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Scientific Basis for Swedish Occupational Standards XIX

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Arbetslivsinstitutet
National Institute for Working Life

National Institute for Working Life

The National Institute for Working Life is Sweden's national centre for work life research, development and training.

The labour market, occupational safety and health, and work organisation are our main fields of activity. The creation and use of knowledge through learning, information and documentation are important to the Institute, as is international co-operation. The Institute is collaborating with interested parties in various development projects.

The areas in which the Institute is active include:

- labour market and labour law,
- work organisation,
- musculoskeletal disorders,
- chemical substances and allergens, noise and electromagnetic fields,
- the psychosocial problems and strain-related disorders in modern working life.

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Preface

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

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

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

This is the 19th volume which is published and it contains consensus reports approved by the Criteria Group during the period July 1997 to June 1998. Previously published consensus reports are listed in the Appendix (p 73).

Johan Högberg
Chairman

Per Lundberg
Secretary

The Criteria Group has the following membership (as of June, 1998)

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Contents

Consensus Report for Dimethylamine (DMA)

December 10, 1997

This report is based primarily on a document compiled by the Nordic Expert Group (1) and on subsequently published articles.

Chemical and physical data. Uses

CAS No.:	124-40-3
Synonym:	N-methylmethane amine
Formula:	CH_3-NH-CH_3
Molecular weight:	45.08
Boiling point:	7.4 °C
Melting point:	- 96 °C
Vapor pressure:	170 kPa (20 °C)
Conversion factors:	1 ppm = 1.87 mg/m^3
	1 mg/m^3 = 0.53 ppm

DMA at room temperature is a volatile gas. The explosion threshold in air is 2.8 to 14%. DMA can also occur as an alkaline solution, 25 – 60% in water. DMA is soluble in water, alcohol and ether. The substance has a strong odor of ammonia, and the odor threshold has been reported to be between 0.047 and 0.34 ppm (1). DMA can combine with nitrite to form dimethylnitrosamine, which is hepatotoxic and carcinogenic (8).

DMA is used as a raw material in the chemical and pharmaceutical industries and as an accelerator in the rubber industry. The substance is used in pesticides, in tanning and in soap production.

DMA occurs naturally in some foods, including cabbage, celery, corn, fish and coffee. It is also formed endogenously in the body. Humans excrete about 15 – 25 mg DMA in urine daily, and the amount increases considerably after intake of fish (4, 16).Uptake, biotransformation, excretion

Uptake, biotransformation, excretion

Four volunteers who drank 15 mg of a radioactively labeled solution of dimethylamine in water excreted 94% of the radioactivity in urine within 72 hours (87% during the first 24 hours), and small amounts (1 – 3%) were recovered in feces and exhaled air. Five percent had been demethylated to methylamine, and the rest of the dose was excreted unchanged. Uptake from the digestive tract was rapid ($t_{1/2}$ = 8 minutes) and the half time for excretion was 6 to 7 hours, with plasma clearance of 190 ml/minute (18).

In three groups of people who ate different amounts of fish – 0, 390 or 1150 g/week – excretion of DMA in urine was independent of fish consumption (16). An earlier study reports that persons who ate fish had increased amounts of DMA in urine (17).

In inhalation studies, rats were exposed to 10 or 175 ppm radioactively labeled DMA for 6 hours. The highest amounts of radioactivity were recovered in nasal mucosa immediately after the exposure, and 78% of the low dose and 87% of the high dose were excreted in urine within 72 hours. After 72 hours 8% (low dose) and 7% (high dose) of the radioactivity remained in the body (11). Rats and mice were given radioactively labeled DMA by gavage in doses of 20 μmol/kg body weight: 91% of the radioactivity was excreted in urine within the first 24 hours, and after 72 hours only 1% remained in the body. Most of the dose (89%) was excreted unchanged, but a small portion had been demethylated (19).

Intake and excretion of naturally occurring methylamines was studied in normal and "germ-free" rats, and net synthesis of DMA was measured with the help of intestinal bacteria (14). The excretion studies indicated that only a small portion of the DMA was metabolized. In vitro, in microsomes from rat livers or nasal and tracheal mucosa, DMA was biotransformed to formaldehyde and dimethylhydroxylamine (10).

Toxic effects

Because of its high pH (12.5 for a 1 M solution), skin contact with DMA can cause irritation and necrosis. One drop in a rabbit's eye caused a blue-white discoloration of the cornea, and within a minute or so it became sclerotic (12). In a study of 5 cases of allergic contact dermatitis caused by rubber gloves, the patients were tested for several rubber chemicals including DMA. DMA was regarded as a possible cause (9).

No exposure-related effects on the eyes were observed in persons occupationally exposed to a mixture of ammonia, dimethylformamide, monomethylamine, DMA and trimethylamine at a total concentration of 20 mg/m^3. Only 75 of 120 exposed persons were examined, however (13).

In another study, 10 volunteers ate either fresh fish or frozen fish which contained high concentrations of DMA formed during freezer storage, and urine concentrations of 3-methyladenine, a DNA alkylation product (which is an indicator of the formation of dimethylnitrosamine), were measured. There was no difference in excretion of 3-methyladenine between the eaters of fresh fish and the eaters of frozen fish. The excretion of 3-methyladenine did not increase when the subjects also took 225 mg sodium nitrate one hour before eating the fish (4).

Rats exposed to 1000 ppm DMA for 6 hours developed corneal edema and tracheitis. Slight tracheitis and epithelial hyperplasia were seen at 600 ppm. When the animals were exposed to 2500 ppm or higher, they developed hemorrhagic tracheitis, corneal necroses and lenticular damage in the eyes, hemorrhages and necroses in nasal mucosa and necrotic foci in livers (15). According to an unpublished study (cited in Reference 15), exposure to 97 or 185 ppm DMA 7 hours/day, 5 days/week for 18 – 20 weeks resulted in corneal

damage in guinea pigs and rabbits but not in rats and mice. The lower dose also caused fatty degeneration and necroses in the livers of all four species.

Exposure to 10 ppm DMA 6 hours/day, 5 days/week for 12 months increased the incidence of inflammation in the ears and respiratory passages of rats. A few animals had degenerative changes in olfactory epithelia. At 50 ppm there were squamous cell metaplasias in respiratory epithelia after 6 months, and inflammation with epithelial hypertrophy and hyperplasia (as well as damage to olfactory epithelia) after 12 months. At 175 ppm the damage was more severe, with perforated nasal septa. Similar effects were observed in mice exposed on the same schedule (2). Similar damage was also seen in rats that were exposed to 175 ppm DMA for 2 years. Minor changes in nasal epithelia and changes in mucociliary transport in the nose were observed after only one day of exposure, and after a week there were rather severe hemorrhages and a loss of olfactory cells (6).

The RD_{50} (50% reduction in respiratory rate) has been calculated to be 573 ppm for rats and 511 ppm for mice (15). Another study (5) reports an RD_{50} of 70 ppm for mice.

Rats, guinea pigs, rabbits, monkeys and dogs exposed to 4.8 ppm DMA 24 hours/day for 90 days showed no pathological changes in liver, kidneys, heart/circulatory system or blood that could be related to the exposure (3). All species had interstitial inflammatory changes in the lungs, but there were no chemically induced histopathological changes. No controls were mentioned, nor was examination of the upper respiratory passages described.

