (42, 44).

Unpublished studies, however, indicated that a 3-minute semi-occlusive application of 0.5 ml undiluted ethylamine resulted in necrosis on intact rabbit skin. Furthermore, it was reported that erythema and light oedema were demonstrated after 3 minutes, and necrosis after 30 minutes, when applying 0.5 ml as a 70% ethylamine solution (semi-occlusive) (13). In other unpublished studies, it was reported that necrotic burn injuries were quickly noted when 70% ethylamine solution was dropped on guinea pig skin (8).

Diethylamine

LD_{50} in rats after peroral administration has been indicated at 540 mg/kg body weight (43) and 500 mg/kg in mice (36). LD_{50} in rabbits upon application to the skin was reported as 580 mg/kg (0.82 ml/kg) (7, 43). LC_{50} over 4 hours inhalation exposure was 4000 ppm (3 of 6 rats died within 14 days) (43).

In a study on mice, the RD_{50} for sensory irritation was established at 202 ppm for 15 minutes exposure (16). In another study on mice, an RD_{50} value of 184 ppm for 30 minutes of exposure was reported, while the threshold concentration for reduction of respiratory frequency (RD_0) was 32 ppm (34). In the same study, the RD_{50} as a measurement of pulmonary irritation through the used of a tracheal cannula (exposure 30 minutes) was established; that value was 549 ppm (Table 2). It was reported that the effect on respiratory frequency reached a plateau within 10 minutes; this applied both to sensory irritation and pulmonary irritation. In mice that were not given a tracheal cannula, reduced respiratory frequency was due only to sensory irritation (34).

Upon inhalation exposure to 53 ppm diethylamine (7 hours/day, 5 days/week, 6 weeks), irritation effects were reported in the respiratory tract (including moderate peribronchitis, light thickening of vessel walls) and in the eyes (oedema and multiple corneal erosions) of rabbits (6 animals/dosage group). At this concentration in the air, areas (foci) with moderate degenerative changes were also noted in the hepatic parenchyma, and possibly very light cardiac muscle degeneration (these later findings were very uncertain). At 109 ppm pneumonitis, marked degenerative changes in the hepatic parenchyma, and nephritis with light tubular changes were seen. No effects on heart muscle were reported at 109 ppm (4).

Rats were exposed through inhalation to 26 or 251 ppm diethylamine for 6.5 hours/day, 5 days/week for up to 24 weeks and examined with regard to local effects (histopathological examination of nostrils, however, was not done at 26 ppm). Blood and inner organs such as the heart, liver, and kidneys were also studied (EKG, histopathological, clinicochemical and haematological examination). No clinical signs of irritation were observed at 26 ppm. A somewhat increased incidence (significant) of bronchiolar lymphoid hyperplasia occur in both sexes for 120 days exposure at 26 ppm, but the effects was judged by the authors as unrelated to exposure (it was also seen among the controls, a non-dose-related increase in incidence). Significant increase of creatinine in the blood was also seen at this level of exposure (only in females), but no signs of kidney damage were observed during histological examination. 26 ppm was not considered as an effect

level in the study (Table 2). At 251 ppm, clinical signs of strong irritation in the eyes and nose were observed (e.g. teariness, reddened nose), as well as histopathological changes in the nose. Furthermore, lower body weight (especially in males) and an increased level of creatinine (females only) and urea nitrogen in the blood were also observed. Kidney damage was not reported in histopathological examination. No signs of degenerative changes in cardiac muscle, changes in EKG, or cardiac-related clinicochemical signs of damage were observer at any level of exposure (29).

In several older Russian studies, effects on liver function and nerve function in the muscles (changes to chronaxy), increased excretion of coproporfyrins, increased cholinesterase activity or concentration in the blood, and changes in the lungs and neurons in the cerebral cortex (histochemical, pathological examination) were reported in experimental animals subjected to continual inhalation exposure to diethylamine at exposure levels under the current Swedish occupational exposure limit value (10 ppm). The study is, however, of poor or unclear quality and has not been taken into consideration in previous evaluations (10, 27).

In a study on rats, the effect of diethylamine on the liver was studied through histopathological examination and analysis of liver enzymes in serum. Diethylamine was neutralised to pH 7.4 with hydrogen chloride, and the resulting solution was administered as a single injection into the abdominal cavity in doses that yielded 250, 500, or 1000 mg diethylamine/kg body weight. Significant dose-dependent increase of liver enzymes (ornithine carbamyl transferase (OCT), ASAT, ALAT) was seen. At the lowest dose, however, only a significant increase of OCT was noted. At this dose, mild degeneration was seen in the histological examination, while both the higher doses resulted in marked degeneration and periportal necrosis. The observed effects (impact on enzymes and histology) were transient (14).

A 2% solution of diethylamine (solvent not indicated) was judged to be an irritant when applied to the eyes of rabbits. Reddening, swelling, and inflammation of the conjunctiva, inflammation of the iris, and cloudy cornea were noted. The corneal clouding demonstrated was maximal after 3 days (3 out of 4 points possible, points according to the Draize scoring criteria) (20, 21). Older studies reported serious eye damage in rabbits when diethylamine was applied (grade 10 out of 10 after 24 hours). An injury grade of 10 means that a 1% solution or stronger can result in serious eye damage (6, 43).

In older studies, it was further reported that diethylamine (undiluted) was a skin irritant and resulted in mild erythema (grade 4 out of 10) when applied to rabbit skin (42, 43). Other (unpublished) data indicated that undiluted diethylamine in contact (occlusive) with undamaged rabbit skin for 3 minutes was corrosive (11). Irritation was reported in a study on guinea pigs (in one animal) when a 30% diethylamine solution was applied, but no further details were given (51).

Diethylamine has been reported as a skin sensitiser in the Guinea Pig Maximisation Test (GPMT) with a multiple-dose design (51). In testing the substance (in acetone:olive oil, 4:1) in the local lymph node assay (LLNA) on mice,

diethylamine has been considered to be a weak skin sensitiser. Increased reaction in the LLNA and cytokine production (IFN-γ, IL-4) was seen after pre-treatment with an irritant (9, 50). Using a still-unvalidated *in vitro* method (measurement of intracellular production of IL-18 and IL-1α in mouse keratinocytes), the same authors noted a similar gradation of the sensitizing potential as in the LLNA (52).

Human data

Ethylamine

No relevant studies have been found.

Diethylamine

In a chamber study with 7 test subjects, all of whom were healthy non-smokers and who were not exposed to high concentrations of particles, vapour, or smoke in their occupations, irritation effects from short-term exposure to diethylamine were examined. Nasal irritation, expressed as swelling (acoustic rhinometry), and air flow (rhinomanometry) in the nose were measured in 5 test subjects (4 men, 1 woman) before, during (only acoustic rhinometry) and after exposure to 25 ppm diethylamine (15 minutes exposure). No consistent effect on these parameters was seen in the group. Odour and subjective nasal and eye irritation were further examined in 5 test subjects (5 men) who were exposed to increasing levels of diethylamine from 0 to 12 ppm (time-weighted average 10 ppm) over 1 hour. Discomfort was evaluated (questionnaire and VAS ratings) among the test subjects every five minutes during exposure. Irritation (up to moderately strong) of the nose and eyes, as well as odour perception, was reported, but the inter-individual variation was large. Significant correlations were found between the estimates of nasal irritation and eye irritation ($r = 0.87$, $p<0.001$) and between the estimates of nasal irritation and odour perception ($r = 0.71$, $p<0.001$) (28). The authors stress that the study has weaknesses, chiefly in the design (knowledge of exposure), variation, and the small number of test subjects. They also mention that the study does not permit estimating the threshold value for mucous membrane irritation (eyes, nose, respiratory tract); at the same time they judge that the data suggests sensory irritation at concentrations around the limit value (10 ppm).

Immediate, intense pain in the eyes and persistent vision impairment after one month (despite adequate treatment) was reported in one person who, as the result of an accident, received a thin stream of diethylamine in one eye (17).

Kaniwa *et al.* (24) investigated 5 cases of allergic contact dermatitis from latex gloves. Diethylamine was one of the substances that were patch tested (tested in 4 of the cases: 1%, 2% or 5% diethylamine in vaseline). In the test, diethylamine resulted in a positive reaction in one case and dubious positive reactions in 2 cases. In another study, positive patch test reactions for diethylamine (1% in vaseline) were seen in 1 of 25 patients who have had positive reactions during a test for individual rubber accelerators and for rubber materials. No positive patch test results for diethylamine were noted in 12 controls without a history of rubber allergy or eczema (25).

Mutagenicity/genotoxicity

Ethylamine

Ethylamine was not mutagenic *in vitro* in *Salmonella* TA98, TA100, TA1535 or TA1537 in testing with or without metabolic activation (32). In another study, ethylamine was reported as a very weak mutagen in *Salmonella* bacteria (strain not indicated) *in vitro*, but no results were shown in the study (35). In an older study, it was reported that ethylamine was not mutagenic on *E. coli* bacteria (Sd-4-73) *in vitro* (49). A later study was also negative in tests with ethylamine alone (0.25-1 M) on *E. coli* (Sd-4), but dose-dependent increase of mutants was seen in tests with ethylamine and nitrite in combination (significantly higher mutation frequency than with nitrite alone) (8, 19). Dose-dependent increase of sister chromatide exchange (SCE) was demonstrated in tests with ethylamine hydrochloride on rodent cells *in vitro* (0.1-5 mM) (45).

Diethylamine

Diethylamine was not mutagenic in testing on *Salmonella typhimurium* TA100, TA1535, TA1537, or TA98 with or without metabolic activation (18, 55). No effect on unscheduled DNA synthesis (UDS) was seen in kidney cells that were isolated from rats 12 hours after administration of diethylamine (500 mg/kg perorally) (26).

Carcinogenicity

Ethylamine

No studies on the carcinogenicity of ethylamine have been found in the literature.

Diethylamine

A few studies of diethylamine exist (see below). These studies have relatively few animals, and reporting on histopathological examinations is limited. In one study (20 animals in the group at the start) diethylamine hydrochloride was given in drinking water (4 g/l) to guinea pigs for up to 30 months. The uptake was estimated to equal 290 mg/animal per day on average (150-420 mg/animal per day), which very roughly calculated corresponds to approximately 400 mg/kg body weight per day (200-600 mg/kg body weight per day). Growth (weight increase) in this group was poorer than for the unexposed group. Furthermore, no animal receiving only diethylamine developed liver carcinomas (histological examination of various organs including the liver). Nor were liver carcinomas seen with administration of diethylamine hydrochloride mixed with sodium nitrite (20 animals: 2 + 0.4 g/l, 20 animals: 4 + 0.8 g/l) in drinking water (pH 7.5). The animals in both these groups were estimated to have consumed an average of 210 mg and 250 mg respectively of diethylamine/animal per day, and 40 mg and 50 mg respectively of sodium nitrite/animal per day. The authors conclude that the

formation of diethylnitrosamine in the stomach was insufficient to induce carcinomas (41).

In a study of 15-day-old mice (30-35 animals/group), liver tumours (of the adenomatous or trabecular type) were seen in 5 of 15 animals (of which 2 were trabecular carcinomas) after a single peroral administration of diethylamine hydrochloride in distilled water (dose: 50 mg/kg body weight). 2 of 17 controls had liver tumours (both were trabecular carcinomas). Upon administration of diethylamine hydrochloride immediately followed by sodium nitrite (single peroral dose, 50 mg/kg body weight of each substance, in distilled water), liver tumours were seen in 14 of 23 animals (of which 4 were trabecular carcinomas). The animals were euthanised in batches for up to 110 weeks. The results of the study suggest the formation of carcinogenic nitrosamine through interaction between diethylamine hydrochloride and sodium nitrite (39).

Effects on reproduction

In a poorly reported study a somewhat increased occurrence (unclear statistical significance) of histological changes in the testicles (including degenerative changes, impaired spermatogenesis) of rats after inhalation exposure to 251 ppm diethylamine for 6.5 hours/day, 5 days/week for up to 24 weeks was seen. The effects, however, were normally unilateral and judged not to be related to diethylamine. Ovaries and uteri were also reported to have been studied in histological examinations, but no effects were reported (29).

Dose effect/dose response relationships

Ethylamine and diethylamine have alkaline properties, which is why direct contact with substances in liquid form (also as diluted solution) can induce local tissue damage. Ethylamine and diethylamine appear to be equally potent irritants, based on alkalinity (pK_b) and animal experiments (irritation/erosion of the eyes and respiratory tract, RD_{50}). See Tables 1 and 2.

Ethylamine

No relevant human studies have been found.

In inhalation studies on rabbits, pronounced irritation effects on the eyes (oedema and corneal erosion) and the respiratory tract were demonstrated at 49 ppm. Lower levels were not tested. At 100 ppm changes in the kidneys were also seen (4). RD_{50} in mice at 15 minutes exposure was 151 ppm (282 mg/m^3) (16), see Table 1.

Diethylamine

Subjective effects of irritation in the eyes and nose were reported in five male test subjects at exposures to increasing levels of diethylamine, from 0 to approximately 12 ppm (time-weighted average 10 ppm) over 1 hour. No objective signs

of nasal swelling were seen, however, in one group of test subjects (4 men, 1 woman) exposed to 25 ppm for 15 minutes (28). The authors stress that the study has weaknesses, chiefly in the design (knowledge of exposure), variation, and the small number of test subjects. They also mention that the study does not permit estimating the threshold value for mucous membrane irritation; at the same time they judge that the data suggests sensory irritation at concentrations around 10 ppm.

26 ppm was regarded as the NOEL in an experimental study in animals, but histopathological examination of nostrils was not done at this concentration (29). Pronounced irritation effects in the eyes (oedema and corneal erosion) and the respiratory tract, as well as focal, moderate degenerative changes in the hepatic parenchyma were observed in another study on rabbits after repeated exposure at 53 ppm. Lower levels were not tested. At 109 ppm, changes in the kidneys were also reported (4). RD_{50} in mice at 30 and 15 minutes exposure was 184 ppm and 202 ppm respectively (16, 34), see Table 2.

A 2% solution of diethylamine was reported to result in serious eye irritation when applied to the eyes of rabbits. Reddening, swelling, and inflammation of the conjunctiva, inflammation of the iris, and cloudy cornea were noted (20, 21).

Animal experiments show that diethylamine can induce contact allergies (9, 50, 51). The occasional cases of contact allergy with diethylamine described have been related to the use of protective rubber gloves (24, 25).

There is no support for diethylamine being carcinogenic, but carcinogenic nitrosamines, including diethylnitrosamine, can be formed in industrial environments through reactions between secondary amines and various nitrosation agents, for example nitrite or nitrogen oxides in the air (23, 39, 41, 46). Formation of diethylnitrosamine from the secondary amine diethylamine and nitrogen oxides in the air has been demonstrated experimentally (11, 37). The formation of diethylnitrosamine can also occur during simultaneous exposure to diethylamine and nitrite in the stomach (10, 40). In a study on mice, this mixture has increased the development of liver cancer (39).

Conclusions

The critical effect of occupational exposure to ethylamine and diethylamine is considered to be mucous membrane irritation of the eyes and respiratory tract. The critical effect level cannot be established, but a study with a few test subjects reports eye and respiratory tract irritation at exposure to 10 ppm diethylamine as a time-weighted average over 1 hour (increasing concentrations from 0 to approximately 12 ppm during exposure). Ethylamine and diethylamine appear to be equally potent irritants.

In liquid form, ethylamine and diethylamine can cause serious eye damage (even in diluted solution).

Animal experiments indicate that diethylamine is a weak contact allergen.

The risk for formation of carcinogenic nitrosamine should be taken into consideration in simultaneous exposure to diethylamine and nitrogen oxides.

Table 1. Effects on laboratory animals upon inhalation exposure to ethylamine.

Air level (ppm)	Exposure	Species	Effects	Ref.
49	7 hrs/day, 5 days/wk, 6 wks	Rabbit	LOAEL. Irritation effects in the respiratory tract (peribronchitis, pneumonitis, thickening of vessel walls in the lungs) and the eyes[1] (oedema in cornea and nicitating membrane, multiple corneal erosions).	4
100	7 hrs/day, 5 days/wk, 6 wks	Rabbit	Irritation effects in the respiratory tract (small haemorrhages, peribronchitis, thickening of vessel walls in the lungs), light to moderate degenerative changes in the renal parenchyma.	4
151	15 min	Mouse	RD_{50}	16
8000	4 hours	Rat	2 of 6 animals died.	44

[1] Corneal injuries were not observed until after 2 weeks of exposure.

Table 2. Effects on laboratory animals upon inhalation exposure to diethylamine.

Air level (ppm)	Exposure	Species	Effects	Ref.
26	6.5 hrs/day, 5 days/wk, up to 24 wks	Rat	NOAEL[1]	29
53	7 hrs/day, 5 days/wk, 6 wks	Rabbit	LOAEL. Irritation effects in the respiratory tract (including moderate peribronchitis, light thickening of vessel walls) and in the eyes (oedema and multiple corneal erosions), occasional foci with moderate degenerative changes in hepatic parenchyma.	4
109	7 hrs/day, 5 days/wk, 6 wks	Rabbit	Irritation effects in the respiratory tract (including broncho-pneumonia), marked degenerative changes in hepatic parenchyma (also regeneration), nephritis with light tubular changes.	4
184	30 min	Mouse	RD_{50}	34
202	15 min	Mouse	RD_{50}	16
251	6.5 hrs/day, 5 days/wk, up to 24 wks	Rat	Clinical signs of strong irritation in eyes and nose, histo-pathological changes in nose (squamous metaplasia, lym-phoid hyperplasia, rhinitis); lower body weight increase, significantly increased level of urea nitrogen in the blood.	29
549	30 min	Mouse	Halved respiratory frequency upon exposure via tracheal cannula (tRD_{50})[2].	34
4000	4 hours	Rat	LC_{50}	43

[1] 26 ppm was not considered as an effect level by the authors (no histopathological examination, however, of nostrils at this concentration).
[2] Measurement of irritation in the lungs.

Potential conflicts of interest

No potential conflicts of interest have been reported.

References

1. ACGIH. Ethylamine. *Documentation of the threshold limit values and biological exposure indices*. 7th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2001:3 pp.
2. Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-290.
3. Andersson E, Järvholm B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 110. Diethylamine, diethylenetriamine, dimethylamine and ethylenediamine*. Arbete och Hälsa 1994;23:1-8. National Institute of Occupational Health, Solna.
4. Brieger H, Hodes WA. Toxic effects of exposure to vapors of aliphatic amines. *Arch Ind Hyg Occup Med* 1951;3:287-291.
5. Bunge AL. Re: "Dermal absorption potential of industrial chemicals: criteria for skin notation". *Am J Ind Med* 1998;34:89-90.
6. Carpenter CP, Smyth HF. Chemical burns of the rabbit cornea. *Am J Ophth* 1946;29:1363-1372.
7. Cavender FL. Aliphatic and alicyclic amines. In: Bingham E, Cohrssen B, Powell CH, eds. *Patty's Toxicology 5th ed*. New York: John Wiley & Sons, Inc, 2001;4:683-815.
8. DECOS: *Health-based recommended occupational exposure limits for ethylamine*. Dutch Expert Committee for Occupational Standards. Voorburg: Directorate-General of Labour of the Ministry of Social Affairs and Employment. Report RA 7/90, 1990.
9. De Jong WH, Tentij M, Spiekstra SW, Vandebriel RJ, Van Loveren H. Determination of the sensitising activity of the rubber contact sensitisers TMTD, ZDMC, MBT and DEA in a modified local lymph node assay and the effect of sodium dodecyl sulfate pretreatment on local lymph node responses. *Toxicology* 2002;176:123-134.
10. DFG. Deutsche Forschungsgemeinschaft. Diethylamin. Gesundheitsschädliche Arbeitsstoffe. *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten.* VCH Verlag Chemie, 1984.
11. DFG. Deutsche Forschungsgemeinschaft. Diethylamin. Gesundheitsschädliche Arbeitsstoffe. *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten.* VCH Verlag Chemie, 1996.
12. DFG. Deutsche Forschungsgemeinschaft. Ethylamin. Gesundheitsschädliche Arbeitsstoffe. *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*. VCH Verlag Chemie, 1984.
13. DFG. Deutsche Forschungsgemeinschaft. Ethylamin. Gesundheitsschädliche Arbeitsstoffe. *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*. VCH Verlag Chemie, 1996.
14. Drotman RB, Lawhorn GT. Serum enzymes as indicators of chemically induced liver damage. *Drug Chem Toxicol* 1978;1:163-171.
15. Fiserova-Bergerova V, Pierce JT, Droz PO. Dermal absorption potential of industrial chemicals: Criteria for skin notation. *Am J Ind Med* 1990;17:617-635.
16. Gagnaire F, Azim S, Bonnet P, Simon P, Guenier JP, de Ceaurriz J. Nasal irritation and pulmonary toxicity of aliphatic amines in mice. *J Appl Toxicol* 1989;9:301-304.

17. Grant WM, Schuman JS. *Toxicology of the eye*. 4th ed. Springfield, Illinois, USA: CC Thomas Publ, 1993:548-549.
18. Hedenstedt A. Mutagenicity screening of industrial chemicals: seven aliphatic amines and one amide tested in the Salmonella/microsomal assay. *Mutat Res* 1978;53:198-199.
19. Hussain S, Ehrenberg L. Mutagenicity of primary amines combined with nitrite. *Mutat Res* 1974;26:419-422.
20. Jacobs GA, Martens MA. An objective method for the evaluation of eye irritation *in vivo*. *Food Chem Toxicol* 1989;27:255-258.
21. Jacobs GA. OECD eye irritation tests on 2 alkalis. *J Am Coll Toxicol* 1992;11:727.
22. Johanson G, Rauma M. *Basis for skin notation. Part 1. Dermal penetration data for substances on the Swedish OEL list*. Arbete och Hälsa 2008;42(2). Göteborgs Universitet, Göteborg.
23. Jönsson LS, Lindh CH, Bergendorf U, Axmon A, Littorin M, Jönsson BAG. N-Nitrosamines in the southern Swedish rubber industries - exposure, health effects, and immunologic markers. *Scand J Work Environ Health* 2009;35:203-211.
24. Kaniwa M-A, Isama K, Nakamura A, Kantoh H, Hosono K, Itoh M, Shibata K, Usuda T, Asahi K, Osada T, Matsunaga K, Ueda H. Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis. *Contact Dermatitis* 1994;31:65-71.
25. Knudsen BB, Hametner C, Seycek O, Heese A, Koch HU, Peters KP. Bioavailability of rubber accelerators in rubber gloves and patch test reactivity. *Dermatol Beruf Umwelt* 2000;48:127-133.
26. Loury DJ, Smith-Oliver T, Butterworth BE. Assessment of unscheduled and replicative DNA synthesis in rat kidney cells exposed *in vitro* or *in vivo* to unleaded gasoline. *Toxicol Appl Pharmacol* 1987;87:127-140.
27. Lundberg P, ed. 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.
28. Lundqvist GR, Yamagiwa M, Pedersen OF, Nielsen GD. Inhalation of diethylamine--acute nasal effects and subjective response. *Am Ind Hyg Assoc J* 1992;53:181-185.
29. Lynch DW, Moorman WJ, Stober P, Lewis TR, Iverson WO. Subchronic inhalation of diethylamine vapor in Fischer-344 rats: organ system toxicity. *Fundam Appl Toxicol* 1986;6:559-565.
30. Lynch DW, Moorman WJ, Lewis TR, Stober P, Hamlin RD, Schueler RL. Subchronic inhalation toxicity of ethylamine (EA) vapor in F-344 rats. *Toxicologist* 1988;8:250.
31. Mitchell SC, Zhang AQ, Smith RL. Ethylamine in human urine. *Clin Chim Acta* 2000;302:69-78.
32. Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 1986;8 Suppl 7:1-119.
33. Neurath GB, Dünger M, Pein FG, Ambrosius D, Schreiber O. Primary and secondary amines in the human environment. *Food Cosmet Toxicol* 1977;15:275-282.
34. Nielsen GD, Yamagiwa M. Structure-activity relationships of airway irritating aliphatic amines. Receptor activation mechanisms and predicted industrial exposure limits. *Chem Biol Interact* 1989;71:223-244.
35. Owais WM, Rosichan JL, Ronald RC, Kleinhofs A, Nilan RA. A mutagenic metabolite synthesized by Salmonella typhimurium grown in the presence of azide is azidoalanine. *Mutat Res* 1983;118:229-239.
36. Patel VK, Venkatakrishna-Bhatt H, Patel NB, Jindal MN. Pharmacology of new glutarimide compounds. *Biomed Biochim Acta* 1985;5:795-803.

37. Pitts JN, Grosjean D, Van Cauwenberghe K, Schmid JP, Fitz DR. Photooxidation of aliphatic amines under simulated atmospheric conditions: Formation of nitrosamines, nitramines, amides, and photochemical oxidant. *Environm Sci Technol* 1978;12:946-953.

38. Rechenberger J. Über die flüchtigen Alkylamine im menschlichen Stoffwechsel. *Hoppe-Seyler's Zeitschrift für physiologische Chemie* 1940;265:275-284.