Mutagenicity, carcinogenicity, teratogenicity

DMA has yielded negative results in most mutagenicity tests, but it induced point mutations in a strain of *Saccharomyces cerevisiae*. Inhalation of 0.27 or 0.54 ppm DMA 24 hours/day for 90 days increased the number of aneuploid myeloblasts in rats. The clinical relevance of this finding is unclear (1).

Exposure to 50 ppm DMA 6 hours /day, 5 days/week for 6 months caused squamous cell metaplasias in the respiratory epithelia of mice. Exposure to 175 ppm DMA on the same schedule caused metaplasias in both rats and mice (2, 6). These reports make no mention of observations in other organs.

Neutralized DMA was given to mice intraperitoneally on days 1 to 17 of gestation: doses were 0.25, 1, 2.5 or 5 mmol/kg body weight. No effects on embryos were observed (7).

Dose-effect / dose-response relationships

The primary effects of short-term exposures to DMA are irritation of mucous membranes and eyes and effects on breathing. In animal studies, these effects have been observed in mice at concentrations of 70 ppm or above and in rats at 100 ppm or above. Exposure levels above 175 ppm affect nasal mucosa. The effects of long-term exposures are summarized in Table 1. The lowest observed effect level (LOAEL) in long-term studies with laboratory animals is 10 ppm: at this level minor changes were observed in epithelial and olfactory cells in the nose. At 50 ppm these effects were more pronounced.

Table 1. Effects observed in laboratory animals after long-term exposures to DMA (from Reference 1).

Dose	Species	Effect	Ref.
5 ppm, 90 days	Rats, guinea pigs, rabbits, dogs, monkeys	Interstitial inflammatory changes in lungs (relevance unclear)	3
10 ppm, 12 months 6 hours/day, 5 days/week	Mice, rats	Minor changes in nasal epithelia and olfactory cells	2
50 ppm, 12 months 6 hours/day, 5 days/week	Mice, rats	Moderate changes in nasal epithelia and olfactory cells, metaplasias	2
97–185 ppm, 8–20 weeks 7 hours/day, 5 days/week	Mice, rats, guinea pigs, rabbits	Corneal damage and effects on livers	14
175 ppm, 1–2 years 6 hours/day	Rats	Metaplasias, severe effects on respiratory epithelia, lower weight gain	2, 6

Conclusions

Judging mostly from animal data, the critical effect of occupational exposure to dimethylamine is its effect on the mucous membranes of the respiratory passages and the sense of smell. Direct contact with an unbuffered aqueous solution of dimethylamine can cause skin corrosion because of its high pH.

Dimethylamine can combine with nitrite to form dimethylnitrosamine, which is carcinogenic and hepatotoxic.

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Consensus Report for Graphite

December 10, 1997

Chemical and physical data. Uses

CAS Nos.:	7782-42-5, 1399-57-1, 12424-49-6, 12751-41-6
Formula:	C
Molecular weight:	12.01
Density:	2.09 – 2.23 g/cm^3
Melting point:	sublimates at 3850 °C (101.3 kPa)

Graphite is a soft, crystalline form of carbon that occurs naturally and can also be produced artificially. Natural graphite may be classified as crystalline or microcrystalline (sometimes referred to as amorphous), and contains various impurities, including quartz. The content of free silica in natural graphite varies considerably, and can be as high as 11% or more (11, 27). Synthetic graphite is almost pure crystalline carbon (21). It can be produced by mixing coal or petroleum coke with coal tar, a small amount of crude oil and in some cases anthracite coal and heating the mixture to 2800 – 3000 °C (1, 17, 24, 27). The quartz content of synthetic graphite is reported to be less than 1% (28).

Graphite is extremely resistant to heat and chemicals, and is therefore used in metallurgy, in foundries, in the chemical industry etc. Natural graphite is used in the production of steel and cast iron and (in powdered form) in casting sand. Natural graphite was once widely used in the production of fireproof materials for blast furnaces, crucibles, solder ladles etc., but it has now been largely replaced by synthetic graphite. Natural graphite is also used in brushes for motors and generators. Carbon electrodes used in steel production, electrochemical processes etc., and components for atomic reactors (neutron moderators) are made with synthetic graphite. Both synthetic graphite and high-purity natural graphite are used in lubricants. Pencils contain natural graphite in microcrystalline form (10, 14, 21, 27).

Uptake, distribution, excretion

No quantitative data were found on uptake of graphite via lungs, skin or digestive tract. Nor are there any quantitative data on distribution or excretion.

Toxic effects

Human data

More than 550 reported cases of pneumoconiosis have been attributed to occupational exposure to dust containing graphite (11, 22, 24, 30, 31, 32). Both simple and progressive forms of pneumoconiosis have been diagnosed, and they are reported to resemble ordinary black lung disease symptomatically as well as on x-rays. The exact composition of the dust is not usually known and quantitative exposure data are usually non-existent, but many cases have been described as mixed-dust pneumoconioses (exposure to graphite and simultaneous or previous exposure to other types of carbon dust and/or quartz) (11, 14, 19, 26).

There are some studies (8, 9, 13, 15, 16, 30) reporting pneumoconioses caused solely or primarily by graphite exposure, and a few of them give analysis results. One of them (15, 16) describes graphite pneumoconiosis in a patient who worked as a polisher of synthetic graphite for 17 years. He had previously worked for 25 years as a mason's helper. Dust from his workplace was found to contain more than 90% carbon and less than 0.02% free silica, and no silicic material was found in examination of his lung tissue. Another study (incompletely reported) states that black lung disease was diagnosed in 8 persons who had worked for at least 15 years at a graphite factory (graphite type not reported), and that no quartz could be identified in analysis of the graphite dust (8). An American study (18) reports severe pneumoconiosis in a worker who had been exposed to graphite dust (graphite type not given) for several years. No silica was found in analysis of either lung tissue or dust from the workplace, and it was noted that the carbon in the lungs was mostly graphite. In a later study (9), however, it is suggested that silica may have played some role in development of the pneumoconiosis in this case. Several other cases of pneumoconiosis in persons exposed to large amounts of dust containing graphite are reported in this article, however, and it is stated that in one of these cases silica probably did not contribute to the development of the disease (9). Analysis of dust from the workplace showed that the dust was composed mostly of graphite and contained traces of crystalline material that was not silica.