39. Rijhsinghani KS, Abrahams C, Krakower C, Swerdlow M, Ghose T. Tumor induction in $C_{57}BL$ x C_3HF_1 mice following single oral administration of diethylamine hydrochloride (DEA HCl) and sodium nitrite ($NaNO_2$). *Cancer Detect Prev* 1982;5:283-290.

40. Sen NP, Smith DC, Schwinghamer L. Formation of N-nitrosamines from secondary amines and nitrite in human and animal gastric juice. *Food Cosmet Toxicol* 1969;7:301-307.

41. Sen NP, Smith DC, Moodie CA, Grice HC. Failure to induce tumours in guinea-pigs after concurrent administration of nitrite and diethylamine. *Food Cosmet Toxicol* 1975;13:423-425.

42. Smyth HF, Carpenter CP, Weil CS. Range-finding toxicity data, list III. *J Ind Hyg Toxicol* 1949;31:60-62.

43. Smyth HF, Carpenter CP, Weil CS. Range-finding toxicity data. List IV. *AMA Arch Ind Hyg Occup Med* 1951;4:109-122.

44. Smyth HF, Carpenter CP, Weil CS, Pozzani UC. Range-finding toxicity data. List V. *AMA Arch Ind Hyg Occup Med* 1954;10:61-68.

45. Speit G, Wolf M, Vogel W. The effect of sulfhydryl compounds on sister-chromatid exchanges. *Mutat Res* 1980;78:267-272.

46. Spiegelhalder B, Preussmann R. Occupational nitrosamine exposure 1. Rubber and tyre industry. *Carcinogenesis* 1983;4:1147-1152.

47. Szabo S, Reynolds ES. Structure-activity relationships for ulcerogenic and adrenocorticolytic effects of alkyl nitriles, amines, and thiols. *Environ Health Persp* 1975;11:135-140.

48. Szabo S, Reynolds ES, Unger SH. Structure-activity relations between alkyl nucleophilic chemicals causing duodenal ulcer and adrenocortical necrosis. *J Pharm Exper Ther* 1982;223:68-76.

49. Szybalski W. Special microbiological systems. II. Observations on chemical mutagenesis in microorganisms. *Ann NY Acad Sci* 1958;76:475-489.

50. Van Och FMM, Slob W, de Jong WH, Vandebriel RJ, van Loveren H. A quantitative method for assessing the sensitizing potency of low molecular weight chemicals using a local lymph node assay: employment of a regression method that includes determination of the uncertainty margins. *Toxicology* 2000;146:49-59.

51. Van Och FMM, Vandebriel RJ, Prinsen MK, De Jong WH, Slob W, van Loveren H. Comparison of dose-responses of contact allergens using the guinea pig maximization test and the local lymph node assay. *Toxicology* 2001;167:207-215.

52. Van Och FMM, van Loveren H, van Wolfswinkel JC, Machielsen AJC, Vandebriel RJ. Assessment of potency of allergenic activity of low molecular weight compounds based on IL-1α and IL-18 production by a murine and human keratinocyte cell line. *Toxicology* 2005;210:95-109.

53. Weast RC, ed. *Handbook of chemistry and physics*. 55th ed. Cleveland, Ohio: CRC Press, 1974.

54. WHO. Safety evaluation of certain food additives. Prepared by the 65th meeting of the joint FAO/WHO expert committee on food additives (JECFA). Aliphatic and aromatic amines and amides. *WHO Food Additives Series* 2006;56:327-403.

55. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environm Mutagen* 1987;9 Suppl 9:1-110.

Consensus Report for Carbon dioxide

June 15, 2011

This consensus report is primarily based on a criteria document from 1976 by NIOSH (64) and a report from EPA published in 2000 (22). A comprehensive literature search was conducted in 2005; this has been supplemented with literature searches in PubMed, most recently in January 2011. References have also been taken from a, as yet unpublished, guidance document for determining emergency limit values (Acute Exposure Guideline Levels) from ORNL-Toxicology & Hazard Assessment Group/March 2010.

Chemical and physical data

CAS number	124-38-9
Synonyms	carbon dioxide, carbonic acid, carbon dioxide snow, dry ice
Molecular formula	CO_2
Molecular weight	44.01 g/mol
Melting point	-78.5 °C, sublimates into gas
Solubility in water	71 mg/100 ml (0 °C), 36 ml/100 ml (60 °C)
Relative gas density	1.53
Conversion factors (at 25 °C)	1 ppm = 1.80 mg/m^3; 1 mg/m^3 = 0.556 ppm
Conversion to %-units:	10,000 ppm = 1%, 1 kPa = 1% 1 mmHg (torr) = 0.13%

Carbon dioxide is a colourless, odourless and non-flammable gas. The gas is heavier than air, which implies a risk of accumulation at low levels in confined spaces and at ground level. Carbon dioxide in solid state can cause frostbite upon contact.

Occurrence Application Exposure

Carbon dioxide is normally present in outdoor air at a concentration of 0.03-0.04% (3). In the "clean" air of Hawaii, the annual average value increased from 0.03% (316 ppm) in 1959 to 0.04% (385 ppm) in 2008 (44). Measured indoor levels of carbon dioxide in 1991 were reported to be 0.035-0.25% (350-2500 ppm) (84). When people are present in a room, the concentration of carbon dioxide increases, as the carbon dioxide produced endogenously in our metabolism is exhaled. The

carbon dioxide concentration has therefore been used as an indicator substance for testing the effectiveness of ventilation in relation to the number of people present in a room. The recommendation of the Swedish Work Environment Authority is for the average concentration of carbon dioxide during one day not to exceed 0.1% (1000 ppm) in non-industrial premises, such as conference halls, office space and classrooms, to prevent the air from being perceived as uncomfortable (3).

The use of snorkels (89, 94) or face masks (69) increase the exposure to carbon dioxide through the increase of the dead space[1] and thus the re-inhalation of a larger volume of air containing endogenously produced carbon dioxide. In a study which sought to compare three different standard methods (artificial physiological/ anatomical models) to test respiratory protective devices, the average inspired concentration of carbon dioxide was stated to be just over 1% (range 0.9-2.06) for three gas masks (2 full face masks, 1 half mask) (9). Unpublished data, described in the same reference (9), indicate an increase in the average concentration of carbon dioxide in the air in the magnitude of 0.2-3.6% for different respiratory protective devices measured in the simulator. The results are summarised in Table 1. In addition, the use of welding helmets (98) and motorcycle helmets, known as integral helmets (6), increase the dead space to the extent that the concentration of carbon dioxide in the inspired air is affected. When using integral helmets, the average concentration of carbon dioxide in the inspired air is reported to be around 1.3% when stationary.

Divers and astronauts are usually referred to as professions with an increased risk of exposure to elevated concentrations of endogenously produced carbon dioxide. In addition, submarine personnel have been studied in several cases and the concentration on board nuclear submarines has been stated to amount to 0.7-1% (75) and, in snorkel-type submarines, as high as 3% (76).

Carbon dioxide is used as a propellant in spray cans for food and cosmetics, as well as in the extraction of beer from kegs. It is also used in fire extinguishers, both in hand-held extinguishers and fixed installations. Carbon dioxide is used in the form of carbonic acid in beer and soft drinks. In solid form (carbon dioxide snow), it is used as a coolant for the refrigeration of food, for example, as well as in the form of pellets in connection with blasting. Carbon dioxide is used as a protective gas during welding and in health care, for example to expand the abdominal cavity during keyhole surgery. Carbon dioxide can also be added to oxygen since it stimulates breathing (54, also see the AGA gas website 20/05/2010: http://www.aga.se).

In the petroleum industry, carbon dioxide is a by-product of the manufacturing of, for example, ammonia, methanol and hydrogen, as well as in processes where carbon monoxide is used, such as hydrogen cracking of petroleum products (38, 54).

[1] The dead space constitutes the volume in the respiratory tract where no gas exchange occurs. The normal volume of the dead space for a man weighing 70 kg is approximately 150 ml (25).

Table 1. Average concentration of carbon dioxide in the inspired air of different respiratory protective devices measured in a simulator. Unpublished data, described in reference (9).

Type of respiratory protective device	Number of tested respiratory protective devices within type	Average carbon dioxide concentration in the inspired air (%)
Powered air-purifying respirators	11	0.2-0.8
Supplied air respirators	20	0.4-0.5
Gas masks	6	0.9-2.6
P-100 air-purifying respirators	27	0.6-2.6
N95 filtering face piece respirators	26	2.3-3.6

Another area of application is supercritical fluid extraction. In this method carbon dioxide is the most used supercritical fluid (7). The technique can be used for extraction of food and drink, for example, to produce decaffeinated coffee or low-fat food products, extract flavour and aromatic substances, analyse the fat content in food or remove harmful substances, e.g. pesticides (7).

High levels of carbon dioxide have been measured when dry ice is used for refrigeration, for example in the poultry industry. Concentrations of 50,000 ppm (5%) were measured in areas with poor ventilation and approximately 5,000 ppm (0.5%) in areas with good ventilation. In a factory where daily measurements were performed over a two month period, carbon dioxide concentrations were found to be 11,500-96,000 ppm, with an average value of 34,000 ppm (1.2-9.6%, and 3.4% respectively) in an area with poor ventilation. Exposure measurements showed consistent values above 0.5% (8 hour time-weighted average) (40). Elevated levels of carbon dioxide are found in fermentation processes, as those in breweries and bakeries (2).

High concentrations of carbon dioxide can be formed in closed spaces associated with the prolonged storage of organic material, e.g., silos and cargo holds. Carbon dioxide is formed when organic material decomposes via microbiological or autooxidative processes. Other gases can also be formed in these processes, such as carbon monoxide (CO), hydrogen sulphide (H_2S), ammonia and other amines, and different hydrocarbons. What is formed and in which proportions depends on several factors, such as the type of organic material, temperature, humidity, size of the storage space and the amount of space filled, which micro-organisms are present in the material, ventilation, etc. The repression of oxygen and the consumption of oxygen during the decomposition of the organic material leads to reduced oxygen levels and, in some cases, entirely anoxic conditions (11, 50, 91, 92). In a study, carbon dioxide concentrations of between 0.5% and 15% and oxygen concentrations between 0% and 20.9% were reported in stairwells adjacent to the cargo hold in a ship transporting timber and wood chips. A strong negative correlation was found between carbon dioxide and oxygen levels and the slope of the regression line indicated that approximately 70% of the oxygen loss

was recovered as CO_2 in the gas phase. Carbon monoxide concentrations were reported to be between 2 and 174 ppm (92). In addition to the transport of wood products, high levels of carbon dioxide have been reported in cargo space containing onions (99) and fish (11). In the case of the latter, low levels of oxygen and high levels of hydrogen sulphide, ammonia and other amines were also reported.

Buildings where high concentrations of carbon dioxide have been measured are also described, with particularly high levels in the basement area. For example, in a building built on top of a former coal mine, concentrations of approximately 10% were measured in the crawl space. These measurements were carried out because the owners had repeatedly sought medical attention for various symptoms associated with periods spent in the basement and crawlspace. Prior investigations of possible causes revealed decreased oxygen levels in the crawl space (14%) which initiated the carbon dioxide measurements, as carbon dioxide was suspected to be the cause of this reduction (49). Even buildings in geothermal areas have been reported to have elevated carbon dioxide concentrations in basement areas (5), sometimes in combination with other gases such as H_2S (20). In the village of Furnas, located in an old volcano crater in the Azores, elevated levels of carbon dioxide have been measured at floor level in several houses, particularly at openings for drainage or cracks in the floor. Levels as high as 10-30% were found in floor cupboards or other unventilated areas. Many bedrooms were located on the ground floor. In these rooms concentrations of approximately 1% carbon dioxide were found early in the morning at a height of around 1 metre, thus at the height where people slept (5). Before the measurements were conducted people living in Furnas were not aware of the of high carbon dioxide levels

Tobacco smoke has been reported to contain 12.5% carbon dioxide in the primary smoke, smoke from the combustion of fuel gas approximately 8.8% and smoke from coal plants 13.7% (1).

Recycling and disposal of carbon dioxide is being discussed as a possible means of reducing carbon dioxide emissions to the atmosphere, from the combustion of fossil fuels and renewable fuels in combined power and heating plants (46). Transport and storage of large amount of carbon dioxide can be expected to lead to leakage and emissions associated with accidents, and the need for accurate risk analysis has recently been expressed (23).

Uptake, biotransformation, excretion

Carbon dioxide is normally produced during cellular respiration (oxidative metabolism). The carbon dioxide formed diffuses freely through biological membranes and is transported with the blood to the lungs where it diffuses through the alveolo-capillary membrane to the alveoli and is then exhaled. This diffusion is rapid and takes place along a concentration gradient. Typically, carbon dioxide concentration in the venous blood is, when it reaches the alveoli, approximately 6% (PCO_2 ~46 mm Hg) and the carbon dioxide concentration in the alveoli

is approximately 5% (PCO_2 ~40 mm Hg). The arterial blood normally has the same carbon dioxide content as the air in the alveoli (25, 52).

The carbon dioxide is transported dissolved directly in the blood (approximately 5%), bound to proteins (primarily haemoglobin) in the form of carbamino groups (approximately 5%) and as hydrogen carbonate (approximately 90%). Hydrogen carbonate is formed when carbon dioxide reacts with water and forms carbonic acid, a weak acid (pKa = 6.1), which dissociates into hydrogen carbonate (bicarbonate) and protons (hydrogen ions) in accordance with chemical equilibrium

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

The first step (the chemical equilibrium between carbon dioxide, water and carbonic acid) is catalysed by the enzyme carbonic anhydrase, which has an extremely high activity and is found in large quantities in red blood cells (25, 52).

In addition to transporting away carbon dioxide, the carbon dioxide/hydrogen carbonate system acts as a buffer system which maintains the acid-base balance in the body and stabilises the pH level, both in the short- and long-term. Normal serum pH ranges from 7.35 to 7.45[2] and deviations from this range can be an indicator of a life-threatening condition in the acid-base and electrolyte balance. Chemoreceptors in the arteries and in the respiratory centre in the medulla oblongata detect carbon dioxide in the blood and affect the respiratory centre that adjusts pulmonary ventilation and exhalation of carbon dioxide so that the balance is maintained (25, 52, 53, 67, 100).

An increase in carbon dioxide in the air, will interfere with the elimination of endogenously produced carbon dioxide from the lungs and thus increase the carbon dioxide in the arterial blood (hypercapnia[2] = carbon dioxide concentration in arterial blood >5,85%). As a result, the above equilibrium shifts to the right with an increase in hydrogen ion concentration and a pH decrease (respiratory acidosis[2] = the blood's pH value below the normal value of 7.35-7.45). This is counteracted by increased pulmonary ventilation and the exhalation of carbon dioxide. Compensatory mechanisms are also activated in the kidneys so as to increase the excretion of hydrogen and chloride ions and the re-absorption of hydrogen carbonate and sodium. The effect on the breathing is instantaneous, while the effect on the kidneys is slower (10, 25, 53).

Toxic and physiological effects

In addition to a suffocating effect caused by the displacement and reduction of oxygen during moments of increased carbon dioxide concentration, carbon dioxide has been reported to cause both direct and indirect respiratory and cardiovascular effects. Many of the effects are mediated via the autonomic and central nervous systems and can be considered physiological adjustments (adaptations). They could be regarded as "non-adverse effects" in a short-term perspective, but

[2] The values of what can be considered as acidosis, hypercapnia and normal pH, vary slightly in different sources. In literature, the terms acidosis and hypercapnia are often used to describe small (within normal range) decreases in pH and increases in carbon dioxide in the blood.

may possibly affect disease processes at prolonged exposure. ACGIH have chosen to designate these effects as “metabolic stress” (2).

Several studies indicate that it takes 3-5 days for the adaptation and compensation of plasma pH after exposure to 3% or higher carbon dioxide concentrations. Following lower exposure (≤2%) however, 2-3 weeks was required for compensation (75, 79). The author hypothesized that the rapid compensation occurs via renal regulation but compensation at low exposure levels of carbon dioxide is primarily due to a buffering capacity in osseous tissues.

In order for carbon dioxide to cause suffocation by displacing oxygen in the air relatively high concentrations are required. An increase of carbon dioxide by, for example, 5%, results in an oxygen decrease of 1%, i.e., if the carbon dioxide level increases from 0.04 to 5.04% then the oxygen level decreases from 21 to 20% and the nitrogen content from 78 to 74% (36).

A large number of not entirely consistent studies, both peer reviewed and non-peer reviewed, have been published on the subject of how carbon dioxide concentrations in the air affect people. The inter-individual variation seems to be large. Table 2 gives a rough idea of which concentrations and exposure times result in acute effects on the lungs/breathing, blood circulation and CNS (22). When the carbon dioxide concentration in the inspired air is close to 7%, the elimination of carbon dioxide becomes difficult and, when the level exceeds approximately 7%, there is a steep increase in carbon dioxide in the arterial blood, regardless of hyperventilation. This results in an accumulation of carbon dioxide which causes headache, CNS depression, confusion and ultimately coma and death (25).

Table 2. Approximate effect levels in humans following short-term exposure to carbon dioxide (22).

Carbon dioxide concentration (%)	Time	Effect
2	several hours	Headache, dyspnea upon mild exertion.
3	1 hour	Mild headache, sweating and dyspnea at rest.
4-5	within a few minutes	Headache, dizziness, increased blood pressure, uncomfortable dyspnea.
6	1-2 minutes	Hearing and visual disturbances.
6	≤16 min	Headache, dyspnea.
6	several hours	Tremors.
7-10	a few minutes	Near unconsciousness, unconsciousness.
7-10	1.5 minutes to 1 hour	Headache, increased heart rate, shortness of breath, dizziness, sweating, rapid breathing.
>10-15	1 to several hours	Dizziness, drowsiness, muscle twitching, unconsciousness.
17-30	within 1 minute	Loss of controlled and purposeful activity, unconsciousness, convulsions, coma, death.

The focus in the following summary is on studies that describe the effects of carbon dioxide at concentrations of 3% and below.

Human data

Short-term exposure

Deaths associated with carbon dioxide exposure have been reported in connection with the handling of carbon dioxide (e.g., fire extinguishers or dry ice) in small confined spaces (54). According to the EPA, 51 incidents with a total of 145 carbon dioxide-related injuries and 72 fatalities were reported internationally between 1975-2000 (22), all of them associated with maintenance and accidents with carbon dioxide-based fire extinguishing systems (also see ref. 19, 28).

In the case of storage and transport of organic material in confined spaces, several accidents have occurred in these areas as well as in adjoining rooms, sometimes with deadly outcome. This has been reported in conjunction with the handling of organic material (e.g., wood chips and fish), on and during the unloading of ships, during cleaning and maintenance of wine vats and cleaning of sewers and sewage treatment plants, as well as during the production of silage (11, 54, 91, 92, 99). Several toxic substances can be formed in these environments, such as carbon dioxide, carbon monoxide, hydrogen sulphide and ammonia, and these, in combination with lowered level of oxygen caused by the displacement and consumption of oxygen, result in a potentially life-threatening atmosphere. The accidents and fatalities reported were most likely due to a combination of two or more of these factors (11, 54, 91, 92). The formation of substances in each environment is dependent on several different factors, see above under the heading Occurrence Application Exposure.

In some of natural disasters, deaths have been attributed to carbon dioxide exposure. At Lake Nyos in Cameroon, it was estimated that 10^9 m^3 of volcanic gases were released from the volcanic lake in 1986, resulting in the deaths of 1,700 people. Similar but smaller scale emissions have occurred at Lake Monoun in Cameroon with a fatality rate of 34, as well as in Dieng, Java, where 142 fatalities were recorded (52).

Carbon dioxide has a potent effect on respiration, with both tidal volume and respiratory rate being stimulated. It should be noted that data from experiments with concentrations of 7-10% are uncertain due to the limited time periods that are possible when studying subjects at these high concentrations (51).

In a study, 10 test subjects were exposed to 1.1% carbon dioxide and 5 subjects to 0.8%, for a period of 30 minutes (55). The minute volume increased by 18% and 10%, respectively, and the alveolar carbon dioxide concentration increased by 0.2% and 0.17%, respectively, compared to prior exposure.

In a figure, Guillerm & Radziszewski summarise acute pH changes in four different experiments, at exposure levels of 2%, 2.8%, 3.7% and 4.2% carbon dioxide. After two hours of exposure, the ΔpH in the arterial blood was 0.00,

-0,02, -0.04 and -0.06, respectively, and, after 24 hours, -0.01, -0.035, -0.03 and -0.04 (30).

Eight fit young men were exposed to 0% (control), 1%, 2%, 3% and 4% carbon dioxide at rest and during exercise (1/2 and 2/3 of the maximal oxygen uptake ability as well as during maximal oxygen uptake on an exercise bike). The individuals were exposed for 15 minutes prior to and during the exercise, which lasted 30 minutes. The respiratory minute volume increased as the exposure and exercise increased, and the arterial pH underwent a linear decrease (at 4% carbon dioxide exposure with 0.034 pH units at rest and 0.102 pH units during exercise at 2/3 of the maximal oxygen uptake ability), when compared to the control level. During exercise several of the subjects experienced dyspnea and pains in the intercostal muscles at the two highest exposure levels. At 4% carbon dioxide, six out of seven test subjects got a headache. The headache usually appeared at the end of a session and dissipated within one hour after exposure (59).

Systemic effects have been reported such as increased heart rate, systolic and diastolic blood pressure, mean arterial blood pressure and stroke volume, as well as an increased variability in the QT interval on the ECG (determination with a 12 lead ECG as a measure of regional repolarisation). Also arterial blood pressure and vascular resistance in the lungs increased. These effects were experienced by the test subjects after 30 minutes of exposure. The gas mixture was adjusted to give an end-tidal (occurring at the end of exhalation of a normal tidal volume) carbon dioxide concentration of 7 kPa (approximately 7%, versus normally 5%). Respiratory rate increased 62% during exposure (47). An end-tidal carbon dioxide concentration of 7 kPa (approximately 7%) and a respiratory rate increase of 62% suggest that the inhaled concentration of carbon dioxide was about 6%.

In a study, test subjects (16 individuals who participated in 72 experiments) re-inhaled exhaled air (the oxygen level was maintained at 30%). After 17-32 minutes, the carbon dioxide concentration was 5.7-9.3%. This showed that 1-8% carbon dioxide resulted in an increase in systolic and diastolic blood pressure and an increased heart rate. A slight increase in pulse was noted already at 1-2% (3-6 minutes) and in blood pressure at 2-3% (6-9 minutes), but an obvious effect (greater than 10% difference with respect to control values) was first noted at exposure levels of 5% carbon dioxide (15 minutes). At 1% (3 min), pulmonary ventilation increased by 32% and subsequently increased steadily until the end of the experiment (8% carbon dioxide). At 5%, the increase was 308%. At this 5% level, several individuals got a headache, sometimes intense, which disappeared within 20 minutes after exposure. Great intra-individual and inter-individual differences were noted in the study (80).

The effect of exposure to 2.5% and 3.5% carbon dioxide for 15-20 minutes on cerebral blood vessels (as measured by inert gas) was examined in 12 and 11 individuals, respectively. A weak/absence of effect was recorded at 2.5%. At 3.5% carbon dioxide, a 10% increase was shown in cerebral blood flow but no increase in blood pressure was noted. Deeper breathing and increased respiratory rate with mild dyspnea were also commonly noted within 10-15 minutes of exposure. The

authors' conclusion was that the threshold concentration for an increase in the cerebral blood flow is above 2.5% carbon dioxide in the air (0.59% increase in arterial carbon dioxide concentration) (66).

In three healthy test subjects, a significant impairment of vision was noted (coherent motion perception) following exposure to 2.5% carbon dioxide over 1 hour (102). The authors commented on the few subjects examined in the study, that in studies of the basic functions of the nervous system one can assume small inter-individual variation and therefore it is preferable to collect a large amount of data from a relatively small number of subjects. The variation between the test subjects was small in the study and no learning effect was noted (102). In another study by the same research group (90) and with the same exposure level and time frame, decrease in stereoacuity (deterioration of stereoscopic depth perception) was recorded in the three test subjects. In both studies, the effects were reversible, and normal vision had returned within two hours after exposure (90, 102). In an older study, a deterioration of vision was noted in an intensity discrimination test involving exposure to 6% carbon dioxide for 3 minutes (27).

In an old study (26) the effects on hearing, measured with an audiometer, were investigated using 6 test subjects. The exposure levels were between 2% and 8.4% carbon dioxide and the exposure time frame was between 5 and 22 minutes. Slight hearing impairment was recorded in one subject at 3.5% and in others at approximately 4%. The hearing impairment worsened with increasing exposure. The impairment was reversible and, in less than 10 minutes following exposure, hearing had returned to normal and, in some cases, even slight short-term improvements were measured. At 2.5% carbon dioxide, no hearing impairment was noted, but a significant effect on respiratory functions was recorded (no further details given).

Short-term memory and logical reasoning were tested in 10 healthy test subjects (3 women and 7 men) during exposure to 0% (control), 4.5%, 5.5%, 6.5% and 7.5% carbon dioxide over 5-20 minutes via a mouthpiece (71). At the two highest exposure levels, a significant increase in the time it took to solve logical problems was noted after 5 and 15 minutes´ exposure, but the answers had the same degree of accuracy as those given during the control exposure. No significant difference was found between men and women nor was there any effect on short-term memory. No effects were seen at the two lowest exposure levels.

In 8 out of 14 patients who had been diagnosed with a panic anxiety disorder (with or without agoraphobia), a 15 minute exposure to 5% carbon dioxide induced a panic attack. Patients who had previously suffered from more frequent panic attacks were those who tended to exhibit a more severe reaction to the carbon dioxide exposure. Placebo exposures with air did not result in any panic attacks in the patients. In experiments where 8 healthy test subjects were exposed to 5% and 7.5% carbon dioxide, 3 experienced panic attacks at 7.5%, but none at 5% (101). Those experiments with healthy test subjects revealed a dose-dependent increase in anxiety, somatic symptoms and plasma cortisol levels. A higher increase in anxiety and somatic symptoms were seen in the patients exposed to 5% carbon dioxide than in the healthy subjects. The plasma cortisol levels were also

significantly higher at 5% carbon dioxide exposure in the sub-group of 8 patients that had reacted with panic attacks than those given placebo and the healthy subjects (101).

A large number of different models of respiratory protective devices, from heavy portable breathing apparatuses (e.g. self-contained breathing apparatus used in firefighting tasks) to simple surgical masks, are used to protect people from harmful substances and particles in the work environment. All types of respiratory protective devices in some way affect the user (56) and result in various types of physiological/psychological stress, including increased expiratory and inspiratory resistance, an increase in dead space, stress due to elevated temperature and humidity, visual field limitation and impaired ability to communicate. The physiological/psychological effects that have been reported to occur during the use of respiratory protective devices include changes in breathing patterns, increased respiratory work, changes in heart rate and cardiac output, changes in tidal volume as well as respiratory rate and minute volume, increased inspiration/expiration time, changes in oxygen consumption and carbon dioxide production, increased anxiety and subjective discomfort and reduced maximal physical work capacity (4, 33, 34, 42, 56, 61, 65). These unwanted effects are often accentuated with increased exercise (56). However, it is not possible to determine to what extent an increase in carbon dioxide concentration, due to increased dead space and/or hypoventilation, contributes to inducing these effects.

The use of respiratory protective devices increases the dead space and it has been shown that an increase in the dead space results in an increase in the end-tidal carbon dioxide concentration (41). One study reports that the use of a disposable mask (N95) for up to one hour results in an increased carbon dioxide concentration in the blood of approximately 0.15% during moderate exercises, but no effects were noted on, for example, respiratory minute volume or heart rate. Respirator fit testing showed a leakage of ≤1% (68). Elevation of arterial carbon dioxide concentrations of the same magnitude has also been reported with the use of welding helmets (98).

Long-term exposure

Long-term studies have been conducted in order to define harmless carbon dioxide levels for living in submarines or space capsules, wherein subjects were exposed twenty-four hours a day. Whether the results from these studies with continuous exposure can be converted to an 8-hour exposure a day is not known.

In a joint project between NASA, ESA and DARA (National Aeronautics and Space Administration, the European Space Agency, Deutsche Agentur für Raumfahrtangelegenheiten), the effects of exposure to 0.7% and 1.2% carbon dioxide were investigated over a period of 23 days in an exposure chamber. In the first study, four healthy young men were exposed to 0.7% carbon dioxide. The men were sealed into the chamber for a total of 26 days. During the first two days, base data were collected from before the exposure was initiated and, on the final day, measurements were made when the exposure had ended. Some base data were

also collected before the men entered the chamber. In the second study, 3 months later, the experiment was repeated with exactly the same design and the same four men that had been exposed in the first study. However, this time the carbon dioxide level was increased to 1.2% (97). Several different examinations were performed, including studies on pulmonary function, physical and mental performance, cerebral blood flow and autoregulation of cerebral vasculature, calcium metabolism and circadian rhythm and sleep, resulting in several publications (18, 21, 31, 32, 39, 58, 70, 85, 88). These 9 studies are briefly described below.

Sexton *et al*. investigated different pulmonary function parameters (85). No significant effects were noted at the group level in spirometry, lung volumes, dead space, closing volume or gas mixing in the lungs. However, a gradual reduction in the diffusion capacity for carbon monoxide was consistently noted (measured with the "single and multi-breath wash-out" method) as well as a decrease in cardiac output (measured with the "inert gas technique") during the exposure period. The size and time frame of the changes were not dose-dependent, but roughly the same regardless of the level of exposure (0.7% or 1.2% carbon dioxide) as well as proving reversible (the day after the end of exposure). The authors concluded that small changes can occur in gas exchange in the lungs, but this was not associated with any adverse health effects, and that the risk of pathophysiological effects on pulmonary function at these exposure levels and time periods is low (85).

Manzey *et al*. examined the four test subjects' cognitive and visuo-motor performance (58). The test battery included grammatical reasoning, memory search and unstable tracking, as well as a subjective assessment of alertness and mood. Significantly poorer results were observed at both exposure levels in tracking performance. In the case of exposure to 0.7% carbon dioxide, the course of the deterioration was such that it could be attributed to the effects of confinement in an exposure chamber. At 1.2%, however, the time frame for the deterioration was such that the effect was related to the carbon dioxide exposure in every case during the first half of the exposure time, and it covaried with decreased subjective alertness. A control group consisted of 4 subjects who underwent the same battery of tests during the same time period, but who were not exposed to carbon dioxide, nor confined. The authors' conclusion was that prolonged exposure to 1.2% carbon dioxide results in a deterioration in visuo-motor performance and alertness, but that the level of deterioration does not appear to be of operational relevance.

Drummer *et al*. examined the effects on calcium metabolism (18). During their time in the chamber, the test subjects received a well-controlled diet with a constant calcium and phosphate intake, enriched in vitamin D. The serum level of calcium and urinary and faecal calcium excretion were measured. The data measured during exposure to 0.7% was used in this investigation as control. Serum calcium was significantly lower at the higher exposure level (1.2%) compared with the lower (0.7%), at 7 and 23 days of exposure. Measurement of biomarkers of bone metabolism (alkaline phosphatase, carboxyterminal procollagen type I propeptide (CPIP) in serum and deoxypyridinoline (DPD)

in urine) indicated reduced bone formation and stimulation of bone resorption at exposure to 1.2% carbon dioxide compared with 0.7% (18).

Cerebral blood flow increased by as much as 35% during the first three days of exposure at both 0.7% and 1.2% carbon dioxide, when compared with the control measurements. Hereafter, the blood flow continually decreased to the control level towards the end of the exposure period. Cerebral blood flow induced by visual stimulus also increased during both exposure levels, while cerebral vascular autoregulation was not affected. Headaches were reported during the start of the exposure to 1.2% carbon dioxide (88).

When exposed to 1.2%, the respiratory minute volume increased by 5% after two days of exposure in relation to the control period, and after 5 days signifycantly by 22%. Hereafter, the minute volume decreased continually, so that it had almost reached the control level when the exposure ended. Changes in the minute volume at the 0.7% exposure could not be assessed, since too few measurements were made. The end-tidal carbon dioxide concentration increased by 0.9% (1.2% exposure) and 1.0% (0.7% exposure) after two days of exposure. From day 5 until the end of the exposure period, the increase was somewhat lower. The authors stress that, during the control measurements prior to the commencement of the exposure period, the respiratory minute volume was somewhat higher (approximately 11 l/min for both exposure experiments) than that which was previously documented. This may have led to the increase in the minute volume being underestimated and the increase of the end-tidal carbon dioxide concentration being overestimated in the study (21).

During exercise (30 and 80 W), the minute and tidal volume increased significantly more during both exposure levels when compared with the increase measured during the control period. No effect on oxygen uptake ability related to exposure was noted (37).

In the study by Gundel *et al*., heart and respiratory rate were measured during deep sleep ("slow wave sleep", SWS) (32). A gradual decrease in respiratory rate was observed over time (exposure to 1.2% carbon dioxide) and an increased heart rate after 2 days of exposure (both exposure levels), which then decreased gradually. The decrease in heart rate never plateaued, but continued to decrease until the end of the exposure period. In the case of all four test subjects, a decrease in arousal was noted (during sleep stage 2 and REM sleep) with an increased carbon dioxide concentration, and two subjects had a reduced occurrence of apnea. The authors conclude that exposure to carbon dioxide up to 1.2% does not have any dramatic effects on the cardio-respiratory system during sleep, but that negative health effects cannot be excluded with regard to longer periods of exposure.

No effects on the circadian rhythm (body temperature, sleep-wake cycle, subjective fatigue, activity) or sleep (quality, quantity or pattern) were observed that could be attributed to carbon dioxide exposure (31, 70).

The results of the NASA/ESA/DARA project are summarised in an overview article by Frey *et al*. (24).

Sinclair *et al*. (87) examined how acute (1 hour) or prolonged (15-20 days) exposure to 3% carbon dioxide affected 4 healthy young men during different levels of exercise (none, low, moderate and heavy exercise; heart rate approximately 55, 95, 135 and 158 beats/minute, respectively) in an exposure chamber. As a control, the test subjects breathed normal air. The difference in respiratory minute volume between air and carbon dioxide exposure more than doubled during the low level exercise compared to at rest, and was approximately 15 l/min lower in air. This difference remained relatively constant for the two higher levels of exercise. Both tidal volume and respiratory rate increased with an increase in exercise, but the prolonged exposure gave a lower respiratory rate and a higher tidal volume than the short-term exposure. Lower arterial pH levels were measured during carbon dioxide exposure and decreased further during exercise. In the case of heavy work, however, the pH levels were the same regardless of the carbon dioxide exposure, which was explained by a reduction in induced metabolic acidosis during carbon dioxide exposure compared with air. Mild headaches and awareness of increased respiratory effort were sporadically reported by the test subjects in connection with exercise and exposure to carbon dioxide (87).

In an exposure chamber, 6 healthy test subjects were examined over a total of 46 days: 8 days prior to exposure (control period), 30 days during exposure to 2% carbon dioxide and 8 days following exposure (30). The minute volume increased rapidly and, after 2 hours of exposure it was 60% higher than before exposure. This gradually decreased so that it reached an average increase level of 42% during the second half of the exposure period. The increase in minute volume was largely due to an increase in tidal volume. No difference was observed between the carbon dioxide concentration in the alveoli and the arterial blood during the control period, nor during or following the exposure period. During exposure, both increased by 0.33% (2.5 torr) and the increase was relatively constant during the entire exposure period. The physiological dead space increased by 8% without causing any alveolar-arterial difference in the carbon dioxide concentration, suggesting that the increase in carbon dioxide concentration does not affect gas exchange in the lung qualitatively. At the beginning of the exposure, a slight pH decrease (ΔpH~0,01) was noted, which was significant day 3. No change in the plasma cortisol levels or electrolytes (Na, Ca, Mg, P) were observed, with the exception of a small decrease in potassium concentration. Oxygen uptake and carbon dioxide excretion increased by approximately 10% due to the increased respiratory work during hyperventilation. According to the authors, no differences were observed in the ECG, EEG, heart rate, blood pressure, psychomotor test or biorhythms, which could be attributed to the exposure. After the exposure was completed, the minute volume quickly returned to the control levels and the alveolar carbon dioxide concentration decreased after approximately one day (30).

At 1% carbon dioxide exposure ("chronic hypercapnia", time frame details not stated), the minute volume increased by 10% and the alveolar carbon dioxide concentration increased by 0.33% (Guillerm *et al*., unpublished data cited by Guillerm & Radziszewski 1979 (30)). Exposure to 0.5% carbon dioxide resulted in an in-

significant increase in minute volume and an increase in alveolar carbon dioxide concentration of 0.26% (personal communication, Davis 1976, cited by Guillerm & Radziszewski 1979 (30)). In another unpublished study described in ref. (30), headaches and abdominal pains were reported during exposure to 3.6% carbon dioxide (which equals 1% increase in alveolar carbon dioxide concentration).

In a submarine used as an exposure chamber, 21 healthy test subjects were exposed to 1.5% carbon dioxide over 42 days, as well as to air for 9 days (control period) prior to the exposure period and 9 days after the carbon dioxide exposure (recovery period) (72, 73, 74). The minute volume increased by 39% during day 1-23 ("uncompensated respiratory acidosis"), which then decreased to 34% during day 24-42 ("compensated respiratory acidosis"). Respiratory acclimatisation to carbon dioxide exposure included a continuous increase of the tidal-volume, while respiratory rate decreased following an initial increase. After 40 days of exposure, the respiratory response (minute volume) decreased during a short-term exposure (15 minutes) to 5% carbon dioxide, compared to during the control period. The effect was observed only in those individuals (n=14) that responded most (>20 l/min) during the control period. Venous plasma calcium concentration and pH were reduced (ΔpH~0.06) during the uncompensated phase but return to normal levels during the compensated phase; alveolar carbon dioxide concentration was increased by approximately 0.33% (2.5 torr) for the entire carbon dioxide exposure period as compared with the control period. The physiological dead space increased by approximately 60% during exposure and the arterial carbon dioxide concentration was higher than the alveolar level, while the converse was true for the oxygen level, suggesting the development of an alveolar dead space. According to the authors, this indicates a deteriorated gas exchange in the lungs and it was calculated that, towards the end of the exposure period, 10% (compared to the normal 3%) of the alveoli were poorly perfused and 9% were poorly ventilated. The authors pointed out that these observed changes in the arterial-alveolar carbon dioxide and oxygen gradients are not dramatic, but that they correspond in terms of size to what is seen when a person rises from a lying position to standing. During the recovery period, the minute volume was somewhat decreased but the alveolar carbon dioxide concentration was still elevated, suggesting a release of stored carbon dioxide from, for example, the osseous tissue (72, 73, 74).

In an overview article, several physiological studies (13 in total) aboard nuclear submarines on patrol are summarised (75). The average concentration of carbon dioxide was between 0.7% and 1.0% and the exposure period was 50-60 days. The respiratory minute volume increased by 40-60% due to increased tidal volume, and the physiological dead space increased by 60%. Studies of acid-base balance revealed cyclical changes in blood pH levels and bicarbonate concentration, with approximately 20 day intervals. Both decreased during the first 17 days after which they increased in the days that followed, and decreased again after 40 days. Plasma levels of calcium were also shown in several studies to follow approximately the same cycle. The author argues that these respiratory changes and changes in acid-base balance were fairly congruent with the results of a 42 day

"laboratory simulated" exposure to 1.5% carbon dioxide (72, 73, 74), see above, and that these cycles are not seen with carbon dioxide exposures above 1.5% (75, 79). The explanation could be that the renal regulation of respiratory acidosis (reabsorption of bicarbonate) does not fully take effect until exposure to carbon dioxide reaches concentrations of 3% and higher, and the authors present the hypothesis that these cyclical changes in acid-base balance are caused by cyclical uptake and release of carbon dioxide from bone tissue (75, 79).

Several long-term studies on humans, both experimental chamber studies and in submarines on patrol, have shown a dramatic decrease (50%) of calcium excretion in urine only a day/few days after the start of exposure to slightly elevated (0.5-1.5%) carbon dioxide levels. Davies & Morris have summarised these studies in a review article from 1979 (12). Referring to an unpublished report, Davies writes in a later publication from 1985 that he considers the observed decrease in calcium excretion to be largely artifactual, and due to crystal formation in 24-hour urine collections stored under hypercapnic conditions (13).

An effect on calcium levels in plasma and urine has been reported (79) and a connection between the absorption of carbon dioxide in bone, reduced calcium levels and osteoporosis has been discussed (see Animal data). These studies have been referred to in later studies involving chronic obstructive pulmonary disease (COPD) patients with osteoporosis. The fact that many COPD patients retain carbon dioxide and have elevated levels of carbon dioxide in their blood is presented as one of several possible explanations for their osteoporosis (14, 16). At least one study showed a correlation between the carbon dioxide concentration in their blood and osteoporosis (16), but another did not (48). In a more recent study on submarine personnel (57), which also refers to Schaefer's hypothesis, reduced bone strength was observed (as measured by acoustic velocity in the tibia which, according to the authors, reflects "bone strength") after 30 days under water with a carbon dioxide concentration of 0.8-1.2%. Former strength was regained after 6 months on land. In addition to the increased level of carbon dioxide as a cause, a lack of sunlight is also mentioned, as well as limited physical mobility, nutritional factors and high coffee consumption.

An illness such as COPD can give rise to an accumulation of carbon dioxide in the body despite normal levels in the inspired air, and the negative effects of this have been discussed in some studies. For example, it was found in a cell study that carbon dioxide inhibits IL-6 and TNF-alpha expression, and reduces the phagocytic activity of macrophages. The authors present the hypothesis that hypercapnia in COPD patients can reduce their resistance to pulmonary infections (96).

It has been hypothesized that there is a connection between prolonged exposure to slightly elevated levels of carbon dioxide and kidney stones in the ureters, as well as infections of the upper respiratory tract (75, 60, 93). A point of departure for this hypothesis is, among other things, that the occurrence among submarine personnel of infections in the upper respiratory tract and kidney stones was 80 cases/1000 individuals and 0.007 cases/1000 man-days, respectively, from 1963-1967. 60% of the days in the underwater environment showed carbon dioxide

concentrations of over 1%. Subsequently, from 1968-1973, the levels were higher than 1% for less than 20% of the days, and the incidences were lower: 30 cases per 1000 individuals and 0.005 (a level equivalent to that of the normal population) cases per 1000 man-days, respectively (93).

Animal and *in vitro* data

Direct carbon dioxide-dependant toxic effects, even without a hypoxic effect, are indicated by a 20% oxygen and 80% carbon dioxide mix, which quickly leads to respiratory failure within 1 minute in exposed dogs and circulatory collapse within a few of minutes (39). A 50% oxygen/50% carbon dioxide mix also leads to decreased respiratory movements, pauses in breathing and death after approximately 1.5 hours, following an initial acute respiratory increase of 1-2 minutes (39).

Two weeks exposure to 8% and 12% carbon dioxide affected the expression of acid-base transporters in the heart, kidneys and brain in mice. No differences were detected for five of the examined transporters, while the increased expression of three acid extruders (NHE1, NBCe1, NBCn1) and reduced expression of an acid loader protein (AE3) were reported. Weight loss was observed in both adult and neonatal mice exposed to 12% (7% and 15% weight reduction, respectively, compared to control animals). Exposure to 8% gave no weight reduction (43).

Mice were exposed to 0%, 5%, 10% or 15% carbon dioxide (with a constant oxygen level of 21%) for 1 hour. Four hours after exposure, lung cells were isolated and a number of proinflammatory cytokines were analysed. An induction and increased secretion of cytokines (RANTES, MIP-1α and β, MIP-2, IP-10, MCP-1, TCA-3 and IL-6) were observed in cells isolated from mice exposed to 10% and 15% carbon dioxide. This presumably occurs via the activation of a phosphatase (PP2A) which in turn activates signalling pathways mediated by NF-κB. The results indicate the presence of a threshold effect, and that levels above 5% carbon dioxide (corresponding to the normal concentration in the alveoli) are required to induce a proinflammatory/inflammatory response (1). Exposure of cell lines to carbon dioxide at a constant oxygen level (21% O_2) induced chemokines involved in the immune response. MCP-1 and proinflammatory cytokines (e.g. IL-8) were also induced. Exposure to 5% carbon dioxide for 48 hours had no effect (which corresponds to the normal concentration in the alveoli and is also the concentration normally used in cell cultivation), while concentrations above 10% caused a dose-dependent induction (1).

Recently published data from the same research group indicates that carbon dioxide (approximately 12.5%) in cigarette smoke causes inflammation of the lung mucosa in mice, and it has been suggested that carbon dioxide in the smoke is a major cause of the smoke's proinflammatory/inflammatory effect (82).

In experiments on guinea pigs (63), the animals were subjected to continuous (24 hours a day) exposure to 1.5% and 3% carbon dioxide for 42 days and up to 6 months (only 1.5% carbon dioxide). On histological examination of the lungs, hyaline membranes and atelectasis were observed in the group exposed to 3%. Incidences were higher at the beginning ("uncompensated respiratory acidosis")

than towards the end of the exposure ("compensated respiratory acidosis"). At exposure to 15% carbon dioxide, incidences at the beginning of the exposure were higher. The authors reached the conclusion that the induction of hyaline membranes is a non-specific effect of decreased pH induced by carbon dioxide rather than a specific effect of carbon dioxide. When exposed to 1.5%, some of the animals exhibited atelectasis but no hyaline membranes − 1 out of 2 animals after 23 days, 2 out of 6 animals after 42 days and 3 out of 4 animals after 6 months of exposure. In contrast to the guinea pigs, neither hyaline membranes nor atelectasis were observed in rats exposed to up to 50% carbon dioxide.

Exposure of female mice to 3% carbon dioxide for 5 hours/day, or 12 hours/day, resulted in effects on the olfactory organ, both behavioural (increased repulsion to the smell of predators) and histological/immunohistochemical (increased number of cells and decreased thickness of the olfactory neuroepithelium/increased number of olfactory neurons and reduced number of mitoses in basal cells), after 2 and 4 weeks. Rodents have been reported to detect carbon dioxide concentrations of ~0,5% and it has also been shown that carbon dioxide concentrations in rat holes are normally approximately 1.4%, which has been cited as an indication that rodents have a high carbon dioxide tolerance (8).

Rats and guinea pigs that underwent continuous exposure to 1.5% carbon dioxide for 91 days and 42 days, respectively, showed morphological changes in their kidneys in the form of an increased incidence of focal calcification, primarily in the tubules of the renal cortex. The incidences increased with the exposure time and reached 100% in rats by the end of the exposure periods and 66% in guinea pigs (5-6 animals were examined at each time point). No calcification was observed in the control group (5 animals were examined at each time point). Guinea pigs were also subjected to continuous exposure to 1% carbon dioxide for 6 weeks. An increased carbon dioxide concentration in the arterial blood and a decrease in pH and bicarbonate concentration were observed during the entire exposure period. After one week of exposure, a significant reduction in calcium level was noted in the bone, followed by an increase to normal levels after 3 weeks, and a subsequent larger reduction after 6 weeks. The reverse was true for the calcium level in plasma. Phosphate concentrations in bone and plasma showed the same changes as calcium. The calcium level in the kidneys increased slightly after one week and then continued to increase (after 3 weeks the level was 27% higher in the exposed animals). No major changes were noted in the control animals (77, 79).

In guinea pigs subjected to continuous exposure to 1% carbon dioxide for up to 6 weeks, an increase in carbon dioxide concentration was observed with an average of 0.5%, as well as a decrease in pH compared to the control animals. Electron microscopic analyses of lung tissue showed no changes after 21 days of exposure. After 28 days, changes were observed, in particular a hypertrophy of alveolar type II cells, and an increase in the size and number of osmiophilic lamellar bodies in these cells. Clusters of type II cells were observed in exposed animals, but not in control animals. Corresponding changes were also noted after

six weeks of exposure. In guinea pigs exposed for 4 weeks to 1% carbon dioxide, the changes persisted after a 2 as well as 4 week recovery period (15, 79).

In a follow-up study, guinea pigs were subjected to continuous exposure to 0.5% carbon dioxide for up to 8 weeks (6 exposed and 4 control animals were examined at each time point). An increase in arterial carbon dioxide by an average of approximately 0.3% was observed, as well as a decrease of pH during exposure, compared to control animals. After 8 weeks of exposure, a significant increase of calcium in the plasma and kidneys was noted, and a non-significant decrease in bone tissue. Following an 8 week recovery period, the concentrations had returned to normal. No ultrastructural changes in type II cells were seen in the lungs (78, 79). The author points out that the guinea pigs used in the study are more sensitive than rats with regard to physiological and histopathological effects, and a reference is made to an unpublished report. An abstract, by partly the same authors, states that even 0.3% carbon dioxide causes elevated calcium levels in the kidneys of guinea pigs after 13 weeks of continuous exposure. The increase was reversible (86).

Mutagenicity Carcinogenicity

No data on mutagenic or carcinogenic effects of carbon dioxide have been found in the literature.

Effects on reproduction

The testicles of rats exposed to 2.5%, 5.0% and 10.0% carbon dioxide for 1, 2, 4 and 8 hours were histologically examined and compared with those of a control group. Degenerative changes were observed after 4 hours at all exposure levels. Consistent findings at 2.5% exposure revealed fragments of spermatids and Sertoli cells in the lumen of seminiferous tubules and degenerative changes of the epithelium. No mature spermatids were observed in the tubules. Sloughing of tubular components and lack of luminal definition were observed at 5%, and all tubules lacked spermatids in advanced stages of spermatogenesis. The changes were more pronounced at 10%. The histological picture did not change significantly after 8 hours of exposure. Testicles examined 36 hours after exposure had a normal histological appearance. The authors discussed the possibility that carbon dioxide regulates the release of spermatozoa from Sertoli cells, and that this may explain the results (95).