In a Japanese study (20) of 256 production workers who made carbon electrodes, 112 of them (43.8%) were reported to have "graphite pneumoconiosis" (x-ray changes). The percentage of cases was markedly higher among those with exposures longer than 10 years, but minor changes could be seen on the x-rays of nearly 40% of the group exposed for 5 – 9 years. The workers were followed for 4 years, and during this time the x-ray changes got worse. Disturbances in lung function were found in the study, but they were reported to be considerably less pronounced than the x-ray changes. Histopathological examinations were made in two cases (case 1: worked in manufacture of carbon electrodes for 24 years; case 2: employed at the factory for 17 years) and revealed extensive connective tissue changes in the lungs. Measured air concentrations at the factory ranged from 14.5 to 138.8 mg/m^3 (average 57.6 mg/m^3), or 328 – 3935 (average 967) particles/cm^3, and 68.8 % of total dust was below 1 μm. X-ray diffraction analysis of dust

deposited at the workplace revealed that more than 99.6% was carbon and less than 0.1% was free silica. Graphite (probably synthetic graphite) was identified in x-ray diffraction analyses of dust from the lungs (2 cases). The authors concluded that graphite or carbon usually causes a relatively mild tissue reaction but that inhalation of large amounts of dust can cause severe pneumoconiosis, and that development of the disease is dependent not only on the nature of the dust but also on its quantity. It should be mentioned that other cases of pneumoconiosis in workers manufacturing carbon electrodes have not been attributed to graphite but to exposure to dust from coke and anthracite coal (33).

Animal data

Rats were exposed to 1, 10, 105 or 520 mg/m^3 synthetic graphite (‹0.1% quartz) for 4 hours: subsequent bronchoalveolar lavage revealed indications of transient inflammation and macrophage activation at the highest dose (2).

In another study (28, 29), rats were exposed to 100 mg/m^3 natural graphite (1.85% silica) or synthetic graphite (‹1% silica) 4 hours/day for 4 days. Biochemical and cytological analyses (bronchoalveolar lavage) 24 hours later (on the fifth day) revealed slight indications of inflammation. The changes were transient, and were somewhat greater after exposure to natural graphite than after exposure to synthetic graphite. The histopathological examinations revealed minimal foci of epithelial hyperplasia in a few animals (synthetic graphite). No biologically significant changes in lung function were observed.

After intermittent inhalation exposure to an aerosol containing 100 or 200 mg/m^3 graphite (purity not reported) for 4 weeks, rats showed concentration-dependent changes on lung function tests which may have indicated some deterioration of lung function. Elevated relative lung weights were also noted, especially two weeks after termination of exposure and in the higher dose group. Bronchoalveolar lavage revealed concentration-dependent (also duration- and frequency -dependent) changes (inflammatory response), which the authors interpreted as effects of irritation. Histological examination revealed no noteworthy effects (3).

In another study (5), no noteworthy effects were seen in the lungs of rats or hamsters after exposure to 1 mg/m^3 unspecified graphite dust 12 hours/day for up to 4 or 3 months, respectively.

Suspensions of synthetic graphite containing 0.44% free silica, or natural graphite containing 12.75% free silica, were given to rats by intratracheal instillation: 3 doses (0.2 ml, 5% graphite) at 1-week intervals. The animals were sacrificed 31, 185, 273 or 366 days after the last dose, and it was found that, whereas the synthetic graphite caused no noticeable inflammatory changes, the natural graphite had induced progressive cellular inflammation. Observed changes in connective tissue (collagen) were slight (23).

In one study (12), intratracheal injections of 50 mg natural graphite were given to rats and the animals were sacrificed 6 to 9 months later: there was an increase of fine reticulin fibers in the lungs, but only slight collagen changes in connective tissue. In another study with rats (4), low-grade but progressive connective tissue changes (reticulin fibers) were

seen 150 – 600 days after an intratracheal dose of a suspension of 100 mg graphite dust (1 ml) containing 1.6% quartz.

Intratracheal injection of 0.5 ml of a suspension of pure synthetic graphite (5 – 10 mg) was reported to cause connective tissue changes (increase of collagen phases) in the lungs of rats 150 or more days after the treatment. The degree of change seemed to be dependent on the amount of dust, however, and did not increase with time (7).

Intratracheal injections (1.5 ml) of a suspension of 100 mg pure graphite (0.24% silica), or 98 mg pure graphite and 2 mg (2%) quartz, were reported to cause low-grade connective tissue changes (reticulin fibers) in the lungs of rats. The changes could be observed after about 11 weeks in the rats given graphite alone, whereas the same degree of fibrosis was seen after about 7 weeks in the rats given both graphite and quartz. After 171 days connective tissue changes were more extensive in the latter group, but they subsequently increased no further (25).

In a study with sheep (6), effects on the lungs were investigated 2, 4, 6 and 8 months after an infusion of 100 mg graphite (suspension) in the respiratory passages. Bronchoalveolar lavage revealed indications of a minor, transient inflammatory process (after 2 months), but no activation of fibrogenic processes was observed.

Carcinogenicity, teratogenicity, mutagenicity

No studies were found.

Dose-effect / dose-response relationships

There is a connection between occupational exposure to natural graphite and the occurrence of pneumoconiosis, but available data do not provide sufficient basis for identifying a dose-response or dose-effect relationship. The frequency and severity of the disease are probably affected by the amount of free silica in the dust.

There are little reliable data on synthetic graphite, but one study (15, 16) reports pneumoconiosis in a person exposed to synthetic graphite containing ‹0.02% free silica, and another study (20) reports the disease in persons exposed to graphite containing ‹0.1% free silica (probably synthetic graphite). Measured air concentrations in the latter study (20) ranged from 14.5 to 138.8 mg/m^3.

The exposure-effect relationships observed in laboratory animals exposed to graphite via inhalation or intratracheal administration are summarized in Tables 1 and 2.

Table 1. Effects of graphite inhalation on experimental animals.

Exposure	Species	Effect	Ref.
520 mg/m^3, 4 hours synthetic graphite (‹0.1% quartz)	Rats	Transient inflammation and macrophage activation in lungs	2
100 mg/m^3, 4 hours/day, 4 days natural graphite (1.85% silica)	Rats	Transient lung inflammation	28, 29
100 mg/m^3, 4 hours/day, 4 days synthetic graphite (‹1% silica)	Rats	Transient lung inflammation, minimal foci of epithelial hyperplasia in lungs	28, 29
100 mg/m^3 , 4 weeks 1 hour/day, 2 days/week; 1 hour/day, 4 days/week; 4 hours/day, 2 days/week; 4 hours/day, 4 days/week unspecified graphite	Rats	Lung inflammation (4 days/week); significantly elevated relative lung weights 2 weeks after termination of exposure (4 hours day/4 days week); changes on lung function tests (significantly higher respiratory rate, significantly lower FEV etc.)	3
1 mg/m^3, 12 hours/day up to 4 months unspecified graphite	Rats	No noteworthy effects on lungs	5
1 mg/m^3, 12 hours/day up to 3 months unspecified graphite	Hamsters	No noteworthy effects on lungs	5

Conclusions

The critical effect of occupational exposure to graphite is pneumoconiosis. In many cases patients have been exposed to natural graphite containing various amounts of free silica, but the disease has also been reported after exposure to synthetic graphite. Animal data, however, indicate that graphite dust containing small amounts of silica causes only minor connective tissue changes in the lungs.

Table 2. Effects on the lungs of experimental animals given graphite by intratracheal instillation.