Female rats exposed once to 6% carbon dioxide for 24 hours, between day 5 and 21 of pregnancy, gave birth to young with a significantly higher birth weight (18.9%), more females than males and more young with skeletal malformations compared with the control group. Also, several heart malformations, including septal defects, overriding aorta, partial transposition of the great vessels and stenosis, were seen in the exposed group. The type of heart malformation depended on which days of the gestation period the exposure occurred (35). This study is difficult to assess, as potential maternal toxicity is not commented on.

An increased degree of skeletal malformations in rabbits has been reported, following exposure to 10-13% carbon dioxide (29). Weight loss and changes in the lungs of rabbit foetuses have also been reported after exposure to 8% carbon dioxide for 8 hours a day, from day 21-28 of pregnancy (62).

Dose-effect/dose-response relationships

Dose-effect/dose-response relationships observed with exposure to carbon dioxide in humans are summarised in Table 3 and in animals in Table 4. The human studies presented were conducted on healthy test subjects or selected groups (submarine crews), and one can expect that adverse effects may occur at lower levels in individuals with moderate respiratory insufficiency or heart disease. In the prolonged studies presented, continuous (24 hours a day) exposure was employed. How the results from these studies can be converted to an 8 hour exposure time frame is unclear. It should also be noted that the use of various types of respiratory protective devices increases the dead space. This can increase the carbon dioxide concentration in the inspired air and further increase the concentration in the inspired air in an environment with elevated carbon dioxide levels.

When humans are exposed to slightly elevated levels of carbon dioxide (≤1.5%), a continuous increase in respiratory minute volume is observed, beginning just above 0.5%. In the case of, for example, prolonged exposure to 1.5%, the increase was 38% (72, 73) and for short-term exposure 10%, and 32% during exposure to 0.8% and 1% carbon dioxide respectively (55, 80), see Table 3. The increase in the end-tidal carbon dioxide level (approximately equal to the arterial carbon dioxide level) remains relatively constant, about 0.2-0.3% in the exposure interval 0.5-2% carbon dioxide, as well as a small pH drop in the blood of approximately 0.01-0.06 pH units, see Table 3. Whether these effects should be regarded as physiological adjustments (adaptations) without negative health consequences is unclear.

Acute visual disorders have been reported in test subjects after approximately 1 hour of exposure to 2.5% carbon dioxide (90, 102). Reversible hearing impairment was observed at 3.5-4% carbon dioxide, but not at 2.5%, during exposures lasting 5-22 minutes (26).

At an exposure level of 0.7% carbon dioxide over 3 days, an increased cerebral blood flow has been reported (88) and after 23 days of exposure, a reduction of the diffusion capacity for carbon monoxide in the lungs and a decrease in cardiac output (85). At somewhat higher exposure levels (1.2%), deterioration in visuo-motor ability and subjectively perceived alertness were reported during 5-23 days of exposure (58), and at 7 and 23 days of exposure, lowered serum calcium levels and indications of decreased bone formation and stimulation of bone resorption (18). These effects occur during prolonged, continuous exposure (≥ 3 days), but it has not been shown, or it is unclear, if they have any impact on health, affect performance ability, or occur at more regular occupational exposure, i.e., 8 hours per day, 5 days a week.

A hypothesis has been put forward that slightly elevated levels (0.5-1.5%) of carbon dioxide affect, among other things, calcium homeostasis, so that the incidence of infections of the upper respiratory tract increases. Thus, it is reported that the incidence of infections in submarine crews in the USA during the years 1963-1967 was 80 cases per 1000 individuals. The carbon dioxide concentration was over 1% during 60% of the days. For the period 1968-1973, the incidence was 30 cases per 1000 individuals, and the carbon dioxide concentration was higher than 1% less than 20% of the days (93). The results from studies on guinea pigs have been presented to support this hypothesis and showed hypertrophy of type II cells in the guinea pigs lungs after exposure to 1% carbon dioxide (15). Cell and animal studies show that elevated carbon dioxide levels can cause inflammatory effects. It is not possible to determine, given current knowledge, whether elevated carbon dioxide levels give rise to inflammation in humans.

A related discussion is that changes in calcium homeostasis may increase calcium levels in the kidneys and increase the risk of kidney stones. Thus, the incidence of kidney stones in submarine crews decreased from 0.007 cases per 1000 man-days from 1963-1967 to 0.005 from 1968-1973 (the 0.005 incidence level is equivalent to that of the normal population) (93). An increase in the incidence of focal calcification in the tubules of the renal cortex of rats and guinea pigs exposed to 1.5% carbon dioxide has also been observed (77), as well as increased calcium levels in the kidneys of guinea pigs exposed to concentrations as low as 0.5% carbon dioxide (78). Inter-species variation and a greater sensitivity to the effects of carbon dioxide have been reported in guinea pigs when compared to rats.

Guinea pigs exposed to 1% carbon dioxide exhibited decreased levels of calcium in their bones. The effect was most pronounced after 6 weeks (77, 79). During exposure to 0.5% for a period of up to 8 weeks, a significant increase of calcium in the plasma and kidneys was observed, as well as a non-significant decrease in the bone tissue (78, 79). This has given rise to the hypothesis that high carbon dioxide levels can cause osteoporosis. As COPD patients retain carbon dioxide, an increased carbon dioxide level has been mentioned as one of several possible explanations for the osteoporosis seen in these patients (14, 16). Submarine personnel exposed to 0.8-1.2% carbon dioxide for 30 days show decreased bone strength, but several factors other than elevated carbon dioxide levels may have caused this (57).

In guinea pigs exposed to 3% carbon dioxide, hyaline membranes and atelectasis were observed in the lungs. Only atelectasis was observed at 1.5% (63).

In rats exposed to 2.5% carbon dioxide for 4 hours, degenerative changes in the testicles were observed (95). The authors discuss the possibility that carbon dioxide regulates the release of spermatozoa from Sertoli cells, and that this may explain the results.

Conclusions

There are no data from which to determine a critical effect or effect level for 8-hours occupational exposure to carbon dioxide. The critical effect of continuous (24 hours a day) exposure is considered to be effects on calcium/bone metabolism. Laboratory animals are affected (calcium/bone metabolism) after 8 weeks of continuous exposure to 0.5% (5,000 ppm) carbon dioxide and human test subjects are affected after 7 days at 1.2% (12,000 ppm). Other effects on human test subjects during continuous exposure to 0.7-1.2% (7,000-12,000 ppm) include effects on the diffusion capacity in the lungs, cerebral blood flow, visuo-motor functions and subjective perceived alertness. Whether any of these effects occur in daily 8 hour exposure is unclear. During short-term exposure, effects on vision have been reported after 60 minutes of exposure to 2.5% (25,000 ppm).

Exposure to high concentrations of carbon dioxide can be fatal. When exposed to approximately 7% (70,000 ppm) and higher, there is an accumulation of carbon dioxide that causes CNS depression and confusion, and eventually coma and death.

The use of protective equipment (respiratory protective devices, welding helmets, integral helmets) can lead to increased exposure due to increased re-inhalation of exhaled carbon dioxide. This can further increase exposure in environments that already have elevated carbon dioxide concentrations.

Table 3. Dose effect/dose-response relationships in humans exposed to carbon dioxide.

CO_2 conc. (%)	Exposure time	Number exposed	Effect	Ref.
0.5	unclear time[1]	-	Slight increase in respiratory minute volume, increase of alveolar carbon dioxide concentration by 0.26%.	Davis 1976[2]
0.7	3 days	4	Increased (35%) cerebral blood flow and increased cerebral blood flow induced by visual stimulus.	88
0.7	23 days	4	Decreased diffusion capacity for carbon monoxide in the lungs and reduction of cardiac output.	85
0.7	23 days	4	Increase (0.6-1.0%) of end-tidal carbon dioxide level during the entire exposure period.	21
0.7-1.0[3]	50-60 days	-	Increase in respiratory minute volume by 40-60% and the dead space by 60%. Cyclical changes in blood pH, bicarbonate and calcium concentration in plasma.	75
0.8	30 min	5	Increase in respiratory minute volume, increase of alveolar carbon dioxide concentration by 0.17%.	55
1.0	unclear time[1]	-	Increase in respiratory minute volume by 10%, increase of alveolar carbon dioxide concentration by 0.33%.	Guillerm *et al.*[2]
1.0	3 min	16	Increase in respiratory minute volume by 32%.	80
1.1	30 min	10	Increase in respiratory minute volume by 18%, increase of alveolar carbon dioxide concentration by 0.2%.	55
1.2	5-23 days	4	Deterioration in visuo-motor ability and subjectively perceived alertness.	58
1.2	7 and 23 days	4	Lower serum calcium levels. Indications of decreased bone formation and stimulation of bone resorption.	18
1.2	23 days	4	Headaches were reported at the beginning of the exposure.	88
1.2	23 days	4	Increased (22%) respiratory minute volume after 5 days of exposure. Increase (0.6-0.9%) of end-tidal carbon dioxide level during the entire exposure period.	21
1.5	42 days	21	Increase in respiratory minute volume by 38%, increase of alveolar carbon dioxide concentration by 0.33%. Lowered pH (ΔpH ~ 0.06) during the first half of the exposure.	72, 73, 74
2.0	2 hours	6	Increase in respiratory minute volume by 60%. Reduction of arterial pH after 24 hours (ΔpH = 0.01).	30
2.0	30 days	6	Increase in respiratory minute volume by 42%, increase of alveolar carbon dioxide concentration by 0.33%. Increased oxygen uptake by 10% due to increased respiratory effort. Lowered pH (ΔpH~0,01) at the beginning of the exposure.	30
2.5	15-20 min	12	No effect on cerebral blood flow. Arterial carbon dioxide concentration increased by 0.59%.	66
2.5	5-22 min	6	No hearing impairment.	26
2.5	about 60 min	3	Visual impairment (decreased stereoscopic sensitivity (depth perception)).	90

Table 3. Continued.

CO_2 conc. (%)	Exposure time	Number exposed	Effect	Ref.
2.5	about 60 min	3	Visual impairment (perception of coherent motion).	102
3.5	15-20 min	11	10% increase of cerebral blood flow. Within 10-15 minutes of exposure increased respiratory minute volume with mild dyspnea.	66
3.5-4	5-22 min	6	Hearing impairment.	26
3.6	-	15	Headache and abdominal pains, 1% increase in alveolar carbon dioxide concentration.	Guillerm *et al*.[2]
4	45 min	7	pH reduced by -0.034 pH units at rest and by -0.102 at work (2/3 of the maximal oxygen uptake ability), when compared to the control level. Headaches experienced by 6 out of 7 test subjects during exercise.	59
5	15 min	14	Triggered panic attacks in 8 out of 14 patients with panic anxiety disorders, but in none of the eight healthy control subjects.	101
5	15 min	16	Increase in respiratory minute volume of 308%. Increased systolic and diastolic blood pressure and increased heart rate (greater than 10% difference from control values). Headaches, sometimes intense, which passed off within 20 minutes after exposure.	80
5	15-30 min	6	59% increase of cerebral blood flow.	45
6	3 min	-	Impairment of vision in a contrast sensitivity test.	27
about 6	30 min	8	Increased respiratory rate (62%), heart rate, systolic and diastolic blood pressure, and increased dispersion of the QT interval on the ECG.	47
6.5	5 and 15 min	10	Increase in time taken to solve logical problems.	71
7	15-30 min	2	130% increase of cerebral blood flow.	45
7.6	2.5-8.5 min	42	Minute volume increased to 52 l/min (range 24-102). Headaches (55% of the test subjects), dizziness (33%), dyspnea (31%). One person became unconscious.	17
10.4	2.5-6.0 min	31	Minute volume increased to 76 l/min (range 40-130). 29 people could not handle 5 minutes exposure due to dyspnea, headaches, dizziness, light-headedness and fainting. Three people became unconscious.	17
7-14	10-20 min	12	Headaches, visual and auditory hallucinations, dyspnea, sweating, dizziness, seizures, nausea and vomiting. Suffocating feelings and agony of death. Upon exposure >10.4% most subjects lost consciousness.	83
20-30	<1 min	-	Loss of controlled and purposeful activity, unconsciousness, convulsions, coma.	22, 51

Conc. = concentration; - = data not available; days = continuous (24 hours a day) exposure; min = minutes
[1] Probably prolonged continuous exposure. "Chronic hypercapnia" mentioned in the article (30).
[2] Unpublished data cited in reference (30).
[3] Several studies in submarines on patrol.

Table 4. Dose effect/dose-response relationships in animals exposed to carbon dioxide.

CO_2 conc. (%)	Exposure time	Number of animals	Species	Effect	Ref.
0.5	8 weeks*	6/time point, 4 control animals	guinea pigs	Increase in arterial carbon dioxide concentration by an average of approximately 0.3% and slightly decreased pH. Increase of calcium in plasma and kidneys and a non-significant decrease in bone. No ultra-structural changes in type II cells were seen in the lungs.	78, 79
1	6 weeks*	6/time point, 3-4 control animals	guinea pigs	Hypertrophy of alveolar type II cells, increase in the size and number of os-miophilic lamellar bodies and clusters of type II cells.	15, 79
1	6 weeks*	6/time point, 3-4 control animals	guinea pigs	Reduced calcium levels in bone.	77, 79
1.5	6 weeks*	6/time point, 5 control animals	guinea pigs	Increasing incidence (up to 66% of animals) with exposure time of focal calcification in the kidneys.	77, 79
1.5	13 weeks*	5-6/time point, 5 control animals	rats	Increasing incidence (up to 100% of animals) with exposure time of focal calcification in the kidneys.	77, 79
1.5	6 months*	2-6/time point, 4 control animals	guinea pigs	Atelectasis in the lungs, 1 out of 2 animals day 23, 2 out of 6 animals day 42, 3 out of 4 animals at 6 months. No atelectasis was observed in control animals.	62
3	6 weeks*	8, 7 control animals	guinea pigs	Hyaline membranes and atelectasis in the lungs of 25% of the exposed animals.	
2.5	4 hours	-	rats	Degenerative changes in the testicles.	95
3	5 hours per day, for 2 or 4 weeks		mice	Effects on the olfactory organ, both behavioural (10 exposed and 10 control animals) and histological/immunohistological (2 exposed animals/time point).	8
10	1 hour	-	mice	Increase in proinflammatory cytokines in lung cells ex vivo.	1

Conc. = concentration; - = data not available
*Continuous (24 hours a day) exposure.

Potential conflicts of interest

No potential conflicts of interest have been reported

References

1. Abolhassani M, Guais A, Chaumet-Riffaud P, Sasco AJ, Schwartz L. Carbon dioxide inhalation causes pulmonary inflammation. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L657-L665.
2. ACGIH. Carbon dioxide. *Documentation of the threshold limit values and biological exposure indices.* 7th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2001: 2 pp.
3. Arbetsmiljöverket (the Swedish Work Environment Authority). Arbetsplatsens utformning. *The Work Environment Authority's Statute Book* AFS 2009:2. The Swedish Work Environment Authority, Solna.
4. Bansal S, Harber P, Yun D, Liu D, Liu Y, Wu S, Ng D, Santiago S. Respirator physiological effects under simulated work conditions. *J Occup Environ Hyg* 2009;6:221-227.
5. Baxter PJ, Baubron J-C, Coutinho R. Health hazards and disaster potential of ground gas emissions at Furnas volcano, Sa˜o Miguel, Azores. *J Volcanology and Geothermal Research* 1999;92:95-106.
6. Brühwiler PA, Stämpfli R, Huber R, Camenzind M. CO_2 and O_2 concentrations in integral motorcycle helmets. *Appl Ergon* 2005;36:625-633.
7. Brunner G. Supercritical fluids: technology and application to food processing. *J Food Engin* 2005;67:21-33.
8. Buron G, Hacquemand R, Pourié G, Brand G. Carbon dioxide effects on olfactory functioning: Behavioral, histological and immunohistochemical measurements. *Toxicol Lett* 2009;188:251-257.
9. Caretti D, Coyne KM. Unmanned assessment of respirator carbon dioxide levels: comparison of methods of measurement. *J Occup Environ Hyg* 2008;5:305-312.
10. Curley G, Contreras M, Nichol AD, Higgins BD, Laffey JG. Hypercapnia and acidosis in sepsis: a double-edged sword? *Anesthesiology* 2010;112:462-472.
11. Dalgaard JB, Dencker G, Fallentin B, Hansen P, Kaempe B, Steensberger J, Wilhardt P. Fatal poisoning and other health hazards connected with industrial fishing. *Br J Ind Med* 1972;29:307-316.
12. Davies DM, Morries JEW. Carbon dioxide and vitamin D effects on calcium metabolism in nuclear submariners: a review. *Undersea Biomed Res* 1979;6 Suppl:S71-S80.
13. Davies DM. Calcium metabolism in healthy men deprived of sunlight. *Ann NY Acad Sci* 1985;453:21-27.
14. de Vries F, van Staa TP, Bracke MSGM, Cooper C, Leufkens HGM, Lammers JWJ. Severity of obstructive airway disease and risk of osteoporotic fracture. *Eur Respir J* 2005;25:879-884.
15. Douglas WHJ, Schaefer KE, Messier AA, Pasquale SM. Proliferation of pneumocyte II cells in prolonged exposure to 1 % CO_2. *Undersea Biomed Res* 1979;6 Suppl:S135-S142.
16. Dimai HP, Domej W, Leb G, Lau KHW. Bone loss in patients with untreated chronic obstructive pulmonary disease is mediated by an increase in bone resorption associated with hypercapnia. *J Bone Miner Res* 2001;16:2132-2141.
17. Dripps RD, Comroe JH. The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4 percent CO_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of carbon dioxide and maximal voluntary hyperventilation. *Am J Physiol* 1947;149:43-51.

18. Drummer C, Friedel V, Börger A, Störmer I, Wolter S, Zittermann A, Wolfram G, Heer M. Joint NASA-ESA-DARA study. Part one: effects of elevated carbon dioxide environment on calcium metabolism in humans. *Aviat Space Environ Med* 1998;69:291-298.
19. Dunford JV, Lucas J, Vent N, Clark RF, Cantrell FL. Asphyxiation due to dry ice in a walk-in freezer. *J Emerg Med* 2009;36:353-356.
20. Durand M, Scott BJ. Geothermal ground gas emissions and indoor air pollution in Rotorua, New Zealand. *Sci Total Environ* 2005;345:69-80.
21. Elliott AR, Prisk GK, Schöllmann C, Hoffmann U. Joint NASA-ESA-DARA study. Part two: hypercapnic ventilatory response in humans before, during, and after 23 days of low level CO_2 exposure. *Aviat Space Environ Med* 1998;69:391-396.
22. EPA. *Carbon dioxide as a fire suppressant: Examining the Risks.* U.S. Environmental Protection Agency, Office of Air and Radiation, Stratospheric Protection Division, 2000.
23. Fogarty J, McCally M. Health and safety risks of carbon capture and storage. *JAMA* 2010;303:67-68.
24. Frey MA, Sulzman FM, Oser H, Ruvters G. Joint NASA-ESA-DARA study. Part one: the effects of moderately elevated ambient carbon dioxide levels on human physiology and performance: a joint NASA-ESA-DARA study - overview. *Aviat Space Environ Med* 1998;69:282-284.
25. Ganong WF. *Review of medical physiology*. 22nd ed. New York: Lange Medical Books/McGraw-Hill, 2005:647-697.
26. Gellhorn E, Spiesman I. The influence of hyperpnea and of variations of O_2- and CO_2-tension in the inspired air upon hearing. *Am J Physiol* 1934;112:519-528.
27. Gellhorn E. The effect of O_2-lack, variations in the carbon dioxide-content of the inspired air, and hyperpnea on visual intensity discrimination. *Am J Physiol* 1936;115:679-684.
28. Gill JR, Ely SF, Hua Z. Environmental gas displacement. Three accidental deaths in the workplace. *Am J Forensic Med Pathol* 2002;23:26-30.
29. Grote W. Disorders of embryonic development induced by increased CO_2 and O_2 partial pressure and reduced atmospheric pressure. *Z Morphol Anthropol* 1965;56:165-194.
30. Guillerm, R, Radziszewski, E. Effects on man of 30-day exposure to a P_{ICO2} of 14 torr (2 %): application to exposure limits. *Undersea Biomed Res* 1979;6 Suppl:S91-S114.
31. Gundel A, Parisi RA, Strobel R, Weihrauch MR. Joint NASA-ESA-DARA study. Part three: characterization of sleep under ambient CO_2-levels of 0.7% and 1.2%. *Aviat Space Environ Med* 1998;69:491-495.
32. Gundel A, Drescher J, Weihrauch MR. Joint NASA-ESA-DARA study. Part three: cardiorespiratory response to elevated CO_2 levels during sleep. *Aviat Space Environ Med* 1998;69:496-500.
33. Harber P, Shimozaki S, Barrett T, Fine G. Determinants of pattern of breathing during respirator use. *Am J Ind Med* 1988;13:253-262.
34. Harber P, Brown CL, Beck JG. Respirator physiology research: answers in search of the question. *J Occup Med* 1991;33:38-44.
35. Haring O. Cardiac malformations in rats induced by exposure of the mother to carbon dioxide during pregnancy. *Circ Res* 1960;8:1218-1227.
36. Henderson R. Carbon dioxide measures up as a real hazard. *Occup Health Saf* 2006;75:64,68-69.
37. Hoffmann U, Schöllmann C, Wackerhage H, Leyk D, Wenzel J. Joint NASA-ESA-DARA study. Part two: effects of chronically increased ambient CO_2 concentrations on aerobic capacity. *Aviat Space Environ Med* 1998;69:397-402.
38. Holmgren K, Sternhufvud C. CO_2-emission reduction costs for petroleum refineries in Sweden. *J Clean Prod* 2008;16:385-394.

39. Ikeda N, Takahashi H, Umetsu K, Suzuki T. The course of respiration and circulation in death by carbon dioxide poisoning. *Forensic Sci Int* 1989;41:93-99.
40. Jacobs DE, Smith MS. Exposure to carbon dioxide in the poultry processing industry. *Am Ind Hyg Assoc J* 1988;49:624-629.
41. Jones NL, Levine GB, Robertson DG, Epstein SW. The effect of added dead space on the pulmonary response to exercise. *Respiration* 1971;28:389-398.
42. Jones JG. The physiological cost of wearing a disposable respirator. *Am Ind Hyg Assoc J* 1991;52:219-225.
43. Kanaan A, Douglas RM, Alper SL, Boron WF, Haddad GG. Effect of chronic elevated carbon dioxide on the expression of acid-base transporters in the neonatal and adult mouse. *Am J Physiol Regul Integr Comp Physiol* 2007;293:R1294-R1302.
44. Keeling RF, Piper SC, Bollenbacher AF, Walker JS. *Atmospheric carbon dioxide record from Mauna Loa 1958 – 2008.* Carbon Dioxide Research Group, Scripps Institution of Oceanography, University of California, La Jolla, California, U.S.A. Accessible at: http://cdiac.ornl.gov/trends/co2/sio-mlo.html (2010-03-16).
45. Kety SS, Schmidt CG. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J Clin Invest* 1948;27:484-492.
46. Khoo HH, Tan RBH. Life cycle investigation of CO_2 recovery and sequestration. *Environ Sci Technol* 2006;40:4016-4024.
47. Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest* 1996;109:1215-1221.
48. Kjensli A, Mowinckel P, Ryg MS, Falch JA. Low bone mineral density is related to severity of chronic obstructive pulmonary disease. *Bone* 2007;40:493-497.
49. Kreiss K, Rao CD, Harrison JM, Kaydos-Daniels SC. Brief report: investigation of a home with extremely elevated carbon dioxide levels -- West Virginia, December 2003. *MMWR Weekly (html version)* 2004;53:1181-1182.
50. Kuang X, Shankari TJ, Bi XT, Lim CJ, Sokhansanj S, Melin S. Rate and peak concentrations of off-gas emissions in stored wood pellets – Sensitivities to temperature, relative humidity, and headspace volume. *Ann Occup Hyg* 2009;53:789-796.
51. Lambertsen CJ. Therapeutic gases: oxygen, carbon dioxide and helium. In: DiPalma JR, ed. *Drill's pharmacology in medicine.* New York: McGraw-Hill Book Co., 1971:1145-1179.
52. Lambertsen CJ. Transport of oxygen and carbon dioxide by the blood. In: Mountcastle VB, ed. *Medical Physiology Vol. 2.* 13th ed. Saint Louis: The C.V. Mosby Company, 1974:1399-1421.
53. Lambertsen CJ. Effects of excessive pressures of oxygen, nitrogen, helium, carbon dioxide and carbon monoxide: implications in aerospace, undersea and industrial environments. In: Mountcastle VB, ed. *Medical Physiology Vol. 2.* 13th ed. Saint Louis: The C.V. Mosby Company, 1974:1563-1597.
54. Langford NJ. Carbon dioxide poisoning. *Toxicol Rev* 2005;24:229-235.
55. Loeppky JA. The effects of low levels of CO_2 on ventilation during rest and exercise. *Aviat Space Environ Med* 1998;69:368-373.
56. Louhevaara VA. Physiological effects associated with the use of respiratory protective devices. A review. *Scand J Work Environ Health* 1984;10:275-281.
57. LuriaT, Matsliah Y, Adir Y, Josephy N, Moran DS, Evans RK, Abramovich A, Eliakim A, Nemet D. Effects of a prolonged submersion on bone strength and metabolism in young healthy submariners. *Calcif Tissue Int* 2010;86:8-13.
58. Manzey D, Lorenz B. Joint NASA-ESA-DARA study. Part three: effects of chronically elevated CO_2 on mental performance during 26 days of confinement. *Aviat Space Environ Med* 1998;69:506-514.