Exposure	Species	Effect	Ref.
100 mg natural graphite (1.6% quartz)	Rats	Low-grade but progressive connective tissue changes (reticulin fibers) after 150-600 days	4
100 mg pure graphite (0.24% silica)	Rats	Low-grade connective tissue changes (reticulin fibers) after 11 weeks	25
100 mg 98 mg pure graphite + 2 mg quartz	Rats	Same as above group after 7 weeks; after 171 days higher degree of fibrosis	25
100 mg unspecified graphite	Sheep	Minor, transient inflammations	6
50 mg natural graphite	Rats	Increase of fine reticulin fibers in lungs after 6-9 months	12
21-22 mg synthetic graphite (0.44% free silica), 3 doses	Rats	No observable inflammatory changes	23
21-22 mg natural graphite (12.75% free silica), 3 doses	Rats	Progressive inflammation	23
5-10 mg pure synthetic graphite	Rats	Increase of collagen phases in lungs after 150-340 days	7

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Consensus Report for Flour Dust

December 10, 1997

This report is based primarily on a criteria document from the Nordic Expert Group (31).

Description, occurrence

Flour dust is dust from cereal grains, usually wheat or rye but sometimes oats, barley, rice or corn. The dust may contain other substances in addition to grain (see Table 1).

The smallest flour dust particles have a diameter of less than 1 μm, and the largest are about 200 μm in diameter. The aerodynamic diameter is around 5 μm for the smallest particles and around 15 – 30 μm for the larger ones. More than half of the particles in flour dust have an aerodynamic diameter greater than 15 μm (18). The protein content of flour is about 10%, but it is considerably higher in particles smaller than 17 μm (31).

Several allergenic substances have been identified in flour. The primary allergens, with molecular weights of about 15 kDa, belong to the group of α-amylase inhibitors (2, 11, 12). It has been suggested that the glycolized forms of these proteins are the most potent allergens (22). Since profilins (proteins with molecular weights of 13 – 15 kDa) from plants other than cereal grains are known allergens, it is assumed that wheat profilin may be

Table 1. Substances that may be found in flour dust (from Reference 31).

Component	Examples
Grain	glycoproteins, starch
Mites	Dermatophagoides, Lepidoglyphus, Tyrophagus, Glycyphagus, Acarus, Blomia
Mould	Penicillium, Aspergillus, Alternaria spp.
Insects	weevils, rice beetles
Enzymes	maltase, α-amylase, protease, cellulase, hemicellulases, xylanase, glucoamylase, glucose oxidase
Chemical additives	preservatives (e.g. sorbic acid, acetic acid), bleach (e.g. benzoyl peroxide, potassium bromate), antioxidants (e.g. ascorbic acid, lauryl or propyl gallate), emulsifiers, vitamins
Other additives	yeast, soy flour, powdered eggs, sugars
Spices and flavorings	anise, cardamom, cinnamon, cloves, ginger, lemon, nutmeg, peppermint, vanilla

one of the allergens responsible for hypersensitivity to flour (28). Both α- and β-amylase from grains are also allergens. Wheat flour contains 0.1 – 1.0 mg α-amylase per gram (7, 17). In addition to the allergens from the grain, flour dust may contain allergens of mite, mould and/or insect origin (31).

Although most exposure to flour dust occurs in bakeries and flour mills, it also occurs in other contexts. Table 2 shows the workplaces and jobs most commonly associated with exposure to flour dust.

Enzyme additives are used in bakeries to improve the qualities of the dough. The most common one is α-amylase from *Aspergillus oryzae*, but other mould enzymes are also used. They were formerly added as powders but are now usually liquids or granules, which reduces the amount of dust (5, 17).

A consensus report for industrial enzymes (19), based on a Nordic criteria document (4), was published by the Criteria Group in June, 1996.

Table 2. Workplaces and jobs in which exposure to flour dust occurs (from Reference 31).

Workplace	Job
Mills	grinding, packaging, cleaning, maintenance
Bakeries	mixing dry ingredients, dough mixing, bread making, cleaning
Pastry shops	weighing, mixing, production
Pasta factories	production
Pizzerias	production
Animal feed factories	mixing
Malt factories	drying, sifting, packing
Farming	grinding, feeding animals

Exposure and uptake

The European Committee for Standardisation (CEN) has defined three categories for dust sampling (9). The *inhalable fraction* consists of particles that are inhaled through the nose and mouth, the *thoracic fraction* is that portion of the particles that can come below the larynx, and the *respirable fraction* consists of particles that penetrate all the way into the respiratory passages. Several reports published in recent years contain monitoring data on flour dust and allergen concentrations. The size distributions of the particles in the dust and the enzyme concentrations in bakeries and mills have also been described (10, 18, 26, 31).

In bakeries, the average concentration of flour dust during a work shift is usually higher at the beginning of a process than at its end. Among the highest total dust concentrations measured are 10 mg/m^3 around mixing dough in bakeries and 11 mg/m^3 in pastry shops (23, 31). In an experimental study, the total dust concentration around weighing of flour

additives was reduced from 45 mg/m^3 to 0.06 mg/m^3 by installing local air intake and exhaust to supplement the existing general ventilation (13).

Brief (30 seconds to 4 minutes) exposures to high dust concentrations are common in bakeries. A 30-minute geometric average of 9 mg/m^3 has been measured around bread making, although the average for the shift was only 0.9 mg/m^3 (24). The allergen concentration followed the same variations as the total dust (26). The highest concentrations at both mills and bakeries were measured in connection with cleaning.

In measurements made in a flour mill, the average concentration of respirable airborne dust was between 0.3 and 0.9 mg/m^3 and the respirable fraction accounted for 23 to 31% of the total dust concentration (1). The respirable fraction was 27% of total dust at small industrial bakeries and 21% at larger bakeries in Denmark (32). For Swedish bakeries, the thoracic fraction has been estimated to be 39% and the respirable fraction 19% of total flour dust (7). The dustiest job was dough mixing: 14.1 mg/m^3 inhalable dust with a thoracic fraction of 26% and a respirable fraction of 9%.

In general, the allergen concentration increases linearly with the total dust concentration. The highest concentrations of wheat antigens are measured around dough mixing (average 5.3 μg/m^3) and the lowest around the ovens (average 0.3 μg/m^3) (16). The concentration of α-amylase varies with the type of bakery and the working area. The most heavily exposed group are the workers who mix the dough, with a highest measured α-amylase exposure of 222 ng/m^3 (15).

In general, the highest concentrations of inhalable dust are found around dough mixers in larger bakeries and around bakers in small bakeries. In the large bakeries it is the dough mixers who have the heaviest exposure, followed by the bread bakers, oven workers, pastry chefs and packers (7, 14).

Toxic effects

Irritative and allergenic effects

Flour proteins are the main cause of allergy among bakers. Both prick tests and bronchial provocation tests have been used to determine sensitivity, and IgE antibodies specific for flour are important indicators in diagnoses of allergy to flour dust (31). In a study of 85 apprentice bakers, 29 healthy bakers chosen at random and 38 bakers with diagnosed occupational disease, 5% of the apprentices, 21% of the healthy bakers and 91% of the sick bakers had positive responses to a prick test with flour. IgE antibodies specific for wheat flour were identified in 13% of the apprentices (17% of the music students who served as controls), 28% of the healthy bakers and 80% of the sick ones. Similarly high frequencies were noted for bronchial hyperreactivity (30).