59. Menn SJ, Sinclair RD, Welch BE. Effect of inspired P_{CO2} up to 30 mm Hg on response of normal man to exercise. *J Appl Physiol* 1970;28:663-671.
60. Messier AA, Heyder E, Braithwaite WR, McCluggage C, Peck A, Schaefer KE. Calcium, magnesium, and phosphorus metabolism, and parathyroid-calcitonin function during prolonged exposure to elevated CO_2 concentrations on submarines. *Undersea Biomed Res* 1979;6 Suppl:S57-S70.
61. Morgan WP. Psychological problems associated with the wearing of industrial respirators: a review. *Am Ind Hyg Assoc J* 1983;44:671-676.
62. Nagai A, Thurlbeck WM, Deboeck C, Ioffe S, Chernick V. The effect of maternal CO_2 breathing on lung development of fetuses in the rabbit. Morphologic and morphometric studies. *Am Rev Respir Dis* 1987;135:130-136.
63. Niemoeller H, Schaefer KE. Development of hyaline membranes and atelectases in experimental chronic respiratory acidosis. *Proc Soc Exp Biol Med* 1962;110:804-808.
64. NIOSH (National Institute for Occupational Safety and Health). *Criteria for a recommended standard*. Occupational exposure to carbon dioxide. HEW Publication No. (NIOSH) 76-194, U.S. Department of Health, Education, and Welfare, 1976.
65. NIOSH (National Institute for Occupational Safety and Health). *NIOSH respirator decision logic.* DHHS/NIOSH Pub. No. 87-108. Washington, D.C.: Government Printing Office, 1987:1-55.
66. Patterson JL, Heyman A, Battey LL, Ferguson RW. Threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. *J Clin Invest* 1955;34:1857-1864.
67. Rhoades RA. Gas transfer and transport. In: Rhoades RA, Tanner GA, eds. *Medical Physiology.* 2nd ed. Philadelphia: Lippincott Williams&Wilkins, 2003:350-362.
68. Roberge RJ, Coca A, Williams WJ, Powell JB, Palmiero AJ. Physiological impact of the N95 filtering facepiece respirator on healthcare workers. *Respir Care* 2010;55:569-577.
69. Saatci E, Miller DM, Stell IM, Lee KC, Moxham J. Dynamic dead space in face masks used with noninvasive ventilators: a lung model study. *Eur Respir J* 2004;23:129-135.
70. Samel A, Vejvoda M, Wittiber K, Wenzel J. Joint NASA-ESA-DARA study. Part three: circadian rhythms and activity-rest cycle under different CO_2 concentrations. *Aviat Space Environ Med* 1998;69:501-505.
71. Sayers JA, Smith REA, Holland RL, Keatinge WR. Effects of carbon dioxide on mental performance. *J Appl Physiol* 1987;63:25-30.
72. Schaefer KE, Hastings BJ, Carey CR, Nichols G. Respiratory acclimatization to carbon dioxid. *J Appl Physiol* 1963;18:1071-1078.
73. Schaefer KE, Nichols G, Carey CR. Calcium phosphorus metabolism in man during acclimatization to carbon dioxide. *J Appl Physiol* 1963;18:1079-1084.
74. Schaefer KE, Nichols G, Carey CR. Acid-base balance and blood and urine electrolytes of man during acclimatization to CO_2. *J Appl Physiol* 1964;19:48-58.
75. Schaefer KE. Physiological stresses related to hypercapnia during patrols on submarines. *Undersea Biomed Res* 1979;6 Suppl:S15-S47.
76. Schaefer KE, Carey CR, Dougherty Jr JH, Morgan CM, Messier AA. Effect of intermittent exposure to 3 % CO_2 on respiration, acid-base balance, and calcium-phosphorus metabolism. *Undersea Biomed Res* 1979;6 Suppl:S115-S134.
77. Schaefer KE, Pasquale SM, Messier AA, Niemoeller H. CO_2-induced kidney calcification. *Undersea Biomed Res* 1979;6 Suppl:S143-S153.
78. Schaefer KE, Douglas WHJ, Messier AA, Shea ML, Gohman PA. Effect of prolonged exposure to 0,5 % CO_2 on kidney calcification and ultrastructure of lungs. *Undersea Biomed Res* 1979;6 Suppl:S143-S153.
79. Schaefer KE. Effects of increased ambient CO_2 levels on human and animal health. *Experientia* 1982;38:1163-1168.

80. Schneider EC, Truesdale E. The effects on the circulation and respiration of an increase in the carbon dioxide content of the blood in man. *Am J Physiol* 1922;63:155-175.

81. Schulte JH. Sealed environments in relation to health and disease. *Arch Environ Health* 1964;8:438-452.

82. Schwartz L, Guais A, Chaumet-Riffaud P, Grévillot G, Sasco AJ, Molina TJ, Abolhassani M. Carbon dioxide is largely responsible for the acute inflammatory effects of tobacco smoke. *Inhal Toxicol* 2010;22:543-551.

83. Sechzer PH, Egbert LD, Linde HW, Cooper DY, Dripps RD, Price HL. Effect of CO_2 inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. *J Appl Physiol* 1960;15:454-458.

84. Seppänen OA, Fisk WJ, Mendell MJ. Association of ventilation rates and CO_2 concentrations with health and other responses in commercial and institutional buildings. *Indoor Air* 1999;9:226-252.

85. Sexton J, Mueller K, Elliott A, Gerzer D, Strohl KP. Joint NASA-ESA-DARA study. Part two: low level CO_2 effects on pulmonary function in humans. *Aviat Space Environ Med* 1998;69:387-390.

86. Shea ML, Messier AA, Bondi KR. Effect of prolonged exposure to low levels of CO_2 concentration on kidney calcium and lung ultra structure. *Fedn Proc* 1981;40:675. (abstract)

87. Sinclair RD, Clark JM, Welch BE. Comparison of physiological responses of normal man to exercise in air and in acute hypercapnia. In: Lambertsen CJ, ed. *Underwater physiology.* New York: Academic Press, 1971:409-417.

88. Sliwka U, Krasney JA, Simon SG, Schmidt P, Noth J. Joint NASA-ESA-DARA study. Part one: effects of sustained low-level elevations of carbon dioxide on cerebral blood flow and autoregulation of the intracerebral arteries in humans. *Aviat Space Environ Med* 1998;69:299-306.

89. Šmejkal V, Vávra J, Bartáková L, Kryl L, Paleček F. The pattern of breathing and the ventilatory response to breathing through a tube and to physical exercise in sport divers. *Eur J Appl Physiol* 1989;59:55-58.

90. Sun M, Sun C, Yang Y. Effect of low-concentration CO_2 on stereo-acuity and energy expenditure. *Aviat Space Environ Med* 1996;67:34-39.

91. Svedberg U, Samuelsson J, Melin S. Hazardous off-gassing of carbon monoxide and oxygen depletion during ocean transportation of wood pellets. *Ann Occup Hyg* 2008;52,:259-266.

92. Svedberg U, Petrini C, Johanson G. Oxygen depletion and formation of toxic gases following sea transportation of logs and wood chips. *Ann Occup Hyg* 2009;53:779-787.

93. Tansey WA, Wilson JM, Schaefer KE. Analysis of health data from 10 years of Polaris submarine patrols. *Undersea Biomed Res* 1979;6 Suppl:S217-S246.

94. Toklu AS, Kayserilioğlu A, Unal M, Ozer S, Aktaş S. Ventilatory and metabolic response to rebreathing the expired air in the snorkel. *Int J Sports Med* 2003;24:162-165.

95. VanDemark NL, Schanbacher BD, Gomes WR. Alterations in testes of rats exposed to elevated atmospheric carbon dioxide. *J Reprod Fertil* 1972;28:457-459.

96. Wang N, Gates KL, Trejo H, Favoreto S, Schleimer RP, Sznajder JI, Beitel GJ, Sporn PHS. Elevated CO_2 selectively inhibits interleukin-6 and tumor necrosis factor expression and decreases phagocytosis in the macrophage. *FASEB J* 2010;24:2178-2190.

97. Wenzel J, Luks N, Plath G, Wilke D, Gerzer R. Joint NASA-ESA-DARA study. Part one: the influence of CO_2 in a space-like environment: study design. *Aviat Space Environ Med* 1998;69:285-290.

98. White T, Schutz A, Lundgren KM. Effects of a welding helmet and dust respirators on respiration at rest and during exercise. *Scand J Work Environ Health* 1975;1:249-253.

99. Williams HI. Carbon dioxide poisoning – report of eight cases with two deaths. *Br Med J* 1958;2:1012-1014.

100. Woodrow P. Essential principles: blood gas analysis. *Nurs Crit Care* 2010;15:152-156.

101. Woods SW, Charney DS, Goodman WK, Heninger GR. Carbon dioxide-induced anxiety: behavioural, physiologic, and biochemical effects of carbon dioxide in patients with panic disordes and healty subjects. *Arch Gen Psychiatry* 1988;45:43-52.

102. Yang Y, Changanian S, Sun M. The effect of moderately increased CO_2 concentration on perception of coherent motion. *Aviat Space Environ Med* 1997;68:187-191.

Consensus Report for n-Butyl acrylate

September 28, 2011

Literature search was performed in PubMed and Toxline in September 2011. This report updates a previous Consensus Report published in Arbete och Hälsa 1985 (31).

Chemical and physical data, Use

CAS No.	141-32-2
Synonyms	butyl-2-propenoate, n-butyl propenoate, acrylic acid n-butyl ester
Formula	$C_7H_{12}O_2$
Structural formula	CH_2=CH-COO-CH_2-CH_2-CH_2-CH_3
Molecular weight	128.17
Density	0.8986 (25 °C)
Melting point	-64 °C
Boiling point	145-148 °C
Vapour pressure	0.53 kPa (20 °C), 0.57 kPa (20 °C)
Saturation concentration	5232 ppm
Log $K_{octanol/water}$	2.38 (25 °C)
Conversion factors	1 mg/m^3 = 0.19 ppm; 1 ppm = 5.32 mg/m^3 (20 °C)
Other data	Polymerises easily under the influence of heat, light, and catalytic agents

n-Butyl acrylate is a colourless, inflammable, highly reactive liquid (3). The substance is poorly soluble in water (0.14% at 20 °C), but soluble in ethanol, ether, and acetone (21). Its odour is described as fruity and pungent. The odour threshold has been reported to be 0.035 ppm (2).

The substance is used as a precursor in the manufacture of polymers and resins, and can form part of copolymers, for example with acrylic acid, acrylates, styrene, butadiene, and unsaturated polyesters. Emulsion polymers, formed through the polymerisation of n-butyl acrylate with water, are a common form of use. Emulsion polymers containing n-butyl acrylate can be part of paints and bonding agents (e.g. for use in seams) or used in surface and paper coatings, textiles, leather, adhesives, and in polish (1, 3, 20, 21). In 2007, 18,500 tonnes of n-butyl acrylate were imported into Sweden as raw materials. That year, the substance formed part of 916 products, of which 241 were available to consumers (Swedish Chemicals Agency, product registry, 2007 http://www.kemi.se/sv/Innehall/Databaser/).

A great deal of exposure data for n-butyl acrylate indicates an 8-hour mean value of <2 ppm in occupational exposure, but brief peak exposures of >2 ppm (occasionally >10 ppm) have been reported (40). In one study, over 196 American monomer production workers (1993-1995), the geometric mean values for laboratory technicians and production operators were <0.4 ppm. American data on 354 polymer production workers (1993-1995) showed geometric mean values for n-butyl acrylate (different people and activities) of <1.12 ppm. Data collected in 2002 from European producers mentioned concentrations (8-hour time weighted average, TWA) of n-butyl acrylate ≤1.6 ppm during production (77 samples), ≤0.8 ppm in laboratories (49 samples), ≤2.25 ppm during drumming (2 samples), ≤0.24 during maintenance and cleaning (5 samples) and ≤1.26 ppm during manufacturing and preparation processes (245 samples) (40).

Uptake, biotransformation, excretion

The uptake of n-butyl acrylate via the gastrointestinal tract is rapid and complete (38, 39). No exposure data on skin absorption has been found. According to theoretical calculations by Fiserova-Bergerova *et al*. skin absorption of n-butyl acrylate could be considerable (12). The calculations, however, have been questioned and criticised as drastically overestimating skin absorption (5). Skin absorption for a saturated water solution (1.4 mg/ml) can, with the use of the NIOSH calculator (http://www.cdc.gov/niosh/topics/skin/skin PermCalc.html, 2011-06-16) be calculated to 1.6-3.3 x 10^{-2} mg/cm^2 per hour (different calculation models). If ECETOC criteria for a skin notation are applied – that is, exposure of 2000 cm^2 of skin (equivalent to the hands and underarms) over 1 hour – the dose absorbed via the skin is 32-66 mg, which corresponds to 13-26% of the dose absorbed through inhalation at the current Swedish threshold limit value of 50 mg/m^3 (assuming inhalation of 10 m^3 of air over 8 hours and 50% uptake).

Studies on rats have shown that n-butyl acrylate is metabolised and excreted rapidly, primarily as carbon dioxide in exhaled air. The principal path for metabolism involves hydrolysis by carboxylesterases into acrylic acid and butanol. Acrylic acid is broken down in normal metabolism via hyrdoxyproprionate and malonate semialdehyde into acetyl-CoA, which oxidizes into carbon dioxide in the Krebs cycle. To a lesser extent, n-butyl acrylate can be conjugated with endogenous glutathione and be excreted as mercapturic acids in the urine (15, 30, 38, 39). Metabolism of n-butyl acrylate via epoxide formation has not been proven and is considered to be unlikely (15, 30).

The distribution and excretion of ^{14}C has been studied in rats after administration of radioactively labelled n-butyl acrylate (peroral administration 4-400 mg/kg body weight) (38, 39). The radioactivity decreased in most organs studied within 24 hours. During measurements after peroral administration (24 hours), approximately 2-3% of the radioactivity was found in the liver, 5-6% in the muscles, and 2-9% in fat. After 48 hours the radioactivity had decreased further; in the liver to approximately 1% from 6% after 0.5 hours. However, somewhat increased ^{14}C activity was measured in epididymal fat and the sciatic nerve, and

largely unchanged activity was measured in red blood cells after 48 hours compared with after 0.5 hours. The radioactivity measured in all three locations was nevertheless low. After injection into the abdominal cavity, the ^{14}C activity measured in red blood cells, epididymal fat and the sciatic nerve was also low and approximately the same after 0.5 and 48 hours (38, 39).

After peroral administration (4-400 mg n-butyl acrylate/kg body weight) around 65-85% of the radioactivity was excreted in exhaled air within 24 hours as $^{14}CO_2$, approximately half of this within 4-6 hours (38, 39). Around 10-15% of the radioactivity was excreted in the urine and approximately 1-2% in faeces over 24 hours. The metabolites N-acetyl-S-(2-carboxyethyl)cysteine and N-acetyl-S-(2-caroboxyethyl)cysteine-S-oxide were identified in the urine (38). Other urinary metabolites such as 3-hydroxyproprionate, citric acid, and isocitric acid have also been identified after injection of n-butyl acrylate into the abdominal cavity of rats (30).

In one inhalation study, rats were exposed to 190, 380, 760, and 1520 ppm (1000, 2000, 4000 and 8000 mg/m^3) of n-butyl acrylate over 6 hours. A dose-related increase of thioethers in the urine was observed, and in total approximately 2.5% of the dose was excreted as thioethers within 24 hours (1000-4000 mg/m^3; 50% lung retention and ventilation volume 0.6 l/kg/minute assumed). Significant decrease of sulfhydryl content in non-protein fractions from the blood, the liver, the lungs and the brain was demonstrated at concentrations ≥2000 mg/m^3 (380 ppm) in measurements after 6 hours of inhalation. When the chemical reactivity of n-butyl acrylate with glutathione was studied *in vitro*, it was discovered that n-butyl acrylate resulted in a rapid decrease in glutathione concentration. The results of the study indicate that glutathione depletion can contribute to the toxic effects at high doses (49).

Several *in vitro* studies have shown that n-butyl acrylate disappears quickly from tissues and the blood. Rapid hydrolysis of butyl acrylate by carboxylesterase from the nasal mucosa of mice was reported in one study (high butyl acrylate concentrations, >5 mM, produced a loss of enzyme activity) (42). Rapid hydrolysis to acrylic acid was further indicated when n-butyl acrylate was added to liver homogenate from rats (33). Only limited conversion of n-butyl acrylate to acrylic acid was noted, however, in rat blood, and binding to red blood cells (a reaction with sulfhydryl groups) was considered likely (33).

Toxic effects

Human data

n-Butyl acrylate has been reported to be a skin irritant in patch testing. Kanerva *et al*. (24) reported, for example, skin irritation in 11 of 46 patients in patch testing with 0.5% or 1% n-butyl acrylate in vaseline. Furthermore, contact allergy for n-butyl acrylate (butyl acrylate) has been demonstrated in patch testing on about 50 persons, primarily in persons exposed to acrylates in their occupations, such as dental care staff, but positive reactions have also been reported in persons with allergic contact eczema that was sensitized through the use of acrylic nails and

eyeglasses. Normally, 0.1-0.5% n-butyl acrylate in vaseline was used for testing. In isolated cases sensitization occurred in connection with the testing (4, 10, 16, 17, 19, 24, 25, 27, 28, 29, 45). Kanerva *et al* (24) reported that 5 of 46 patients had positive results (1982-1986) indicative of sensitization in patch testing with 0.5% or 1% n-butyl acrylate in vaseline. In later studies, the authors reported that in total 12 of 242 patients (1985-1995) with previous exposure to (meth)acrylate compounds had positive reactions when patch tested with 0.1-0.5% n-butyl acrylate (25, 27). A British study reported that 9 of 244 patients who had occupational or other types of acrylate exposure (e.g. acrylic fingernails) were positive in patch testing with 0.5% butyl acrylate (45). Cross-reactions with other acrylates have however been reported (23, 26), which makes it difficult to conclude what persons with positive patch test reactions to n-butyl acrylate were originally sensitized to.

No studies of n-butyl acrylate and asthma have been found in the literature.

Animal data

n-Butyl acrylate has low acute toxicity. The LD_{50} for peroral administration has been reported to be between 3.7 and 8.1 g/kg body weight (rats) and 7.5 g/kg body weight (mice) in published studies (6, 41, 43, 48). The LD_{50} for skin application (rabbits) has been reported to be between 1.8 and 5.7 g/kg body weight (6, 41, 48). LC_{50} for rats over 4 hours of exposure (mortality within 24 hours) was calculated in one study as 2730 ppm. 9/10 animals survived exposure at 2035 ppm and all animals survived at 1990 ppm (34). In an unpublished study, LC_{50} (4 hours) for rats with exposure via head and nose was reported to be 1957 ppm (10,300 mg/m^3). No clinical symptoms were observed at an exposure level of 513 ppm (2700 mg/m^3) (40).

In a briefly described inhalation study on rats and hamsters, distinct clinical signs of toxicity (e.g. dyspnoea, bloody secretion from eyes and nose) and death were reported in connection with exposure to average concentrations of 817-820 ppm n-butyl acrylate for 5-6 hours per day over 4 days (11).

Increased blood glucose was seen at all concentrations in an inhalation study on rats with exposures to 190, 380, 760, and 1520 ppm (1000, 2000, 4000 and 8000 mg/m^3) of n-butyl acrylate over 6 hours. The increase was significant and dose-dependent, compared with an unexposed control group, at levels >190 ppm (49).

In a long-term study, male and female rats (172 animals per dose group) were exposed to n-butyl acrylate through whole-body inhalation exposure for 6 hours per day, 5 days a week for up to 24 months (Tables 1 and 2). For the first 13 weeks the concentration in the air was 0, 5, 15, and 45 ppm. For the remainder of the experiment the exposure levels were 0, 15, 44, and 134 ppm. Histopathological examinations of many organs and tissues, ophthalmological observation (external changes, pupil reflexes), recording of body weights and organ weights, haematological examinations, urine analysis and clinical observations were part of the study (the animals were euthanized after 12, 18, 24 or 30 months). No exposure related signs of systemic toxicity were seen. In some of the animals (number of animals not stated) lower organ weights (kidneys, liver, heart, thyroid

gland) were seen, but the findings did not correlate with histopathological changes in these organs and were deemed not toxicologically relevant. Irritation effects (expressed as histological changes, see below) were detected in nasal mucosa and corneas, while no irritation-related changed were observed in larynges, tracheae, or lungs. A dose-related increase in the number of animals with hyperplasia of reserve cells (basal cells under the olfactory epithelium) and loss of olfactory and other cells (ciliated cells) in the nasal mucosa was noted in the study. A dose-related increase of the number of animals with atrophy of the olfactory epithelium (reported to be very mild at 15 ppm) was seen during the follow-up period. In many animals, damaged olfactory epithelia were thus replaced with respiratory epithelia. A significantly increased number of rats with clouding of, or new vessel formation in, the cornea was reported to be 134 ppm, while no significant increase in such effects was noted at lower exposure levels. Partial regression of new vessel formation in the cornea was detected during the recovery period (9, 36). In summary, the authors of the study (36) considered 15 ppm as a concentration that produced no effects in the nasal mucosa (NOEL). The results were not fully reported in the article but do, however, indicate a significant effect at that level, and the Swedish Criteria Group considered 15 ppm to be a LOAEL. DFG (9), who had access to supplementary information from BASF, is also of the opinion that no NOAEL existed in the study. DFG (9) also made Benchmark Dose calculations,

Table 1. Number of rats with pathological findings in nasal mucosa after inhalation exposure to n-butyl acrylate (9, 36).

Effects	Months	Males				Females			
		0 ppm	15 ppm	44 ppm	134 ppm	0 ppm	15 ppm	44 ppm	134 ppm
Hyper-plasia[a]	12	0/10	0/11	0/13	0/12	0/11	0/10	0/10	0/10
	18	0/16	0/18	1/15	0/18	0/17	0/20	1/16	0/19
	24	0/19	0/19	2/16	0/15	0/16	1/19	1/18	0/23
	24 + 6	0/41	1/36	17/40	3/40	0/41	0/36	2/42	7/33
	Total	0/86	1/84	20/84[d]	3/85	0/85	1/85	4/86	7/85[c]
Hyper-plasia[b]	12	0/10	0/11	0/13	5/12	0/11	0/10	0/10	9/10
	18	0/16	0/18	8/15	18/18	0/17	0/20	3/16	18/19
	24	0/19	2/19	11/16	15/15	0/16	6/19	5/18	20/23
	24 + 6	0/41	0/36	10/40	16/40	0/41	0/36	4/42	4/33
	Total	0/86	2/84	29/84[d]	54/85[d]	0/85	6/85[c]	12/86[d]	51/85[d]
Atro-phy	12	0/10	0/11	0/13	0/12	0/11	0/10	0/10	0/10
	18	0/16	4/18	0/15	0/18	0/17	0/20	3/16	0/19
	24	0/19	0/19	0/16	0/15	0/16	0/19	0/18	0/23
	24 +6	0/41	6/36	13/40	16/40	1/41	1/36	2/42	2/33
	Total	0/86	10/84[d]	13/84[d]	16/85[d]	1/85	1/85	5/86	2/85

[a] without loss of olfactory cells or ciliated cells.
[b] with loss of olfactory cells or ciliated cells.
[c] $p<0.05$
[d] $p<0.01$

which resulted in the following values on the lower (95%) confidence interval for the Benchmark Dose (for a 5% increased incidence compared with the control group): 2.7 ppm (males) and 2.8 ppm (females) for loss of olfactory cells or ciliated cells in combination with hyperplasia of reserve cells after 24 months exposure and 6.9 ppm (males) for atrophy of the olfactory epithelium after 24 months exposure and 6 months follow-up time.

Effective local hydrolysis and associated high concentration of acrylic acid have been reported to be a possible cause of the lesions (e.g. in the nasal mucosa) that were observed in experimental animals during exposure to n-butyl acrylate (21, 42).

In an unpublished study, male and female rats (40 animals per dose group) were exposed to 21, 108, 211, and 546 ppm n-butyl acrylate for 6 hours per day, 5 days a week over 13 weeks (1, 40). In ACGIH (1), 21 ppm was reported to be a NOAEL in the study, based on the absence of both irritation effects (eyes and airways) and indications of systemic toxicity. Furthermore, smaller changes – e.g. influence on body weight gain and relative liver weight were reported, but no histopathological changes were found at an exposure level of 108 ppm. Irritation of nasal mucosa and eyes was reported at 211 ppm, while exposure to 546 ppm was reported to produce severe irritation effects (such as bloody excretions from the eyes and nose, metaplasia of the olfactory epithelium, pneumonitis and extensive necrosis in the lungs) and many deaths (31/40 animals) (Klimisch *et al*., 1978, cited in ref. 1). The same study was referred to in a summarizing report (40). There, however, the NOAEL in the study was reported to be 108 ppm and the LOAEL to be 211 ppm. Irritation of the eyes and mucous membranes and significant reduction in body weight gain were reported at 211 ppm. In females there were also reduced potassium values and increased activity of alkaline phosphatases (40).

Unpublished data show that eye effects of widely different degrees of severity (no damage to severe effects, e.g. iritis) were observed in rabbit eyes after application of 0.5 ml undiluted n-butyl acrylate (5 rabbits; exposure time 24 hours) (40). Degrees of damage rating 2 or 3 out of 10 from application of butyl acrylate to rabbit eyes were reported in published studies (6, 41).

Primary skin irritation in rabbits rated at 2 or 3 out of 10 was reported in two older studies (6, 41). In another study, it was reported that n-butyl acrylate was not a skin irritant when a 30% solution was applied to the ears of mice (the highest tested concentration) over 4 days in a test that measures ear swelling (18). A newly-published study on n-butyl acrylate investigated cytotoxicity *in vitro* (two different models of cultured skin from humans) and skin irritation *in vivo* (rabbits). A weak cytotoxicity was demonstrated in the *in vitro* experiment. In the experiment on rabbits, 0.32 ml of solution (various concentrations) was applied to the skin and the area was covered (24 hours). Skin irritation was evaluated according to Draize scoring criteria and the index for primary skin irritation was calculated. The lowest concentration that produced erythema was

calculated at 0.6%, that is, the substance was shown to have low skin-irritant activity (44).

In an unpublished study, moderate to strong erythema and oedema was reported after 24 hours in all exposure groups from application of n-butyl acrylate (99% purity) to rabbit skin (occlusive over 1, 5, or 15 minutes, or 20 hours). The 20-hour exposure also caused "mild necrosis". The effects were reversible and much weaker 8 days after the exposure (40).

n-Butyl acrylate was demonstrated to be a potent contact allergen on guinea pigs in the Guinea Pig Maximization Test (GPMT) and Freund's Complete Adjuvant Test (FCAT). Butyl acrylate has been reported to sensitize skin in other tests as well (35, 47). In tests on mice, n-butyl acrylate was reported to sensitize skin in the local lymph node assay (LLNA), but was judged to have weak skin-sensitizing properties. The EC_3 value (the estimated concentration needed to triple cell proliferation in lymph nodes, relative to controls) was reported by Dearman *et al.* as 11.2% n-butyl acrylate, and in the Hayes & Meade study was around 30% (7, 18). n-Butyl acrylate was negative in another skin sensitization test on mice (Mouse Ear Swelling Test, MEST) (18). MEST is a considerably less sensitive test than GPMT, FCAT, and LLNA and is not included in the OECD guidelines for predictive testing of contact allergy. Cross-reactions between n-butyl acrylate and other acrylates have been reported. In a very few cases, sensitization to methacrylates has also led to cross-reactivity against n-butyl acrylate (18, 46).

Mutagenicity/genotoxicity

n-Butyl acrylate was not mutagenic in germ cells in the sex-linked recessive lethal (SLRL) test on fruit flies using exposure via oral administration or injection into adult flies (13). Nor was significant increase of chromosomal aberrations demonstrated in cytogenetic examinations of bone marrow from hamsters and rats after inhalation exposure to an average of 817 ppm and 820 ppm respectively for 5-6 hours per day over 4 days (euthanasia 5 hours after completed exposure) (11). In a Russian study cited in IARC (21) it was reported that n-butyl acrylate induced chromosomal aberrations in the bone marrow of rats from injecting the substance into the abdominal cavity (300 mg/kg body weight; single injection).

n-Butyl acrylate was not mutagenic in testing on bacteria (Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100) with or without metabolic activation (40, 50, 52). Furthermore, no mutagenic or genotoxic potential of n-butyl acrylate was reported in *in vitro* tests on hamster cells (SHE cells) in studies of micronuclei, DNA repair (UDS) or morphological cell transformation (14, 51). Chromosomal aberrations were induced *in vitro* in tests on CHO cells, but only at cytotoxic concentrations without metabolic activation (1, 40).

In an inhalation study (whole-body exposure), rats of both sexes (172 animals per dose group) were exposed to n-butyl acrylate for 6 hours per day, 5 days a week for up to 24 months. For the first 13 weeks the concentrations in the different exposure groups were 0, 5, 15, and 45 ppm, and thereafter 0, 15, 44, and 134

ppm. The authors' opinion was that no exposure-related increase of tumours was demonstrated in the study (21, 36).

No epidermal tumours were found after application of 25 µl of a 1% solution of n-butyl acrylate in acetone to the skin of male mice 3 times weekly throughout their lifespan (0.2 mg/mouse per application, 40 animals). One mouse in the butyl acrylate group had epidermal hyperplasia, and one mouse in the group was diagnosed with a fibrosarcoma (localized outside the treated area). The authors concluded that n-butyl acrylate was not carcinogenic in this study (8).

IARC concluded in 1986 that there is inadequate evidence for the carcinogenicity in experimental animals and made the overall evaluation that n-butyl acrylate is not classifiable as to its carcinogenicity to humans (group 3) (21).

Effects on reproduction

In an inhalation study on rats (30 animals per group) with exposures of 0, 25, 137, and 251 ppm of n-butyl acrylate 6 hours per day, days 6-15 of gestation, the proportion of resorptions per female was significantly increased in both high-dose groups (23.6%, 31% against 11.6% in the control group). No teratogenic effects or impaired foetal growth was demonstrated in the groups exposed to n-butyl acrylate. Dose-dependent maternal toxicity (significantly impaired weight gain, secretions from eyes and nose) was seen during the exposure period at the two highest exposure levels (32).

In another study on rats (27-29 animals per group) with inhalation exposure to an average of 103, 203, and 303 ppm n-butyl acrylate, 6 hours per day, days 6-20 of gestation, significant and concentration-dependent reduction of both food consumption and absolute weight gain was reported among dams in all dosage groups (especially in both high-exposure groups) compared with the control group. Furthermore, dose-dependent significantly lower body weight in foetuses in the two highest exposure groups was observed. No treatment-related increase of embryo or foetal mortality or foetal malformations was demonstrated in the study. 103 ppm was judged as the NOAEL for developmental toxicity (37).

In an unpublished study, it was reported that no effects on the prostate, testicles, epididymis, seminal vesicles, uterus, or ovaries were demonstrated in microscopic examinations of rats exposed to 21, 108, 211, or 546 ppm n-butyl acrylate for 6 hours per day, 5 days a week, for 13 weeks (40).

In another unpublished study, 100, 1000, 1500, 2000, 2500, 3000, and 4000 mg/kg bodyweight of n-butyl acrylate was administered in cottonseed oil to mice (approximately 27-30 animals per group) daily via gavage on days 6-15 of gestation (deaths at dosage levels ≥1000 mg/kg per day: 1/30, 1/27, 1/29, 2/30, 2/30, all). Maternal toxicity, expressed as significantly reduced weight gain, was reported at doses ≥1500 mg/kg per day (significant increase of relative liver weight was found at 1000 mg/kg per day). Significantly reduced foetal weights was also seen at doses ≥1500 mg/kg per day. Significant increase in resorptions and embryo toxicity, e.g. cleft palate, exencephaly, cardiovascular lesions and fused ribs, was reported at dosage levels ≥2500 mg/kg per day. Only slightly

increased toxicity, primarily expressed as a small increase in skeletal variations (delayed ossification) in the offspring, was noted at 1000 mg/kg per day (1, 22, 40). ACGIH considered 100 mg/kg body weight per day as a NOAEL for both maternal toxicity and effects on the foetuses (1).

Dose-effect/dose-response relationships

There is no data for evaluating the dose-effect/dose-response relationships in humans from exposure to n-butyl acrylate. Effects on laboratory animals upon inhalation exposure is summarised in Table 2.

Dose-dependent irritation effects in nasal mucosa were demonstrated in histopathological examinations in an inhalation study on rats with long-term exposure to n-butyl acrylate. At 15 ppm, a slight increase in animals with hyperplasia of basal cells under the olfactory epithelium and loss of olfactory and other cells (ciliated cells) in the nasal mucosa was noted after 2 years of exposure. Very mild atrophy of the olfactory epithelium was also reported at this concentration, mainly among males ($p<0.01$). At 44 ppm, these effects were more frequent (hyperplasia and loss of cells also appeared earlier) and at 134 ppm effects on the cornea were also observed. Benchmark Dose calculations produced the following values on the lower (95%) confidence interval for the Benchmark Dose (for a 5% increased incidence compared with the control group): 2.7 ppm (males) and 2.8 ppm (females) for loss of olfactory cells or ciliated cells in combination with hyperplasia of basal cells after 2 years exposure and 6.9 ppm (males) for atrophy of the olfactory epithelium after 2 years exposure and 6 months follow-up time (9, 36). ACGIH regarded 21 ppm as the NOAEL in an unpublished study on rats, based on the absence of irritation effects, among other things (1). In a study on rats no overt signs of irritation were observed at an exposure level of 25 ppm (32). Effective local hydrolysis and associated high concentration of acrylic acid may be a cause of the lesions seen, for example in the nasal mucosa, after inhalation exposure to n-butyl acrylate (21, 42).

A NOAEL of 103 ppm for developmental toxicity was reported in a study with inhalation exposure of rats during a part of gestation (37). In an older study on rats with exposures to 0, 25, 137, and 251 ppm of n-butyl acrylate during a part of gestation, the proportion of resorptions per female was significantly increased in both high-dose groups (32). Some maternal toxicity was seen at 137 ppm (about 25% decreased weight gain and irritation), but it is uncertain whether this could explain the increase of resorptions in this exposure group. (More pronounced maternal toxicity in the form of irritation and impaired weight gain was observed at 251 ppm).

Animal experiments show that n-butyl acrylate is a skin sensitizer (7, 18, 35, 47). Contact allergy to n-butyl acrylate has also been reported in humans (4, 10, 16, 17, 19, 24, 25, 27, 28, 45). It can, however, be difficult to determine what persons with positive patch test to n-butyl acrylate were originally sensitized to. Cross-reactions between n-butyl acrylate and other acrylates have been reported.

In a very few cases, sensitization to methacrylates has led to cross-reactivity to n-butyl acrylate (18, 23, 24, 46).

Conclusions

Based on animal studies, the critical effect of occupational exposure to n-butyl acrylate is considered to be mucous membrane irritation. In long-term exposure on rats, changes to mucous membranes in the respiratory tract occurred, indicating irritative effects at an airborne concentration of 15 ppm.

In an older study, an increase was seen in resorptions in rats at exposure to 137 ppm during gestation. Effects on mothers in the form of impaired weight gain and irritation occurred at this level of exposure, but it is uncertain whether this could explain the increase of resorptions.

Exposure of skin to n-butyl acrylate can cause contact allergy. Theoretical calculations indicate that exposing skin to n-butyl acrylate in liquid form can result in significant skin absorption.

Table 2. Effects on laboratory animals from inhalation exposure to n-butyl acrylate.

Air level (ppm)	Exposure	Species	Effects	Ref.
15[1]	6 hrs/day, 5 days/wk, 24 months	Rat	Hyperplasia of nasal mucosa, very mild atrophy of olfactory epithelium; no increase in frequency of tumours.	9, 36
21	6 hrs/day, 5 days/wk, 13 wks	Rat	NOAEL in the study (irritation effects, systemic toxicity).	1[5]
44[2]	6 hrs/day, 5 days/wk, 24 months	Rat	Hyperplasia of nasal mucosa, atrophy of olfactory epithelium; no increase in frequency of tumours.	9, 36
103	6 hrs/day, days 6-20 of gestation	Rat	NOAEL in the study for developmental toxicity; poorer weight gain in dams.	37
108	6 hrs/day, 5 days/wk, 13 wks	Rat	Effect on body weight gain and relative liver weight.	1[5]
134[3]	6 hrs/day, 5 days/wk, 24 months	Rat	Hyperplasia of nasal mucosa, atrophy of olfactory epithelium clouding and new vessel formation in cornea; no increase in frequency of tumours.	9, 36
137	6 hrs/day, days 6-15 of gestation	Rat	Increased proportion of resorptions; maternal toxicity (poorer weight gain, signs of irritation in eyes and nose).	32
190	6 hours	Rat	Increase of blood glucose (not significant).	49
203	6 hrs/day, days 6-20 of gestation	Rat	Lower body weight in foetuses; poorer weight gain in dams.	37

Table 2. Continued.

Air level (ppm)	Exposure	Species	Effects	Ref.
211	6 hrs/day, 5 days/wk, 13 wks	Rat	Irritation of mucous membranes in eyes and nose, significantly lower body weight gain; clinical and chemical analysis: effect on potassium and alkaline phosphatases in females.	1[5], 40
251	6 hrs/day, days 6-15 of gestation	Rat	Increased proportion of resorptions; maternal toxicity (poorer weight gain, signs of irritation in eyes and nose).	32
303	6 hrs/day, days 6-20 of gestation	Rat	Lower body weight in foetuses; poorer weight gain in dams.	37
380	6 hours	Rat	Increase of blood glucose.	49
546	6 hrs/day, 5 days/wk, 13 wks	Rat	Many deaths, severe irritation effects in eyes and respiratory tract (e.g. bloody secretions from eyes and nose, pneumonitis, necrosis in lungs).	1[5]
817-820	5-6 hrs/day, 4 days	Rats, hamsters	Dyspnoea, bloody secretions from nose and eyes, death; no increase in chromosomal aberrations in bone marrow cells[4].	11
1990	4 hours	Rat	10/10 animals survived.	34
2730	4 hours	Rat	LC_{50}	34

[1]5 ppm for the first 13 weeks.
[2]15 ppm for the first 13 weeks.
[3]45 ppm for the first 13 weeks.
[4]Euthanasia 5 hours after completed exposure.
[5]BASF report (Klimisch *et al*., 1978) cited in refs. 1 and 40, and others (effects/effect levels are reported differently in refs. 1 and 40; figures from ref. 1 have been given preference in use).

Potential conflicts of interest

No potential conflicts of interest have been reported.

References

1. ACGIH. n-Butyl acrylate. *Documentation of the threshold limit values and biological exposure indices*. 7th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2003: 6 pp.
2. Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-290.
3. Bisesi MS. Esters of mono- and alkenyl carboxylic acids and mono- and polyalcohols. In: Bingham E, Cohrssen B, Powell CH, eds. *Patty´s Toxicology*, 5th ed., vol 6. New York: John Wiley & Sons inc, 2001:597-633.
4. Björkner B, Dahlquist I. Contact allergy caused by UV-cured acrylates. *Contact Dermatitis* 1979;5:403-404.
5. Bunge AL. Re: ”Dermal absorption potential of industrial chemicals: criteria for skin notation”. *Am J Ind Med* 1998;34:89-90.

6. Carpenter CP, Weil CS, Smyth HF. Range-finding toxicity data: List VIII. *Toxicol Appl Pharmacol* 1974;28:313-319.
7. Dearman RJ, Betts CJ, Farr C, McLaughlin J, Berdasco N, Wiench K, Kimber I. Comparative analysis of skin sensitization potency of acrylates (methyl acrylate, ethyl acrylate, butyl acrylate, and ethylhexyl acrylate) using the local lymph node assay. *Contact Dermatitis* 2007;57:242-247.
8. DePass LR, Fowler EH, Meckley DR, Weil CS. Dermal oncogenicity bioassays of acrylic acid, ethyl acrylate, and butyl acrylate. *J Toxicol Env Health* 1984;14:115-120.
9. DFG. Deutsche Forschungsgemeinschaft. n-Butyl acrylate. In: Greim H, ed. *Occupational Toxicants. Critical data evaluation for MAK values and classification of carcinogens*, vol 12. Weinheim, Germany: Wiley-VCH Verlag, 1999:57-62.
10. DFG. Deutsche Forschungsgemeinschaft. n-Butyl acrylate. In: Greim H, ed. *Occupational Toxicants. Critical data evaluation for MAK values and classification of carcinogens*, vol 16. Weinheim, Germany: Wiley-VCH Verlag, 2001:35-40.
11. Engelhardt G, Klimisch HJ. n-Butyl acrylate: Cytogenetic investigations in the bone marrow of Chinese hamsters and rats after 4-day inhalation. *Fundam Appl Toxicol* 1983;3:640-641.
12. Fiserova-Bergerova V, Pierce JT, Droz PO. Dermal absorption potential of industrial chemicals: Criteria for skin notation. *Am J Ind Med* 1990;17:617-635.
13. Foureman P, Mason JM, Valencia R, Zimmering S. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ Mol Mutagen* 1994;23:208-227.
14. Fritzenschaf H, Kohlpoth M, Rusche B, Schiffmann D. Testing of known carcinogens and noncarcinogens in the Syrian hamster embryo (SHE) micronucleus test in vitro; correlations with in vivo micronucleus formation and cell transformation. *Mutat Res* 1993;319:47-53.
15. Greim H, Ahlers J, Bias R, Broecker B, Hollander H, Gelbke HP, Jacobi S, Klimisch HJ, Mangelsdorf I, Mayr W, Schön N, Stropp G, Stahnecker P, Vogel R, Weber C, Ziegler-Skylakakis K, Bayer E. Assessment of structurally related chemicals: Toxicity and ecotoxicity of acrylic acid and acrylic acid alkyl esters (acrylates), methacrylic acid and methacrylic acid alkyl esters (methacrylates). *Chemosphere* 1995;31:2637-2659.
16. Guerra L, Vincenzi C, Peluso AM, Tosti A. Prevalence and sources of occupational contact sensitization to acrylates in Italy. *Contact Dermatitis* 1993;28:101-103.
17. Hambly EM, Wilkinson DS. Contact dermatitis to butyl acrylate in spectacle frames. *Contact Dermatitis* 1978;4:115.
18. Hayes BB, Meade BJ. Contact sensitivity to selected acrylate compounds in B6C3F1 mice: Relative potency, cross reactivity, and comparison of test methods. *Drug Chem Toxicol* 1999;22:491-506.
19. Hemmer W, Focke M, Wantke F, Götz M, Jarisch R. Allergic contact dermatitis to artificial fingernails prepared from UV light-cured acrylates. *J Am Acad Dermatol* 1996;35:377-380.
20. IARC. Some chemicals used in plastics and elastomers. *IARC Monographs on the Evaluation of the Carcinogenic Risk of chemicals to Humans.* Vol 39. Lyon: International Agency for Research on Cancer 1986,39:67-79.
21. 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;71:359-366.
22. John JA, Wroblewski DJ, Schwetz BA. Teratogenicity of experimental and occupational exposure to industrial chemicals. *Issues Rev Teratol* 1984;2:267-324.
23. Jordan WP. Cross-sensitization patterns in acrylate allergies. *Contact Dermatitis* 1975;1:13-15.
24. Kanerva L, Estlander T, Jolanki R. Sensitization to patch test acrylates. *Contact Dermatitis* 1988;18:10-15.

25. Kanerva L, Estlander T, Jolanki R, Tarvainen K. Statistics on allergic patch test reactions caused by acrylate compounds, including data on ethyl methacrylate. *Am J Contact Derm* 1995;6:75-77.

26. Kanerva L,Estlander T, Jolanki R. False negative patch test reaction caused by testing with dental composite acrylic resin. *Int J Dermatol* 1996;35:189-192.

27. Kanerva L, Jolanki R, Estlander T. 10 years of patch testing with the (meth)acrylate series. *Contact Dermatitis* 1997;37:255-258.

28. Kiec-Swierczynska M. Occupational allergic contact dermatitis due to acrylates in Lodz. *Contact Dermatitis* 1996;34:419-422.

29. Koppula SV, Fellman JH, Storrs FJ. Screening allergens for acrylate dermatitis associated with artificial nails. *Am J Contact Derm* 1995;6:78-85.

30. Linhart I, Hrabal R, Smejkal J, Mitera J. Metabolic pathways of 1-butyl (3-^{13}C)acrylate. Identification of urinary metabolites in rat using nuclear magnetic resonance and mass spectroscopy. *Chem Res Toxicol* 1994;7:1-8.

31. Lundberg P, ed. Swedish Criteria Group for Occupational Standards. Acrylic and methacrylic acids and their esters. *Scientific Basis for Swedish Occupational Standards.* VI. Arbete och Hälsa 1985;32:6-21. National Board of Occupational Safety and Health, Solna, Sweden.

32. Merkle J, Klimisch HJ. N-Butyl acrylate: prenatal inhalation toxicity in the rat. *Fund Appl Toxicol* 1983;3:443-447.

33. Miller RR, Ayres JA, Rampy LW, McKenna MJ. Metabolism of acrylate esters in rat tissue homogenates. *Fund Appl Toxicol* 1981;1:410-414.

34. Oberly R, Tansy MF. LC50 values for rats acutely exposed to vapors of acrylic and methacrylic acid esters. *J Toxicol Environ Health* 1985;16:811-822.

35. Parker D, Turk JL. Contact sensitivity to acrylate compounds in guinea pigs. *Contact Dermatitis* 1983;9:55-60.

36. Reininghaus W, Koestner A, Klimisch HJ. Chronic toxicity and oncogenicity of inhaled methyl acrylate and n-butyl acrylate in Sprague-Dawley rats. *Food Chem Toxicol* 1991;29:329-339.

37. Saillenfait AM, Bonnet P, Gallissot F, Protois JC, Peltier A, Fabriès JF. Relative developmental toxicities of acrylates in rats following inhalation exposure. *Toxicol Sci* 1999;48:240-254.

38. Sanders JM, Burka LT, Matthews HB. Metabolism and disposition of n-butyl acrylate in male Fischer rats. *Drug Metab Disp* 1988;16:429-434.

39. Sapota A. The dynamics of distribution and excretion of butyl-(2,3-^{14}C)-acrylate in male wistar albino rats. *Pol J Occup Med Env Health* 1991;4:55-66.

40. SIDS (Screening Information Data Sets) for N-Butyl acrylate (CAS No 141-32-2). *OECD SIDS Initial Assessment Report for 15th SIAM.* Boston, Massachusetts, UNEP publications, 2002:1-143.

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

42. Stott WT, McKenna MJ. Hydrolysis of several glycol ether acetates and acrylate esters by nasal mucosal carboxylesterase *in vitro*. *Fundam Appl Toxicol* 1985;5:399-404.

43. Tanii H, Hashimoto K. Structure-toxicity relationship of acrylates and methacrylates. *Toxicol Lett* 1982;11:125-129.

44. Tokumura F, Matsui T, Suzuki Y, Sado M, Taniguchi M, Kobayashi I, Kamiyama M, Suda S, Nakamura A, Yamazaki Y, Yamori A, Igarashi R, Kawai J, Oka K. The potential dermal irritating effect of residual (meth) acrylic monomers in pressure sensitive adhesive tapes. *Drug Chem Toxicol* 2010;33:1-7.

45. Tucker SC, Beck MH. A 15-year study of patch testing to (meth)acrylates. *Contact Dermatitis* 1999;40:278-279.

46. Van der Walle HB, Bensink T. Cross reaction pattern of 26 acrylic monomers on guinea pig skin. *Contact Dermatitis* 1982;8:376-382.
47. Van der Walle HB, Klecak G, Geleick H, Bensink T. Sensitizing potential of 14 mono (meth) acrylates in the guinea pig. *Contact Dermatitis* 1982;8:223-235.
48. Vernot EH, MacEwen JD, Haun CC, Kinkead ER. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol Appl Pharmacol* 1977;42:417-423.
49. Vodicka P, Gut I, Frantik E. Effects of inhaled acrylic acid derivatives in rats. *Toxicology* 1990;65:209-221.
50. Waegemaekers THJM, Bensink MPM. Non-mutagenicity of 27 aliphatic acrylate esters in the Salmonella-microsome test. *Mutat Res* 1984;137:95-102.
51. Wiegand HJ, Schiffmann D, Henschler D. Non-genotoxicity of acrylic acid and n-butyl acrylate in a mammalian cell system (SHE cells). *Arch Toxicol* 1989;63:250-251.
52. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ Mutagenesis* 1987;9 Suppl 9:1-110.

Consensus Report for Ethanolamine

May 30, 2012

This report updates a previous Consensus Report published in Arbete och Hälsa 1992 (38). Literature search was performed in PubMed and Toxline in November 2011.

Chemical and physical data, EU classification

CAS No.	141-43-5
Synonyms	2-ethanolamine, monoethanolamine, 2-aminoethanol, 2-hydroxy ethylamine, 1-amino-2-hydroxyethane
Structural formula	$HO\text{-}CH_2\text{-}CH_2\text{-}NH_2$
Molecular weight	61.08
Melting point	10.3 ºC
Boiling point	170.8 ºC
Vapour pressure	0.05 kPa (20 ºC)
Saturation concentration	490 ppm
Log P_{ow}	-1.91
Density	1.02 g/ml
Conversion factors	1 ppm = 2.53 mg/m^3; 1 mg/m^3 = 0.39 ppm

EU classification:
Acute toxicity - hazard category 4[1]; H332, harmful if inhaled.
Acute toxicity – hazard category 4[1]; H312, harmful in contact with skin.
Acute toxicity – hazard category 4[1]; H302, harmful if swallowed.
Corrosive on skin – hazard category 1B; H314, causes severe skin burns and eye damage.
Concentration ≥5%: Specific target organ toxicity – single exposure (STOT-SE) – hazard category 3; H335, may cause respiratory irritation.