In a survey of 176 bakers and 24 slicers and wrappers, coughing fits and shortness of breath were more prevalent among the bakers (20% compared to 4%), and 11% of the bakers met the criteria for work-related asthma. Bronchial hyperreactivity and positive prick tests for wheat flour and ordinary allergens were more prevalent in this group than among the other bakers (28).

In a study of about 400 bakery workers, subjects were divided into three groups on the basis of their exposure to wheat allergens. Average exposures were 0.1 μg/m^3 for the low-exposure group, 0.7 μg/m^3 for the middle group, and 3.8 μg/m^3 for the high-exposure group. A correlation between allergen exposure and wheat-specific IgE sensitization was found in both atopics and non-atopics. The prevalence of work-related symptoms was higher in groups with higher exposure (2.4 in the medium-exposure group and 2.7 in the high-exposure group), and the correlation was stronger for those who were sensitized than for those who were not (14).

To quantify the risk of developing asthma, about 3000 bakers were compared with unexposed controls. The relative risk of developing asthma while employed in a bakery was 1.8 times that for the controls. There were 3.0 cases of asthma per 1000 person-years among the bakers, compared with 1.8 per 1000 among controls. The incidence increased with increasing cumulative dust dose, to 3.4 cases per 1000 person-years with a cumulative dust dose of ›30 mg-year/m^3 (6).

In a study of 183 bakery workers who were exposed to flour dust concentrations up to 4 mg/m^3 (geometric means 0.01 – 3.0), 13% reported work-related symptoms involving the eyes and nose (itchy eyes, runny nose, sneezing) or had diagnosed rhinitis, and 9% reported work-related respiratory symptoms (chest tightness, wheezing, shortness of breath, chronic cough) or had diagnosed asthma. A prick test for flour was positive for 5% of them, and 28% were positive to some antigen present in bakeries (flour, yeast, enzymes, mites or mould). When the dust concentration was 1.7 – 11.0 mg/m^3 (geometric means), 30% of 96 bakery workers reported symptoms involving the eyes and nose, 17% reported respiratory symptoms, and 35% were positive to some antigen found in bakeries (23).

In one study, bakery workers and millers were divided into three exposure groups: low (104 workers, average ‹1 mg/m^3), medium (90 workers, average 1 – 5 mg/m^3) and high (62 workers, average ›5 mg/m^3). Symptoms involving the eyes and nose were reported by 11%, 15% and 31% respectively, and respiratory symptoms by 5%, 3% and 11% respectively. Prick tests for bakery antigens were positive in 17%, 25% and 30% respectively (8, 25).

Respiratory symptoms and results on metacholine provocation tests have been reported for 44 workers exposed to flour and 164 controls who were not exposed to flour dust but may have been exposed to other types of dust. The average exposure to flour dust was below 3.5 mg/m^3 with the exception of ”special bread baking,” where the average was 41.3 mg/m^3. There was no statistically significant difference between the exposed group and controls when the symptoms were compared individually, but the exposed group reported ”one or more symptoms” significantly more often than controls. Positive metacholine tests were more common among those exposed to flour dust (3).

In a study of 99 bakers from 56 traditional bakeries, 117 bakers from 9 bread factories, and 81 packers (as controls) from the same factories, the measured total flour dust concentrations were on average 0.9 – 2.1 mg/m^3 in the traditional bakeries and 1.0 – 14.3 mg/m^3 in the factories. The subjects were medically examined to determine whether they had occupational asthma and/or rhinitis. Asthma was diagnosed in 8.6% of the factory

bakers, 4.7% of the traditional bakers and 0% of controls, and occupational rhinitis in 16.2% of the factory bakers, 7.4% of the traditional bakers and 1.2% of controls (27, 32).

Of 322 employees of modern bakeries, flour-packaging plants and mills who responded to a questionnaire, 14% reported work-related respiratory symptoms, 29% reported symptoms involving the eyes or nose, and 9% reported skin symptoms. Sensitization was checked with a prick test given to 335 persons: 5% were positive for flour allergens and an equal number were positive for α-amylase (8).

Bakers are a high-risk group for hand eczema and contact urticaria (20, 21).

Dose-response / dose-effect relationships

Despite the existence of a large number of reports on sensitization and allergies following exposure to flour dust, there are few reports giving a relationship between exposure levels and effects. A summary of studies reporting both exposures and effects is given in Table 3. The studies have been described in the foregoing text. High, brief (up to 30 minutes) exposure peaks are common, but available scientific data provide insufficient basis for identifying a relationship between exposure and effect.

Table 3. Relationships between exposure to flour dust and reported symptoms.

Number exposed	Average dust concentration (mg/m^3)	Occupation-related symptoms (%)			Positive prick test (%)		Ref.
		eyes/nose	respiratory passages	skin	flour	bakery allergens	
104	‹ 1	11	5	2	2	17	8, 25
378	0.9 - 2.1	7	5	NR	NR	34	32
183	0.01 - 3.0	13	9	NR	5	28	23
90	1 - 5	15	3	10	6	25	8, 25
62	› 5	31	11	10	5	30	8, 25
117	0.6 - 6.0	16	9	NR	NR	36	32
96	1.7 - 11.0	30	17	NR	5	35	23
44	0.7 - 41.3 aeroallergens $\mu g/m^3$	18	23	5	11	NR	3
90	‹ 100	11	4	1	1	15	8, 25
83	100 - 215	14	4	6	5	28	8, 25
83	› 230	27	10	13	6	26	8, 25

NR = not reported

Conclusions

The critical effect of exposure to flour dust is symptoms involving the eyes and respiratory passages, including asthma. Flour dust can cause allergic reactions in respiratory passages and skin. It is impossible to establish a NOAEL on the basis of available data. It is also impossible to assess the relevance of exposure peaks.

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Consensus Report for Butyl Acetates

February 11, 1998

This report, which treats the isomers n-butyl acetate, isobutyl acetate, sec-butyl acetate and tert-butyl acetate, is based primarily on a criteria document produced in collaboration with the Dutch Expert Committee for Occupational Standards (21). The Criteria Group published a previous consensus report (13) for n-butyl acetate in June, 1984.

Chemical and physical data. Uses

n-butyl acetate

Names:	n-butyl acetate, normal butyl acetate, 1-butyl acetate, acetic acid butyl ester
CAS No.:	123-86-4
Formula:	CH_3-CO-O-$(CH_2)_3$-CH_3
Molecular weight:	116.16
Boiling point:	127 °C (101.3 kPa)
Melting point:	- 77 °C (101.3 kPa)
Vapor pressure:	1.07 kPa (20 °C)
Distribution coefficient:	log K_{ow} = 1.82
Conversion factors:	1 mg/m^3 = 0.207 ppm; 1 ppm = 4.83 mg/m^3

At room temperature n-butyl acetate is a clear, volatile liquid with a fruity odor. The reported odor threshold is 10 ppm (21). The vapors can combine with air to make an explosive mixture, and the explosion threshold has been reported to be 1.2 to 7.5% (volume) in air. In water, and in reaction to light, the ester breaks down to acid and alcohol. The substance is soluble in water (7 g/liter at 20 °C) and mixes with alcohols, ether, ketones, esters, hydrocarbons and other organic solvents.