At room temperature, ethanolamine is a clear, colourless hygroscopic liquid with a mild, ammonia-like odour (30, 38). The odour threshold was reported in one study to be 2.6 ppm (52). The substance is miscible with water, methanol and acetone, easily forms salts with inorganic and organic acids, and can be esterified (30, 36,

[1] higher classification may be used if access to other data exists; 1=highest hazard classification and 4=lowest hazard classification (http://www.kemi.se/Documents/Publikationer/Trycksaker/Faktablad/FbCLPdecember2011.pdf)

38). A 10% aqueous solution of ethanolamine has a pH of 12.1 (9). The pH value for a 30% aqueous solution has been reported to be 12.75 (52).

Use/occurrence

Ethanolamine can be found in different types of detergents, for example wax removers. It is also used as rustproofing and an emulsifier, for example in cutting fluids. Ethanolamine additionally occurs as an absorber, for example in natural gas to remove carbon dioxide and hydrogen sulphide, and as a dispersant for agricultural chemicals. It is also used industrially in organic synthesis. Ethanolamine can be added to cosmetics, for example hair dyes, home permanents, and hair care products (2, 3, 6, 7, 16, 26, 34, 35, 38, 43).

The median concentration of ethanolamine in the respiratory zone of workers in machinery workshops was reported in a Finnish study to be 57 $\mu g/m^3$ (the measured values varied between 4 and 345 $\mu g/m^3$; 29 samples) during 2 hours of work. The cutting fluids used were miscible with water, and the concentration of ethanolamine in diluted cutting fluid was around 0.2-1.5%. Skin exposure was estimated based on the amount of ethanolamine washed off (one hand). A comparison between skin and inhalation exposure showed that skin exposure was approximately 50 times higher than inhalation exposure for those workers who only used cutting fluids containing ethanolamine. A median value was used in the calculation of the amount of ethanolamine on the skin of one hand and in inhaled air (median: 54 $\mu g/m^3$) for 2 hours and ventilation was assumed to be 30 l per minute (25).

Uptake, biotransformation, excretion

Ethanolamine can be taken up through the skin and the gastrointestinal tract (31, 37, 46). There is no reliable quantitative data on uptake via the gastrointestinal tract or lungs. According to theoretical calculations by Fiserova-Bergerova *et al*. skin absorption of ethanolamine could be considerable (13). The calculations in the study, however, have been questioned and criticised as drastically overestimating skin absorption for many of the reported substances (5). One *in vitro* study compared the skin absorption (6 hours) of radioactively labelled ethanolamine in humans and different animal species. The absorptions decreased as follows: mice>rabbits>rats>humans. Skin absorption on 1.8 cm^2 of human skin was 0.6% (undiluted) and 1.1% (22% aqueous solution) respectively, and the steady-state rate of penetration was 7.9 $\mu g/cm^2/hr$ (undiluted) and 9.7% $\mu g/cm^2/hr$ (22% aqueous solution) respectively (46). If the ECETOC criteria (12) for a skin notation are applied – that is, exposure of 2000 cm^2 of skin (equivalent to the hands and underarms) over 1 hour – the dose absorbed via the skin is approximately 16 mg for undiluted ethanolamine, which corresponds to 40% of the dose absorbed through inhalation at the current Swedish threshold limit value of 8 mg/m^3 (assuming inhalation of 10 m^3 of air over 8 hours and 50% uptake). According to data from Sun *et al.* 19.4 mg should be absorbed upon skin

application of a 22% aqueous solution (46), which corresponds to approximately 50% of the dose absorbed through inhalation. Skin exposure to ethanolamine in liquid form can thus result in significant skin absorption. There is, however, some uncertainty in calculating skin uptake, as poor mass balance was reported in the study by Sun *et al.* (46).

In experiments where ^{14}C-labbeled ethanolamine (in ethanol) was applied to human skin transplanted onto mice or directly to mouse skin, it was reported that just over 50% of the radioactivity in both cases had penetrated the skin after 24 hours – that is, it had been excreted or was found in different organs. The distribution of radioactivity to different organs, exhaled air, urine and faeces were also similar for both experiments. In the application of ^{14}C-labelled ethanolamine (in ethanol) to transplanted human skin, 24.3% of the radioactivity remained in the liver after 24 hours, 2.5% in the kidneys, and 1% in the lungs, brain, and heart combined. 18.5% of the dose was found in exhaled air (CO_2); 4.6% and 1.8% of the radioactivity was found in the urine and faeces, respectively. The study further demonstrated that ethanolamine could be metabolised to a certain extent in the skin, but more comprehensive metabolism took place in the liver. The main metabolites in the urine were urea and glycine. Of the excreted radioactivity in the urine, approximately 10% was recovered in ethanolamine; 40% in urea; 20% in glycine; 4-6% in serine, uric acid and choline, respectively; and 12% as unidentified metabolites (31). There was no clear difference, for example in the exhalation of radioactive carbon dioxide, between mice that were given ethanolamine on transplanted skin and directly on their own skin respectively, and it cannot be ruled out that the animals took in an amount of ethanolamine via the gastrointestinal tract (through grooming). The estimations of skin absorption in the study by Klain *et al.* (31) are thus considered uncertain.

In a poorly described study on rats excretion of ethanolamine in urine (3 days) was reported to be 6.3%, 37% and 48% after peroral administration of 33, 330, and 530 mg/kg body weight. At the higher doses, almost all was excreted within the first 24 hours (37).

Ethanolamine is found in the normal metabolism of humans and animals. The substance is part of lipid and protein metabolism (it can be formed from the amino acid serine and converted to choline) and is incorporated into phospholipids in the cell membrane (6, 7, 9, 31, 37, 38, 52). Normal excretion of ethanolamine in the urine (24 hours) was reported in one study to be 12.2 (range: 4.8 - 22.9) mg/day in men and 29.9 (range: 12.9 - 57) mg/day in women. The average value for men and women, expressed in terms of body weight, was reported to be 0.16 mg/kg/day and 0.49 mg/kg/day respectively. These values for normal excretion of ethanolamine in the urine was lower than the corresponding values reported for rats (1.46 and 1.26 mg/kg body weight per day for males and females, respectively) and rabbits (approximately 0.9 mg/kg body weight per day) (37).

Toxic effects

Human data

A few studies (see below) describe the development of asthma, asthma-like symptoms and damage to airways upon exposure to products that contain ethanolamine (29, 43, 44). Since these studies deals with mixed exposures and provocation tests (when performed) being carried out with the products in question and not ethanolamine per se, its role in the observed effects is unclear.

In a suicide attempt, a man ingested 600 ml of an alkaline laundry detergent (pH 11.7) containing 3.3% ethanolamine. The patient vomited and had asthma-like symptoms, and was diagnosed with corrosive esophagogastritis and bronchial asthma. He died after several days due to his breathing problems, despite treatment. Serious damage (such as necrosis) in the respiratory mucus membranes were seen in the histological examination (29).

A case of asthma linked to a job, and considered to be ethanolamine-related, was reported in Savonius *et al*. (44). The patient had worked 18 years cleaning floors, and was exposed to various cleaning chemicals, including a wax remover containing 8% ethanolamine and 9% sodium metasilicate. She had been working for more than 10 years when she started displaying symptoms. When using the wax remover (in hot water) she began to wheeze, her nose began to run, and she developed an irritating cough. She also occasionally noticed a fever during work. Spirometry showed normal values, and the patient had no bronchial hyperreactivity. The asthma diagnosis was based on provocation tests with the wax remover. Provocation induced an immediate, long-lasting asthmatic reaction and fever (38 ºC after 7 hours). FEV_1 decreased by 27%. Maximal PEF-reduction was 24%. Moreover, PEF measurements over 2 weeks were reported to show a pattern typical of occupational asthma (44). A later study (43) reported work-related cases of asthma which had been diagnosed at the Finnish Institute of Occupational Health between 1994 and 2004. Specific provocation tests with different agents and measurements of lung function (FVC, FEV_1, FEV%, PEF) were performed. The study included twenty women with cleaning work ("patients") who had symptoms in their airways (including dyspnea and cough; 3 with no asthma diagnosis). Provocation tests with products containing ethanolamine (5 patients) precipitated asthma in four cases, and it was concluded that either ethanolamine or triethanolamine was the most likely cause. (The fifth patient reacted only in testing with pure triethanolamine.) 15 of 20 patients experienced either no or mild bronchial hyperreactivity in histamine provocation tests, but it is not stated which patients were tested with products containing ethanolamine. Prick tests with ethanolamines (n = 9; how many were tested with monoethanolamine is unclear) were reported to be negative.

Suuronen *et al*. (47) investigated the incidence of occupational allergic respiratory disorders in people who worked in the manufacture of metal products, for example machine fitters, grinders, and machine tool workers. Finnish registry data of occupational illnesses from 1992 to 2001 were analysed. No cases of ethanolamine-related asthma were reported (47).

In recent years, ethanolamine has been reported to be a common cause of allergic contact eczema in metalworkers exposed to water-based cutting fluids. Positive patch test results have been demonstrated in tests using 2% ethanolamine in vaseline in several large studies with patch testing of metalworkers who had work-related eczema (15, 16, 17, 18, 19). Suspicions have been expressed that the positive results of testing with 2% ethanolamine in vaseline indicate irritation owing to alkalinity rather than contact allergy. The fact that the portion of positive patch test reactions was significantly higher in people who had been exposed to cutting fluids than in people without known occupational exposure to ethanolamine has been interpreted to mean that this test preparation could detect contact allergy, even if a number of weak positive test responses may be false positives (16, 18). Lessmann *et al.* (35) reported that the reaction index (RI) did not indicate alkalinity as a primary cause of the irritation or inconclusive reactions to ethanolamine (2% in vaseline).

In a large German study the patch test results (1999-2001) from 20 dermatology departments (part of IVDK, the Information Network of Departments of Dermatology) were analysed. Positive reactions to 2% ethanolamine in vaseline were obtained in 13 of 119 metalworkers who were exposed to cutting fluid and who had work-related eczema (17). The same authors reported positive test results with ethanolamine (2% in vaseline) during the period from April 2000 to July 2002 in 3 of 53 metalworkers exposed to cutting fluids (5 dermatology departments, IVDK) (15). An analysis that included metalworkers who were patch tested at 31 dermatology departments in 2002 and 2003 because of eczema that was suspected to be related to cutting fluids reported positive test reactions to ethanolamine (2% in vaseline) in 23 of 199, while "doubtful" reactions were found in 16 people; a reaction due to irritation was seen in one person (16). A later study conducted a retrospective analysis of IVDK patch test results (2% ethanolamine in vaseline) from 1999 to 2003 for 370 metalworkers with suspected cutting oil-related eczema and 452 patients with no known occupational exposure to ethanolamine (age-matched control group). Positive results were seen in 45 metalworkers and 6 subjects in the control group; "doubtful" reactions were seen in 26 and 18 people, respectively. Additional reactions caused by irritation were reported for 2 subjects in the control group (18). A study published in 2006 reported positive patch test reactions to 2% ethanolamine in vaseline in 11 of 99 metalworkers with suspected occupational eczema from cutting oil (19).

A German multi-centre project (about 50 clinics within IVDK) collected data from 1992 to 2007 on patients with suspected allergic contact eczema. Of 9,602 patients, 8,830 had negative results, 335 questionable results and 19 follicular reactions in patch tests with ethanolamine (2% in vaseline). 363 patients had positive reactions and 55 were reported to have irritant reactions. Metalworkers were the dominant occupational group among ethanolamine-positive patients. 118 of the 363 ethanolamine-positive patients either had been or were metalworkers occupied in cutting, grinding, drilling or similar work. The prevalence of positive reactions in patch tests using ethanolamine in sub-groups consisting of men (5,884

in total) was also reported in the study. The prevalence for men who did not work in the metallurgical industry (n=2,866), men who worked in the metallurgical industry (n=3,018) and men who worked in the metallurgical industry and who were also exposed to water-based cutting fluids (n=632) were 2.9%, 7.0%, and 15.2% respectively. Many patients with positive patch test reactions to ethanolamine also had positive reactions to diethanolamine. In summary, the authors concluded that damage to the skin barrier (caused by 'wet' work, skin irritation from alkaline cutting fluids or solvents, and possibly mechanical effects) may be a contributing factor to ethanolamine sensitization in workers exposed to water-based cutting fluids (35).

In a Finnish study that, among other things, investigated work-related skin disorders in people working in the manufacture of metal products (for example machine setters, grinders, machine tool workers), two cases of allergic contact eczema related to ethanolamine were reported. The results were based on registry data from 1992 to 2001 for occupational diseases and patch testing, but the authors reported that there may be an underdiagnosis of contact allergy to ethanolamine, since it was not always used in the patch tests (47). In some further studies on metalworkers (about twenty people with eczema in total), positive patch test results for ethanolamine were reported in a few of them (3, 4, 28, 33, 35).

Ethanolamine has also been reported to cause allergic contact eczema in association with other forms of exposure, for example to hair dyes. A German study reported on patch test results from about forty clinics within IVDK from 2003 through 2006. Positive patch test results were obtained for ethanolamine (2% in vaseline) in 11 of 595 female hair salon clients and 7 of 401 female hairdressers. A significant change over this period of time (4 years) was observed, with a higher prevalence of positive reactions to ethanolamine during 2005 and 2006 (49). Earlier data (1998-2000) registered at IVDK showed that 4 of 22 patients with suspected sensitivity to the contents of hair dye reacted positively in patch tests with ethanolamine (2% in vaseline), which was part of the products (10).

Positive reactions to ethanolamine (2% in vaseline), as well as to other substances, was also reported in a dental assistant with work-related hand eczema. Ethanolamine was part of a disinfectant she used that also contained other sensitizing substances (48).

Based on the data for human sensitization reported above, the conclusion is that ethanolamine is a weak contact allergen.

Animal data

Ethanolamine is moderately acutely toxic in peroral administration or skin application. The LD_{50} for peroral administration in rats was reported in some studies to be between 1.7 and 3.3 g/kg (21, 45, 50). Unpublished data indicates an LD_{50} of around 1 g/kg for skin application (rabbits) (1).

In an older inhalation study (52), dogs were exposed to 6, 12, 26, or 102 ppm; guinea pigs to 15 or 75 ppm; and rats to 5, 12, or 66 ppm of ethanolamine (Table

1). Exposure (whole-body exposure) was mainly continuous and lasted for up to 90 days. Mild changes in behaviour and a certain amount of skin irritation were reported at an exposure of 5-6 ppm (see below). Rats exposed to 5 ppm were somewhat slower in their movements and had thinner fur on certain parts of their body after 3 weeks of exposure. Discoloured fur was seen in all rats after 12 days. The dogs exposed (6 ppm) also became somewhat less active after a couple weeks of exposure, but no abnormal values for pulse, temperature, or heartbeat or respiratory sounds were noted (recorded only in dogs). The dogs' fur gradually became more yellow and a little greasy, something which was reported to cause discomfort and skin irritation. Hair loss and small scabs were observed in skin that came in contact with the floor. A somewhat thicker epithelium, with an increase in the amount of exfoliated cells, was seen in histological examinations of both dogs and rats. At exposures to 12-15ppm, the laboratory animals became less alert and sunk into lethargy. This occurred in rats and guinea pigs after 3 to 10 days, while no changes in behaviour were seen in dogs at the beginning of the exposure. After several days of exposure, the dogs' fur became dingy and their skin became irritated (especially skin areas that came in contact with the floor). Depression and lethargy were observed later, but the dogs recovered their normal behaviour after approximately 3 weeks. Histological examinations (12-15 ppm) reported the same type of changes to the skin as for exposure to 5-6 ppm. Dogs exposed to 26 ppm of ethanolamine displayed immediate signs of restlessness and discomfort. Their respiration became rapid and shallow. Within a few days they were less alert, and after that in a condition bordering on lethargy. Their fur became wet and greasy within 2 days; skin that came in contact with the floor became irritated and developed small ulcers within 1 week. No treatment-related histopathological changes in other tissues than the skin were reported; nor were any noteworthy effects reported in biochemical/haematological parameters (5-26 ppm). At higher levels of exposure (66-102 ppm) both rodents and dogs were markedly affected. 83% of the rats and 75% of the guinea pigs died within 3-4 weeks. The dogs became apathetic within a few days and one dog (of three) died. Ulcers on the skin and areas with necrosis (all the way down to the underlying muscles in certain cases) were observed. Inflammatory changes in the lungs, and changes in the liver and kidneys (histopathology) were also seen at these air levels (66-102 ppm). Furthermore, at 102 ppm mild corrosive injuries in the mucous membranes of the upper respiratory tract, histopathological changes in the spleen and effects on the blood (lower Hb and hematocrit, increased number of white blood cells, relative decrease in lymphocyte, altered albumin/globulin ratio) were reported. In summary, the authors concluded that continual exposure to 12-15 ppm ethanolamine over a longer period caused skin irritation and lethargy, and exposure to 5 ppm produced minimal effects. They calculated that the retained dose in rats at 12 ppm corresponded to 36-48 mg/kg body weight per day (it was assumed that ventilation was 0.3-0.4 m^3/day, body weight 250 gram and uptake 100%) (52). Some skin exposure to the substance in liquid form may have occurred, however. The study reported that ethanolamine condensed on all surfaces in the exposure chamber at

102 ppm, making the fur wet and greasy. Wet/greasy fur and small ulcers on the skin that came in contact with the floor were also seen at lower air levels.

The summary of an unpublished inhalation study with ethanolamine (Exp key repeated dose toxicity: inhalation.001) is available (2012-05-15) as part of the industry's registry dossier from the ECHA homepage, http://echa.europa.eu/. The results and conclusions of the study are difficult to evaluate, however, as they have not been completely reported.

An older, briefly described study in which ethanolamine was administered in food (doses 160-2670 mg/kg per day) to rats for 90 days reported that changed liver or kidney weights were noted at daily doses of 640 mg/kg and death at 1280 mg/kg. The maximum daily dose that produced no toxic effects (NOAEL) was reported to be 320 mg/kg (45).

In experiments on rats with injections of neutralised ethanolamine into the abdominal cavity (500 mg/kg body weight), a 50% inhibition of GABA aminotransferase activity in the brain was detected. Significantly increased GABA (gamma-aminobutyric acid, a signalling substance) content in the brain was reported (the GABA aminotransferase enzyme breaks down GABA). During *in vitro* experiments, the IC_{50} (the concentration that produces 50% inhibition) for the inhibition of GABA aminotransferase in rat brains was 3.9 mmol/l, and significant inhibition of the enzyme appeared at concentrations of >0.5 mmol/l. The authors reported that ethanolamine inhibited GABA aminotransferase more effectively than the antiepileptic (GABA-increasing) medicine Valproat, but also reported that ethanolamine was a relatively weak inhibitor of GABA aminotransferase (39). Another *in vitro* experiment showed that ethanolamine (neutrallised) inhibited the enzyme acetylcholinesterase at high concentrations (50% inhibition at 40 mmol/l) (21).

A study on guinea pigs using inhalation through tracheal cannula of an aerosol of an ethanolamine solution (3.3% solution, pH 12.0) or of an aerosol of a potassium hydroxide solution (pH 12.0) reported that bronchial contractions were most pronounced upon exposure to ethanolamine. Different methods were used to further investigate whether substances known for inducing bronchial contractions (e.g. histamine, acetylcholine) were involved in ethanolamine-induced bronchial constriction. The authors report that the results indicate that asthma-like symptoms induced by ethanolamine aspirated into the lungs could be partially due to a stimulating effect of ethanolamine on histamine-H_1 and muscarinic receptors (30).

A French study showed that undiluted ethanolamine was highly irritating when instillated into rabbit eyes. Bleeding that lasted for several days began approximately 30 minutes after instillation (11). An older study reported that one drop of ethanolamine in the eye of a rabbit could cause damage corresponding to 9 on a scale of 10 after 24 hours (20). Mild eye irritation was reported for a 10% ethanolamine solution in an *in vivo* Draize test (41). One *in vitro* test (EYTEX) roughly classified both undiluted ethanolamine and a 10% aqueous solution of ethanolamine as a severe to extreme eye irritant, while a 1% aqueous solution was classified as a moderate to severe eye irritant (41).

Undiluted ethanolamine has been reported as highly irritant to skin in experiments on rabbits (index: 7 of a maximum of 8). Necrotic changes were seen in histological examinations. (11). No skin damage was reported from the application of a 1%, 5%, or 10% ethanolamine solution (in acetone) to the skin of mice and histological evaluation under a light microscope after 20 hours. *In vitro* tests on mouse skin, however, indicated a mild toxic effect in the form of increased lactate dehydrogenase activity from 5% and 10% ethanolamine solutions in acetone (but not from the 1% solution) (24). Unpublished data (cited in Reference 32) reports that aqueous solutions containing 25%, 50% or 75% ethanolamine are corrosive to rabbit skin.

Two experiments on guinea pigs (GPMT) using induction and subsequent provocation with ethanolamine (provocation with 0.41%, 2.05%, and 4.1%) produced 3, 2, and 3 positive reactions out of 15 and 0, 1, and 1 positive reaction out of 15 respectively after 3 days. In experiment I, 2 out of 15 animals reacted to the vehicle (water). In experiment II, no animals reacted to the vehicle (physiological saline). There were no positive reactions after 3 days from provocation with ethanolamine, water or physiological saline in the control animals, who were not induced with ethanolamine (1 of 12 control animals had a reaction to the physiological saline after 2 days) (35, 51). Nor were any clear skin sensitizing effects reported in tests with 10%. 30%, or 70% ethanolamine as a hydrochloride in the local lymph node assays (LLNA) on mice. The study from 2007 is unpublished, but it was reported that it had been carried out according to OECD guideline 429 (35).

Mutagenicity/genotoxicity

Ethanolamine was not mutagenic in different *in vitro* tests on bacteria (*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 or TA100, *Escherichia coli* WP_2 och WP_2 *uvrA*) with or without metabolic activation. Nor were mitotic gene conversions induced in the *Saccharomyces cerevisiae* yeast fungus in tests with or without metabolic activation. Neither induction of structural chromosome damage in rat liver cells nor morphological cell transformations in hamster embryo cells were seen in other *in vitro* experiments (8, 22, 27, 42).

Carcinogenicity

No cancer studies of ethanolamine in experimental animals have been found in the literature.

A retrospective cohort study of auto workers investigated the relationship between the incidences of bladder or lung cancer (1985-2004) and exposure to cutting fluids. No relationships were demonstrated between bladder or lung cancer and any of the types of cutting fluids that may have contained ethanolamines (it was unclear which ethanolamines). Nor was the duration of exposure to ethanolamines (no exposure, >1 year, ≥1 year) associated with increased risk of bladder

cancer or lung cancer (safety data sheets were used to identify exposure to ethanolamines) (14).

Effects on reproduction

An older, poorly documented inhalation study reported that spermatogenesis appeared to decrease in guinea pigs exposed to 75 ppm for up to 24 days (75% of the animals died) and that spermatogenesis was suppressed in dogs exposed to 102 ppm for up to 30 days (one of three dogs died) (52).

Reproductive effects in rats and rabbits were investigated in a study with application of ethanolamine to skin during gestation. Ethanolamine was applied to the surface of the skin (6 hrs/day under occlusion) as a 1% - 22.5% (rats) and 0.5% - 3.75% (rabbits) aqueous solution. The ethanolamine exposure in the groups was 10, 25, 75, or 225 mg/kg per day (rats) and 10, 25, or 75 mg/kg per day (rabbits); the animals were exposed on days 6-15 (rats) or 6-18 (rabbits) of gestation. The parameters evaluated included number of implantations, resorptions and dead foetuses, litter size, foetal body weight, foetal sex ratio and variations/malformations. No statistically significant effects on reproduction in rats or rabbits were found. Significantly reduced body weight gain (not significantly decreased food intake) was noted in dams (rat) at exposure to 225 mg/kg per day; skin irritation and necrosis of the exposed surfaces were seen in this exposure group. Weight gain for dams (rabbit) in the high-dosage group (75 mg/kg per day) was also impaired during gestation, though not significantly. The rabbits in the high-dosage group developed severe skin irritation with necroses, while milder skin irritation was observed in several rabbits exposed to 25 mg/kg per day. No significant treatment-related effects on liver and kidney weights was noted in rats or rabbits at any level of exposure. Nor were significant effects seen for haematological parameters in any group (only rabbits were evaluated) (36).

A study on rats using gavage with 40, 120 or 450 mg ethanolamine/kg per day (in aqueous solution) for days 6-15 during gestation (40 animals per group) reported no significant and clearly treatment-related reproductive effects (number of implantations, resorptions, living foetuses, litter size, sex ratio, foetal weights and variations/malformations were among the outcomes studied). The NOEL for developmental toxicity was reported to be 450 mg/kg per day. Treatment-related toxicity was seen, however, in mothers in the high-dosage group in the form of decreased weight gain and poorer food intake; the NOEL for maternal toxicity was reported to be 120 mg/kg per day (23).