The isomer n-butyl acetate is used as a solvent in a wide variety of contexts: nitrocellulose, paints, cosmetics etc. It occurs as a component in artificial flavorings, photographic film, glues, plastics and safety glass, and is used as an extractant in the pharmaceutical industry (24). Exposure levels averaging 9 mg/m^3 with peaks as high as 1500 mg/m^3 have been recorded in the paint industry (12, 22). In one study, the measured concentration of n-butyl acetate around spray painting (where there was simultaneous exposure to several solvents) ranged from 37.6 to 134 mg/m^3 (21). There are several sets of monitoring data from painting and from the paint industry (21) but there is seldom mention of which isomer of butyl acetate was measured. In most cases, it was probably n-butyl acetate and/or isobutyl acetate.

isobutyl acetate

Names:	isobutyl acetate, 2-methyl-1-propyl acetate, acetic acid isobutyl ester
CAS No.:	110-19-0
Formula:	CH_3-CO-O-CH_2-$CH(CH_3)_2$
Molecular weight:	116.16
Boiling point:	117 °C (101.3 kPa)
Melting point:	- 99 °C (101.3 kPa)
Vapor pressure:	2.0 kPa (20 °C)
Distribution coefficient:	log K_{ow} = 1.60
Conversion factors:	1 mg/m^3 = 0.207 ppm; 1 ppm = 4.83 mg/m^3

At room temperature isobutyl acetate is a clear liquid with a fruity odor. The reported explosion threshold in air is 2.4 to 10.5% (volume). The substance is soluble in water (7.0 g/liter at 20 °C), alcohol, acetone and ether.

Isobutyl acetate is used as a solvent in paints and paint removers, and is a component of hydraulic fluid (24). Concentrations up to about 100 mg/m^3 have been measured in the paint industry, and concentrations in the range 37 – 134 mg/m^3 have been measured around spray painting (21).

sec-butyl acetate (exists in D and L forms)

Names:	sec-butyl acetate, secondary butyl acetate, 2-butyl acetate
CAS No.:	105-46-4
Formula:	CH_3-CO-O-$CH(CH_3)$-CH_2-CH_3
Molecular weight:	116.16
Boiling point:	112 – 117 °C (101.3 kPa)
Melting point:	- 74 °C (101.3 kPa)
Vapor pressure:	2.5 kPa (20 °C)
Conversion factors:	1 mg/m^3 = 0.207 ppm; 1 ppm = 4.83 mg/m^3

At room temperature sec-butyl acetate is a clear liquid with a fruity odor. The reported explosion threshold in air is 1.7 – 9.8% (volume). The isomer is soluble in water (30 g/liter at 20 °C), alcohol, acetone and ether.

Sec-butyl acetate is used as a solvent for nitrocellulose and nail polish, and in surface treatment of paper. No monitoring data on occupational exposures were found.

tert-butyl acetate

Names:	tert-butyl acetate, tertiary butyl acetate, acetic acid tert-butyl ester
CAS No.:	540-88-5
Formula:	CH_3-CO-O-$C(CH_3)_3$
Boiling point:	97 – 98 °C (101.3 kPa)
Melting point:	no data available
Vapor pressure:	no data available
Distribution coefficient:	log K_{ow} = 1.38
Conversion factors:	1 mg/m^3 = 0.207 ppm; 1 ppm = 4.83 mg/m^3

At room temperature tert-butyl acetate is a clear liquid with a fruity odor. It is virtually insoluble in water but dissolves in solvents such as alcohol and ether.

Tert-butyl acetate is used as a solvent for paint and as an anti-knock additive in motor fuels (24). No monitoring data on occupational exposures were found.

Uptake, biotransformation, excretion

There are no quantitative data on uptake of butyl acetates.

When anesthetized rats were exposed via the trachea to n-butyl acetate, 34,000 mg/m^3 for 1 hour or 4800 mg/m^3 for 5 hours, constant blood levels of n-butyl acetate and n-butanol were rapidly reached. The n-butyl acetate was eliminated from blood within 1 minute after termination of the 1-hour exposure, and the halving time for n-butanol was 5 minutes (4, 6). In a similar experiment with tert-butyl acetate there was a steady increase of blood levels during the exposures, and a two-phase elimination of the acetate, with halving times of 5 and 70 minutes, when exposure was terminated (4).

Butyl acetates are readily hydrolyzed to acid and alcohol in blood, liver, small intestines and respiratory passages, and this has been demonstrated in vitro in homogenates (3, 11). When n-butyl acetate was added to human blood samples the halving time for hydrolysis was 4 minutes, but when tert-butyl acetate was tested the same way the halving time was 300 minutes (4).

The acetic acid formed in this process is oxidized via the tricarboxylic acid cycle to carbon dioxide and water. Isobutanol and n-butanol are metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to the corresponding acids, which are oxidized to carbon dioxide. The isomer sec-butanol is metabolized, also by alcohol dehydrogenase, to methyl ethyl ketone, which is either excreted (in exhaled air or urine) or further metabolized. Tert-butanol is metabolized more slowly. It is eliminated in urine as glucuronide conjugates and acetone, and in exhaled air as acetone and carbon dioxide (23).

Using a system containing cytochrome P-450 2B4 (from rabbit liver), it was demonstrated that sec-butyl acetate was first hydroxylated to an unstable hemiketal (2-hydroxy-2-acetoxybutane) and then broken down to 2-butanone (methyl ethyl ketone) (16).

Toxic effects

Human data

When volunteers were exposed to n-butyl acetate, most of them reported that 3 to 5 minutes of exposure to 970 mg/m^3 was irritating to the throat and that 1450 mg/m^3 was irritating to the nose and eyes as well (15). In a later study, volunteers were exposed to 70, 350, 1050 or 1400 mg/m^3 for 20 minutes or to 70 or 700 mg/m^3 for 4 hours. The highest concentrations caused minimal irritation of eyes and respiratory passages (7).

A worker in penicillin production developed eczema on the hands, arms and face, and had a positive reaction to a patch test with n-butyl acetate (5% in olive oil). This study also included a control group of 36 patients, all of whom tested negative (17). In sensitization studies with human subjects, n-butyl acetate (4 or 10% in petroleum jelly) was reported to cause no irritation or sensitization. The North American Contact Dermatitis Group listed n-butyl acetate as an eczema-causing ingredient in cosmetics after 1 of 149 patients given a patch test had a positive reaction (2).

There are several epidemiological studies in which n-butyl acetate was one of several solvents to which exposure had occurred. Irritation effects and effects on the nervous system were found in these studies, but it is impossible to determine how much n-butyl acetate contributed to these effects.

No data on human exposures to the other isomers were found.

Animal data

n-butyl acetate: No skin irritation was noted when 0.5 ml n-butyl acetate was applied to the backs of rabbits under gauze (semiocclusive) for 4 hours, but severe irritation resulted from a 24-hour period of occlusion (21). Instillation of 0.005 ml n-butyl acetate in the eyes of rabbits caused severe burns (19). Instillation of n-butyl acetate solutions of 100%, 30%, 10% and 3% resulted in Draize scores of 8, 11, 19 and 2, respectively (9).

N-butyl acetate was not sensitizing when tested in the classical guinea pig maximization test, nor was it sensitizing in the alternative mouse ear swelling test (MEST) (5). In studies with two different strains of mice, the RD_{50} (50% reduction of respiratory rate) was determined to be 3470 mg/m^3 for one strain and 8340 mg/m^3 for the other (1, 10, 14).

LC_{50} studies with rats have yielded results ranging from 740 mg/m^3 to nearly 43,000 mg/m^3. Values of 740, 1800, 5055, 9700, 32,000 and 42,930 mg/m^3 have been reported, all of which apply to 4 hours of exposure (unpublished data, cited in Reference 21). The design of the study with the lowest reported value is such that the animals were probably exposed to higher concentrations (21). The clinical observations made in these studies include eye irritation and effects on the nervous system (hypoactivity, ataxia, increased respiratory rate, coma). Examination of the animals that died revealed discoloration of the lungs, alveolar hemorrhages, necrotic epithelial cells in alveoli and edema.

In an unpublished study reviewed in the criteria document (21), Sprague-Dawley rats (both sexes) were exposed to n-butyl acetate 6 hours/day, 5 days/week for 13 weeks. Concentrations were 0, 2420, 7260 or 14,520 mg/m^3. All the animals survived. Lower body weights and necroses in olfactory epithelia were seen the two highest dose groups (all

animals in the highest dose group and 10/20 animals in the second-highest dose group). No exposure-related effects were observed in the lowest dose group. In a similar unpublished study also cited in the criteria document, neurotoxicity was investigated with exposures of 13 – 14 weeks. No indications of neurotoxicity were seen in any of the exposure groups.

isobutyl acetate: The substance has been tested for eye and skin irritation, but not by the standardized methods now in use. Isobutyl acetate was found to be "slightly irritating" to the skin of rabbits and caused "moderate " inflammation in rabbit eyes (20). An RD_{50} of 3890 mg/m^3 was established for mice, as a measure of bronchial irritation (1,14). Four hours of exposure to 38,900 mg/m^3 killed 4 of 6 rats (20).

sec-butyl acetate: There are no data on sec-butyl acetate.

tert-butyl acetate: There is an estimated RD_{50} for mice of about 76,000 mg/m^3 (1, 14). No other data on tert-butyl acetate were found.

Mutagenicity, carcinogenicity, teratogenicity

N-butyl acetate has yielded negative results in mutagenicity tests with various strains of *Salmonella typhimurium*, both with and without the addition of metabolizing systems. It induced no chromosome aberrations or polyploidy in hamster fibroblasts (8, 18, 25).

There are no data on mutagenicity for the other three isomers.

No carcinogenicity data were found for any of the isomers.

An unpublished reproduction toxicity study is reviewed in the criteria document (21). Groups of rats exposed during and/or before gestation to 7260 mg/m^3 n-butyl acetate showed toxic effects (lower relative body weights and absolute liver weights, higher relative kidney and lung weights). In addition, their pups weighed less and had a higher incidence of ossification. Similar results were obtained in a parallel study with rabbits, where exposure was the same (21).

There are no reproduction toxicity data for the other isomers.

Dose-response / dose-effect relationships

Irritation of eyes, skin and mucous membranes was seen in volunteers after 4 hours of exposure to 700 mg/m^3 n-butyl acetate (7), and after a few minutes of exposure to about 1000 mg/m^3 (15).

Toxic effects were seen in rabbits and rats exposed to 7260 mg/m^3 n-butyl acetate for 13 weeks (21), and 2420 mg/m^3 can be regarded as the NOAEL in these animal studies. An RD_{50} of 3470 mg/m^3 has been estimated for mice (7, 14).

For the other isomers, there are too little data to support an estimate of a dose-response or dose-effect relationship.

Conclusions

The critical effect of occupational exposure to *n-butyl acetate* is irritation of eyes, skin and mucous membranes. For *isobutyl acetate*, irritation is probably the critical effect, but the data are less convincing. For the other isomers, there are no data indicating a critical effect.

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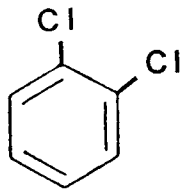
Consensus Report for Dichlorobenzenes

February 11, 1998

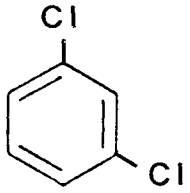
This report is based on a document (12) produced by the Nordic Expert Group. It covers the three isomers of dichlorobenzene: ortho-dichlorobenzene (o-DCB), meta-dichlorobenzene (m-DCB) and para-dichlorobenzene (p-DCB).

Chemical and physical data. Uses

o-DCB

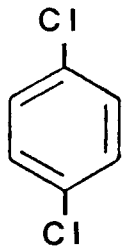
Names:	ortho-dichlorobenzene, 1,2-dichlorobenzene
CAS No.:	95-50-1
Formula:	$C_6H_4Cl_2$
Structure:	
Molecular weight:	147.01
Melting point:	- 17 °C
Boiling point:	180 °C
Vapor pressure:	0.20 kPa (25 °C)
Conversion factors:	1 mg/m^3 = 0.1663 ppm; 1 ppm = 6.01 mg/m^3

m-DCB

Names:	meta-dichlorobenzene, 1,3-dichlorobenzene
CAS No.:	541-73-1
Formula:	$C_6H_4Cl_2$
Structure:	
Molecular weight:	147.01
Melting point:	- 25 °C
Boiling point:	173 °C
Vapor pressure:	0.31 kPa (25 °C)
Conversion factors:	1 mg/m^3 = 0.1663 ppm; 1 ppm = 6.01 mg/m^3

p-DCB

Names:	para-dichlorobenzene, 1,4-dichlorobenzene
CAS No.:	106-46-7

Formula:	$C_6H_4Cl_2$
Structure:	
Molecular weight:	147.01
Melting point:	53 °C
Boiling point:	174 °C
Vapor pressure:	0.13 kPa (25 °C)
Conversion factors:	1 mg/m^3 = 0.1663 ppm; 1 ppm = 6.01 mg/m^3

Both o-DCB and m-DCB are colorless liquids at room temperature, whereas p-DCB is a solid (clear or whitish crystals). All three isomers mix with alcohol, ether and benzene.

The isomer o-DCB is used as a solvent for tar, rubber etc., as a de-greaser for metals, leather etc., and as an ingredient in polishing compounds. It is also used in the synthesis of herbicides and insecticides. The isomer m-DCB is used in the production of chlorophenols. In general, p-DCB has the same areas of use as o-DCB (12). Earlier, p-DCB was used in scent cakes for urinals and in mothballs, but these uses are now prohibited in Sweden (19).

Uptake, biotransformation, excretion

With occupational exposure, DCB is taken up via inhalation and skin contact. There are no quantitative data on uptake. Judging from available data, DCB seems to be taken up rather easily via the lungs and the digestive tract (12). In most animal studies DCB has been given orally.

There are no quantitative data on distribution of DCB in human subjects. Small amounts of o-DCB and p-DCB have been found in blood, fatty tissue and breast milk of subjects exposed in the general environment. When rats were given radioactively labeled p-DCB, the highest concentrations of radioactivity were recovered in fat, kidneys and liver, and the lowest in lungs, muscles and plasma. The distribution was the same regardless of the method of administration: inhalation, ingestion or subcutaneous injection. Rats showed some gender differences in distribution of p-DCB in kidneys and liver; these differences are probably related to the nephrotoxic effects observed in males and the hepatotoxic effects seen in females (12, 27).