In an older study, rats were administered an aqueous solution of ethanolamine (0.25-2.5%) via gavage during days 6-15 of gestation. The ethanolamine doses in the groups (10 animals per group, 34 in the control group) were 0, 50, 300 or 500 mg/kg body weight per day. No significant effect on the number of implantations were reported for any group. The sum total of dead or malformed foetuses per female, however, was dose-dependent and increased significantly in all exposed groups (4.7, 6.1 and 6.4 respectively vs. 1.6). There was a significant increase in embryolethality solely in the high-dosage group. An increase in malformed

foetuses (including variation and small foetuses) was seen in all dosage groups, but without a dose-response relationship. The increased incidence of small foetuses was reported as an expression of intrauterine growth inhibition (this seems to have particularly affected some females in the medium-dosage group). Impaired weight gain in mothers (group average) was not demonstrated in any of the exposed groups. Signs of maternal toxicity (initially lethargy, followed by increased activity and "agitation") was seen, however, in some rats in the high-dose group within 1 hour after gavage, but all animals appeared normal after 8 hours (40). The study has been criticised regarding its design (it was not designed for risk assessment), the number of animals in the exposed groups and the classification of malformations, and because there was no dose-response relationship for any of the reported malformations (23, 36).

The summary of an unpublished multigenerational study with ethanolamine hydrochloride (Exp key toxicity to reproduction.001) is available (2012-05-15) as part of the industry's registry dossier from the ECHA homepage, http://echa.europa.eu/. The results and conclusions of the study are difficult to evaluate, however, as they have not been completely reported.

Dose-effect/dose-response relationships

There are no human data on which to base a dose-effect or dose-response relationship for occupational exposure to ethanolamine. The odour threshold for ethanolamine has been reported to be 2.6 ppm (52).

An older experimental study on animals (52) with mainly continual inhalation exposure to ethanolamine reported mild behavioural changes and a certain amount of skin irritation after exposure to 5-6 ppm for some time. At 12-15 ppm, serious behavioural changes (lethargy) and skin irritation were reported. The theoretically calculated dose taken up during inhalation exposure to 12 ppm was 36-48 mg/kg body weight per day (rats). Reduced spermatogenesis was reported at air levels around 75-102 ppm. Many animals died at these air levels, however, and the study was inconclusively reported as regards effects on sperm. Skin exposure to the substance in liquid form (especially at higher air levels) cannot be ruled out. Furthermore, the extent to which the observed behavioural changes depended on irritation cannot be evaluated (52).

Increased embryolethality was observed in experiments on animals using per-oral administration of high doses of ethanolamine (500 mg/kg body weight per day) during gestation. Transient effects on behaviour, but no effect on weight gain, were observed in dams in this dosage group (40).

Normal excretion of ethanolamine in the urine (24 hours) in humans has been reported to be 5-57 mg/day. Average values of 0.16 and 0.49 mg/kg body weight per day for men and women respectively have been reported. These values for normal excretion of ethanolamine in the urine were lower than the values reported for rats and rabbits (37).

Conclusions

There are no human data from which to derive a critical effect for occupational exposure to ethanolamine, but based on the chemical properties of the substance, the critical effect is considered to be irritation of the mucous membranes. An older study on laboratory animals with mainly continual exposure reported a certain amount of skin irritation and mild effects on behaviour at air levels of 5-6 ppm and serious changes in behaviour (lethargy) at 12 ppm. Skin exposure to the substance in liquid form cannot be ruled out; this could have influenced the results.

Direct contact with ethanolamine as a liquid (even as a diluted solution) can result in corrosive injuries to eyes and skin. Exposing skin to ethanolamine in liquid form can result in significant skin absorption. Skin contact with ethanolamine can also induce allergic contact eczema.

Table 1. Effects on laboratory animals from inhalation exposure[1] to ethanolamine (52).

Exposure		Species	Effects
ppm	time[2]		
5	24 hrs/day, 7 days/wk, 40 days	Rat	Discolouration of fur after 12 days; subsequent partial hair loss and somewhat slower movements; somewhat thicker skin epithelium with increased amount of exfoliated cells.
6	24 hrs/day, 7 days/wk, 60 days	Dog	Fur became slightly greasy and gradually more yellow; animals somewhat less alert/active after a couple of weeks; a certain amount of skin irritation, hair loss and small scabs on the skin that came in contact with the floor; a somewhat thicker epithelium, with an increase in the amount of exfoliated cells.
12	24 hrs/day, 7 days/wk, 90 days	Dog	Dingy fur after some time; skin irritation (in particular skin that came in contact with the floor) and temporary (3 weeks) listlessness/lethargy; a somewhat thicker skin epithelium, with an increase in the amount of exfoliated cells.
12	24 hrs/day, 7 days/wk, 90 days	Rat	Less active after approximately 3 days, lethargy after 10 days; approximately 10% lower weight gain; temporarily thinned fur (certain areas); a somewhat thicker skin epithelium, with an increase in the amount of exfoliated cells.
15	24 hrs/day, 7 days/wk, 90 days	Guinea pigs	Less active after approximately 3 days, lethargy after 10 days; approximately 10% lower weight gain; a somewhat thicker skin epithelium, with an increase in the amount of exfoliated cells.
26	24 hrs/day, 7 days/wk, 90 days	Dog	Immediate signs of restlessness and discomfort; rapid and shallow respiration; listlessness/lethargy after a couple of days; mild tremors in the back legs; wet/greasy fur; small ulcers and thinned fur on skin that came in contact with the floor.
66[3]	24 hrs/day, 7 days/wk, 30 days	Rat	37 of 45 died; restlessness, apathy, wet/greasy and thinned fur; scabs on the skin; heavy breathing effort; histopathological changes in the skin, lungs, liver, and kidneys.
75	24 hrs/day, 7 days/wk, 24 days	Guinea pigs	17 of 22 died; clear effects (see rats, 66 ppm); histopathological changes (see rats, 66 ppm); decreased spermatogenesis.
102[3]	24 hrs/day, 7 days/wk, 30 days	Dog	1 of 3 died; restlessness, vomiting, apathy/lethargy, fever; wet/greasy fur, ulcerations on the skin; histopathological changes in the skin (inflammation, necrosis), airways (mild burns, inflammation, haemorrhage), liver, kidneys, and spleen; haematological changes; suppressed spermatogenesis in the testicles.

[1] There may have been skin exposure to ethanolamine in liquid form. Ethanolamine condensed on all surfaces in the exposure chamber at 102 ppm, which was reported as having caused the wet and greasy fur. Wet/greasy fur and small ulcerations on the skin that came in contact with the floor were also seen at lower exposure levels.

[2] Number of days indicates maximum exposure time – that is, the time for the animals that survived the whole period.

[3] The standard deviation (air level) for these exposures was approximately 30%.

Potential conflicts of interest

No potential conflicts of interest have been reported.

References

1. ACGIH. Ethanolamine. *Documentation of the threshold limit values and biological exposure indices*. 7th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2001:2 pp.
2. Bello A, Quinn MM, Perry MJ, Milton DK. Characterization of occupational exposures to cleaning products used for common cleaning tasks-a pilot study of hospital cleaners. *Environ Health* 2009;8:doi:10.1186/1476-069X-8-11.
3. Bhushan M, Craven NM, Beck MH. Contact allergy to 2-aminoethanol (monoethanolamine) in a soluble oil. *Contact Dermatitis* 1998;39:321.
4. Blum A, Lischka G. Allergic contact dermatitis from mono-, di- and trietanolamine. *Contact Dermatitis* 1997;36:166.
5. Bunge AL. Re: "Dermal absorption potential of industrial chemicals: criteria for skin notation". *Am J Ind Med* 1998;34:89-90.
6. Cavender FL. Aliphatic and alicyclic amines. In: Bingham E, Cohrssen B, Powell CH, eds. *Patty´ Toxicology 5th ed*. John Wiley & Sons, Inc, New York. 2001;4:683-815.
7. Cosmetic Ingredient Review (CIR) Expert Panel. Final report on the safety assessment of triethanolamine, diethanolamine and monoethanolamine. *J Am Coll Toxicol* 1983;2:183-235.
8. Dean BJ, Brooks TM, Hodson-Walker G, Hutson DH. Genetic toxicology testing of 41 industrial chemicals. *Mutat Res* 1985;153:57-77.
9. DFG. Deutsche Forschungsgemeinschaft. 2-Aminoethanol. In: Greim H, ed. *Occupational Toxicants. Critical data evaluation for MAK values and classification of carcinogens*, vol 12. Weinheim, Germany: Wiley-VCH Verlag, 1999:15-35.
10. DFG (Deutsche Forschungsgemeinschaft). *The MAK Collection for Occupational Health and Safety.* MAK Value Documentation for 2-Aminoethanol, 2001. Wiley online library: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb14143d0033/pdf
11. Dutertre-Catella H, Lich NP, Huyen VN, Truhaut R, Shechter E. Etude comparative de l´agressivité cutanée et oculaire des éthanolamines (mono-, di, tri et poly)* [Comparative study and eye irritation by ethanolamines (mono, di, tri and poly)]. *Arch Mal Prof* 1982;43:455-460. (in French, English summary)
12. ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). *Strategy for skin notation.* ECETOC Document 1993;31.
13. Fiserova-Bergerova V, Pierce JT, Droz PO. Dermal absorption potential of industrial chemicals: Criteria for skin notation. *Am J Ind Med* 1990;17:617-635.
14. Friesen MC, Costello S, Eisen EA. Quantitative exposure to metalworking fluids and bladder cancer incidence in a cohort of autoworkers. *Am J Epidemiol* 2009;169:1471-1478.
15. Geier J, Lessmann H, Frosch PJ, Pirker C, Koch P, Aschoff R, Richter G, Becker D, Eckert C, Uter W, Schnuch A, Fuchs T. Patch testing with components of water-based metalworking fluids. *Contact Dermatitis* 2003;49:85-90.
16. Geier J, Lessmann H, Dickel H, Frosch PJ, Koch P, Becker D, Jappe U, Aberer W, Schnuch A, Uter W. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermatitis* 2004;51:118-130.
17. Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids: results of the research project "FaSt". *Int Arch Occup Environ Health* 2004;77:543-551.
18. Geier J, Lessmann H, Schnuch A, Uter W. Diagnostic quality of the patch test preparation monoethanolamine 2% pet. *Contact Dermatitis* 2005;52:171-173.

19. Geier J, Lessmann H, Becker D, Bruze M, Frosch PJ, Fuchs T, Jappe U, Koch P, Pföhler C, Skudlik C. Patch testing with components of water-based metalworking fluids: results of a multicentre study with a second series. *Contact Dermatitis* 2006;55:322-329.
20. Grant WM, Schuman JS. *Toxicology of the eye*. 4th ed. Springfield, Illinois, USA: CC Thomas Publ, 1993:654-655.
21. Hartung R, Cornish HH. Cholinesterase inhibition in the acute toxicity of alkyl-substituted 2-aminoethanols. *Toxicol Appl Pharmacol* 1968;12:486-494.
22. Hedenstedt A. Mutagenicity screening of industrial chemicals: seven aliphatic amines and one amide tested in the Salmonella/microsomal assay. *Mutat Res* 1978;53:198-199. Abstract.
23. Hellwig J, Liberacki AB. Evaluation of the pre-, peri-, and postnatal toxicity of monoethanolamine in rats following reperated oral administration during organogenesis. *Fundam Appl Toxicol* 1997;40:158-162.
24. Helman RG, Hall JW, Kao JY. Acute dermal toxicity: *In vivo* and *in vitro* comparisons in mice. *Fundam Appl Toxicol* 1986;7:94-100.
25. Henriks-Eckerman ML, Suuronen K, Jolanki R, Riala R, Tuomi T. Determination of occupational exposure to alkanolamines in metal-working fluids. *Ann Occup Hyg* 2007;51:153-160.
26. Henriks-Eckerman ML, Suuronen K, Jolanki R. Analysis of allergens in metalworking fluids. *Contact Dermatitis* 2008;59:261-267.
27. Inoue K, Sunakawa T, Okamoto K, Tanaka Y. Mutagenicity tests and in vitro transformation assays on triethanolamine. *Mutat Res* 1982;101:305-313.
28. Irigoyen JA, Borrero PG. Occupational allergic contact dermatitis from monoethanolamine in a metal worker. *Allergol Immunopathol* 2011;39:187-188.
29. KamijoY, Soma K, Inoue A, Nagai T, Kurihara K. Acute respiratory distress syndrome following asthma-like symptoms from massive ingestion of a monoethanolamine-containing detergent. *Vet Human Toxicol* 2004;46:79-80.
30. Kamijo Y, Hayashi I, Ide A, Yoshimura K, Soma K, Majima M. Effects of inhaled monoethanolamine on bronchoconstriction. *J Appl Toxicol* 2009;29:15-19.
31. Klain GJ, Reifenrath WG, Black KE. Distribution and metabolism of topically applied ethanolamine. *Fundam Appl Toxicol* 1985;5:S127-S133.
32. Knaak JB, Leung HW, Stott WT, Busch J, Bilsky J. Toxicology of mono-, di-, and triethanolamine. *Rev Environ Contam Toxicol* 1997;149:1-86.
33. Koch P. Occupational allergic contact dermatitis from oleyl alcohol and monoethanolamine in a metalworking fluid. *Contact Dermatitis* 1995;33:273.
34. Lavoué J, Bégin D, Gérin M. Technical, occupational health and environmental aspects of metal degreasing with aqueous cleaners. *Ann Occup Hyg* 2003;47:441-459.
35. Lessmann H, Uter W, Schnuch A, Geier J. Skin sensitizing properties of the ethanolamines mono-, di-, and triethanolamine. Data analysis of a multicentre surveillance network (IVDK*) and review of the literature. *Contact Dermatitis* 2009;60:243-255.
36. Liberacki AB, Neeper-Bradley TL, Breslin WJ, Zielke GJ. Evaluation of the developmental toxicity of dermally applied monoethanolamine in rats and rabbits. *Fundam Appl Toxicol* 1996;31:117-123.
37. Luck JM, Wilcox A. On the determination of ethanolamine in urine and the factors affecting its daily output. *J Biol Chem* 1953;205:859-866.
38. Lundberg P (ed). Criteria Group for Occupational Standards. Ethanolamine. *Scientific Basis for Swedish Occupational Standards. XIII.* Arbete och Hälsa 1992;47:5-9. National Institute of Occupational Health, Solna, Sweden.
39. Löscher W. Effect of 2-aminoethanol on the synthesis, binding, uptake and metabolism of GABA. *Neurosci Letters* 1983;42:293-297.

40. Mankes RF. Studies on the embryopathic effects of ethanolamine in Long-Evans rats. Preferential embryopathy in pups contiguous with male siblings in utero. *Teratog Carcinog Mutagen* 1986;6:403-417.
41. Matsukawa K, Masuda K, Kakishima H, Suzuki K, Nakagawa Y, Matsushige C, Imanishi Y, Nakamura T, Mizutani A, Watanabe R, Shingai T, Kaneko T, Hirose A, Ohno Y. Interlaboratory validation of the *in vitro* eye irritation tests for cosmetic ingredients. (11) EYETEX™. *Toxicology in vitro* 1999;13:209-217.
42. Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 1986;8 Suppl 7:1-119.
43. Mäkelä R, Kauppi P, Suuronen K, Tuppurainen M, Hannu T. Occupational asthma in professional cleaning work: a clinical study. *Occup Med* 2011;61:121-126.
44. Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational asthma caused by ethanolamines. *Allergy* 1994;49:877-881.
45. Smyth HF, Carpenter CP, Weil CS. Range-finding toxicity data: List IV. *AMA Arch Ind Hyg Occup Med* 1951;4:119-122.
46. Sun JD, Beskitt JL, Tallant MJ, Frantz SW. In vitro skin penetration of monoethanolamine and diethanolamine using excised skin from rats, mice, rabbits, and humans. *J Toxicol - Cut Ocular Toxicol* 1996;15:131-146.
47. Suuronen K, Aalto-Korte K, Piipari R, Tuomi T, Jolanki R. Occupational dermatitis and allergic respiratory diseases in Finnish metalworking machinists. *Occup Med* 2007;57:277-283.
48. Ulrich S, Skudlik C, John SM. Occupational allergic contact dermatitis from monoethanolamine in a dental nurse. *Contact Dermatitis* 2007;56:292-293.
49. Uter W, Lessmann H, Geier J, Schnuch A. Contact allergy to hairdressing allergens in female hairdressers and clients – current data from the IVDK, 2003-2006. *JDDG* 2007;5:993-1001.
50. Vernot EH, MacEwen JD, Haun CC, Kinkead ER. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol Appl Pharmacol* 1977;42:417-423.
51. Wahlberg JE, Boman A. Alkanolamines – sensitizing capacity, cross reactivity and review of patch test reactivity. *Dermatosen* 1996;44:222-224.
52. Weeks MH, Downing TO, Musselman NP, Carson TR, Groff WA. The effects of continuous exposure of animals to ethanolamine vapor. *Am Ind Hyg Assoc J* 1960;21:374-381.

Summary

Montelius J (ed). Swedish Criteria Group for Occupational Standards. *Scientific Basis for Swedish Occupational Standards.* XXXII. Arbete och Hälsa 2013;47(6):1-83. University of Gothenburg, Sweden.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish Work Environmental Authority from October, 2010 through May, 2012.

Key Words: n-Butyl acrylate, Carbon dioxide, Consensus report, Diethylamine, Ethanolamine, Ethylamine, Occupational exposure limit (OEL), Risk assessment, Scientific basis, Toxicology.

Sammanfattning

Montelius J (ed). Kriteriegruppen för hygieniska gränsvärden. *Vetenskapligt underlag för hygieniska gränsvärden.* XXXII. Arbete och Hälsa 2013;47;(6):1-83. Göteborgs Universitet.

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Nyckelord: n-Butylakrylat, Dietylamin, Etanolamin, Etylamin, Hygieniskt gränsvärde, Koldioxid, Riskvärdering, Toxikologi, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2012;46(6):1-81.

APPENDIX

Consensus reports in this and previous volumes

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

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

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

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

Hydroquinone	October 21, 1989	1991;8	XI
Indium	March 23, 1994	1994;30	XV
Industrial enzymes	June 5, 1996	1996;25	XVII
Isocyanic Acid (ICA)	December 5, 2001	2002;19	XXIII
Isophorone	February 20, 1991	1992;6	XII
Isopropanol	December 9, 1981	1982;24	III
Isopropylamine	February 7, 1990	1991;8	XI
Isopropylbenzene	June 2, 1982	1982;24	III
Lactates	March 29, 1995	1995;19	XVI
Lactate esters	June 2, 1999	1999;26	XX
Laughing gas	June 7, 2006	2006;11	XXVII
Lead, inorganic	February 29, 1980	1981;21	I
revised	September 5, 1990	1992;6	XII
revised	December 8, 2004	2005;17	XXVI
Lithium and lithium compounds	June 4, 2003	2003;16	XXIV
Lithium boron nitride	January 27, 1993	1993;37	XIV
Lithium nitride	January 27, 1993	1993;37	XIV
Maleic anhydride	September 12, 1989	1991;8	XI
Manganese	February 15, 1983	1983;36	IV
revised	April 17, 1991	1992;6	XII
revised	June 4, 1997	1997;25	XVIII
Man made mineral fibers	March 4, 1981	1982;9	II
revised	December 1, 1987	1988;32	IX
Mercury, inorganic	April 25, 1984	1984;44	V
Mesityl oxide	May 4, 1983	1983;36	IV
Metal stearates, some	September 15, 1993	1994;30	XV
Methacrylates	September 12, 1984	1985;32	VI
Methanol	April 25, 1985	1985;32	VI
Methyl acetate	March 28, 1990	1991;8	XI
Methylamine	August 25, 1982	1983;36	IV
Methylamyl alcohol	March 17, 1993	1993;37	XIV
Methyl bromide	April 27, 1988	1988;32	IX
Methyl chloride	March 4, 1992	1992;47	XIII
Methyl chloroform	March 4, 1981	1982;9	II
4,4´-methylene-bis-(2-chloroaniline)	February 4, 2004	2005;7	XXV
Methylene chloride	February 29, 1980	1981;21	I
4,4'-Methylene dianiline	June 16, 1987	1987;39	VIII
revised	October 3, 2001	2002;19	XXIII
Methyl ethyl ketone	February 13, 1985	1985;32	VI
Methyl ethyl ketone peroxide	February 13, 1985	1985;32	VI
Methyl formate	December 12, 1989	1991;8	XI
Methyl glycol	October 6, 1982	1983;36	IV
Methyl iodide	June 30, 1979	1981;21	I
Methylisoamylamine	September 5, 1990	1992;6	XII
Methylisoamylketone	February 6, 2002	2002;19	XXIII
Methylisocyanate (MIC)	December 5, 2001	2002;19	XXIII
Methyl mercaptane	September 9, 1986	1987;39	VIII
Methyl methacrylate	March 17, 1993	1993;37	XIV
Methyl pyrrolidone	June 16, 1987	1987;39	VIII
α-Methylstyrene	November 1, 2000	2001;20	XXII

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

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

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

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2010;44(4). A Johnson and T C Morata. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 142. Occupational exposure to chemicals and hearing impairment.

2010:44(5). J Montelius (Ed.) Scientific Basis for Swedish Occupational Standards XXX. Swedish Criteria Group for Occupational Standards.

2010:44(6). B Sjögren, A Iregren and J Järnberg. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 143. Phosphate triesters with flame retardant properties.

2010;44(7). G Aronsson, W Astvik och K Gustafsson. Arbetsvillkor, återhämtning och hälsa – en studie av förskola, hemtjänst och socialtjänst.

2010;44(8). K Torén, M Albin och B Järvholm. Systematiska kunskapsöversikter; 1. Betydelsen av fukt och mögel i inomhusmiljö för astma hos vuxna.

2010;44(9). C Wulff, P Lindfors och M Sverke. Hur förhåller sig begåvning i skolåldern och psykosocial arbetsbelastning i vuxenlivet till olika aspekter av självrapporterad hälsa bland yrkesarbetande kvinnor och män?

2010;44(10). H Kantelius Inhyrningens logik Långtidsinhyrda arbetare och tjänstemäns utvecklingsmöjligheter och upplevda anställningsbarhet.

2011;45(1). E Tengelin, A Kihlman, M Eklöf och L Dellve. Chefskap i sjukvårdsmiljö: Avgränsning och kommunikation av egen stress.

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2011;45(3). J Montelius (Ed.) Vetenskapligt Underlag för Hygieniska Gränsvärden 31. Kriteriegruppen för hygieniska gränsvärden.
2011;45(4). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety. 144. Endotoxins.

2011;45(5). Ed. Editors: Maria Albin, Johanna Alkan-Olsson, Mats Bohgard, Kristina Jakobsson, Björn Karlson, Peter Lundqvist, Mikael Ottosson, Fredrik Rassner, Måns Svensson, and Håkan Tinnerberg.
55th Nordic Work Environment Meeting.
The Work Environment – Impact of Technological, Social and Climate Change.

2011;45(6). J Montelius (Ed.) Scientific Basis for Swedish Occupational Standards XXXI. Swedish Criteria Group for Occupational Standards.

2011;45(7). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety. 145. Aluminium and aluminium compounds.

2012;46(1). Birgitta Lindell. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 146. Polychlorinated biphenyls. (PCBs)

2012:46(2). K Torén, M Albin och B Järvholm.
Systematiska kunskapsöversikter;
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2012:46(3). G Sjögren Lindquist och E Wadensjö. Kunskapsöversikt kring samhällsekonomiska kostnader för arbetsskador.

2012;46(4). C Mellner, G Aronsson och G Kecklund. Segmentering och integrering– om mäns och kvinnors gränssättningsstrategier i högkvalificerat arbete.

2012;46(5) T. Muhonen. Stress, coping och hälsa under kvinnliga chefers och specialisters karriärer.

2012;46(6). J Montelius (Ed.) Vetenskapligt Underlag för Hygieniska Gränsvärden 32. Kriteriegruppen för hygieniska gränsvärden.

2012;46(7) Helene Stockmann-Juvala. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 147. Carbon monoxide.

2013;47(1) I Lundberg, P Allebeck, Y Forsell och P Westerholm.
Systematiska kunskapsöversikter;
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Occupational Safety and Health in Mining. Anthology on the situation in 16 mining countries.

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2013;47(4). K Jakobsson och P Gustavsson.
Systematiska kunskapsöversikter;
5. Arbetsmiljöexponeringar och stroke – en kritisk granskning av evidens för samband mellan exponeringar i arbetsmiljön och stroke.

2013;47(5) M Hedmer, M Kåredal, P Gustavsson and J Rissler. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 148. Carbon nanotubes.

2013;47(6). J Montelius (Ed.) Scientific Basis for Swedish Occupational Standards XXXII. Swedish Criteria Group for Occupational Standards.