Dichlorobenzenes are biotransformed and excreted primarily in urine. The biotransformation process has three phases: cytochrome P-450 metabolism, conjugation reactions, and enterohepatic circulation of metabolites and their metabolism by intestinal enzymes. Figure 1 shows the biotransformation pathways for o-DCB and p-DCB. The information presented in the figure is also supported by other studies.

In studies of cytochrome P-450 isoenzymes, it was found that CYP2E1 plays the largest role in the biotransformation of o-DCB (4). Individual differences in CYP2E1 enzyme activity in the liver, due to induction or inhibition by other chemical substances, may affect the individual health risk. Excessive consumption of alcohol, for example, can affect the

metabolism of DCB (26). Determination of 2,5-dichlorophenol in urine can be used as an index of exposure to p-DCB. There is no such method for monitoring exposure to o-DCB or m-DCB (12).

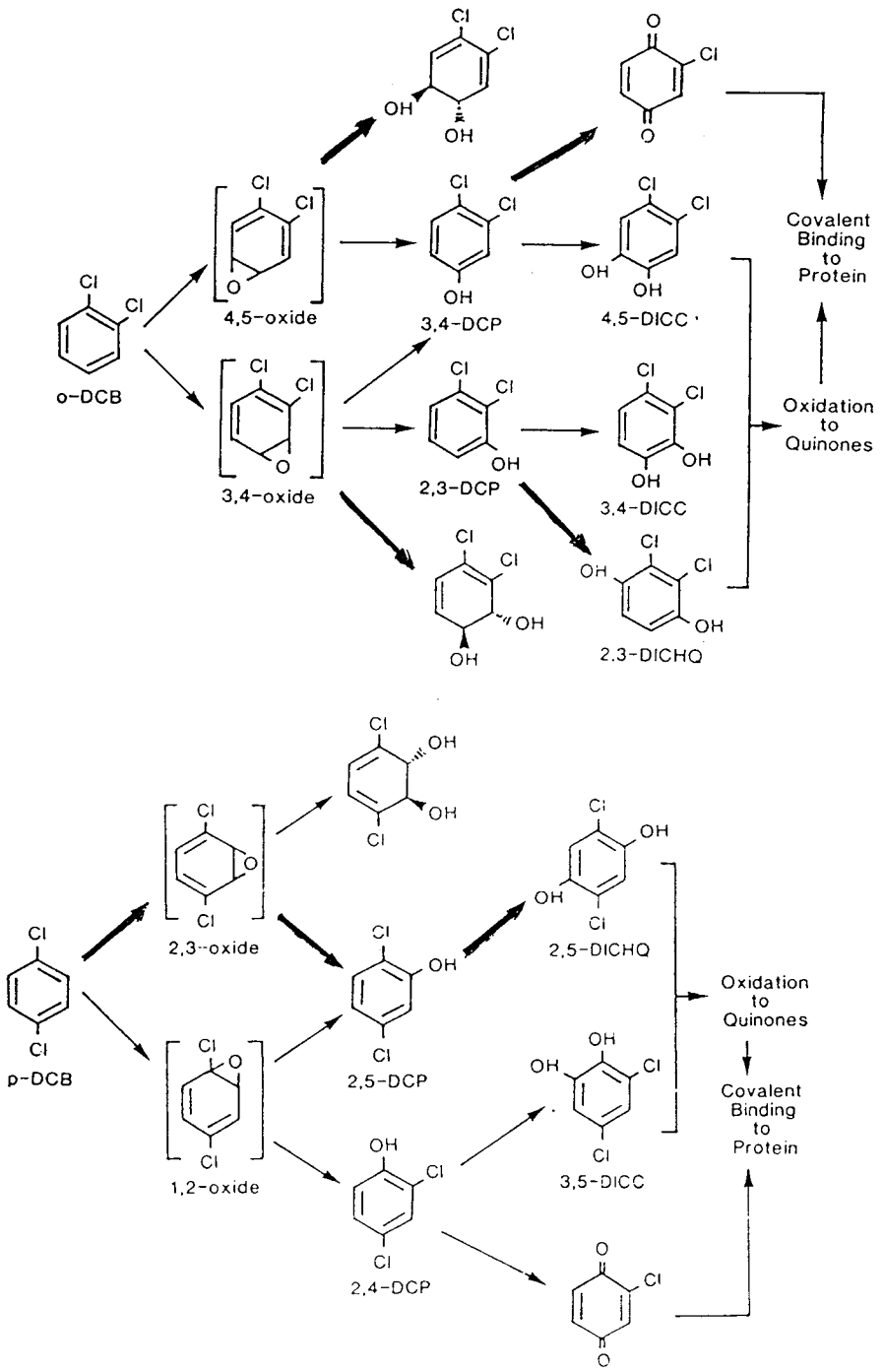


Figure 1. A schematic diagram of oxidation of o-DCB and p-DCB in microsomes. The heavy arrows mark the main metabolic pathways (from References 2, 12).

Toxic effects

Human data

Air concentrations of o-DCB were measured in an industrial study. Concentrations in 40 samples analyzed ranged from 1 to 44 ppm, with an average of 15 ppm. At these levels the odor was regarded as unpleasant. Subjects experimentally exposed to o-DCB in concentrations up to 50 ppm showed no evidence of eye or nose irritation, but noticed the odor. When the concentration exceeded 100 ppm, subjects developed watery eyes, coughing and shortness of breath (17). When 26 workers were accidentally exposed to o-DCB for four workdays (8 hours/day), most of them developed eye, nose and throat irritation; ten of them also had severe headaches and felt groggy, nauseous and dizzy. Only four of them reported no symptoms. The air concentration was defined as a "characteristic strong odor" (30).

The odor of p-DCB was recognizable at concentrations of 15 ppm or more, and p-DCB vapors in the concentration range 80 – 160 ppm were considered extremely uncomfortable; above 160 ppm it became difficult to breathe. No symptoms of irritation were reported at 15 – 85 ppm (average 45 ppm) (16).

There is a case report of a woman who, after six years of excessive, non-occupational use of p-DCB (in the form of mothballs), developed symptoms that progressed to severe CNS effects with ataxia, slurred speech, muscular weakness in the legs and delayed reflexes. The symptoms disappeared within eight months after exposure was stopped (20). In another case, a woman developed encephalopathy with severe visual disturbances, ataxia, tremor etc. after several months of exposure to p-DCB vapors ("sniffing"). The woman recovered rapidly after exposure was stopped (25).

Animal data

o-DCB. An RD_{50} (50% decline in respiratory rate) of 181 ppm has been determined for mice. The lowest concentration tested, 116 ppm, resulted in a respiratory rate 26% below normal (7).

Male rats were experimentally exposed to 539 – 977 ppm for up to 10 hours and dose-dependent effects were observed. At the highest dose, the animals survived for two hours. The symptoms seen were lethargy, loss of balance, eye irritation, breathing difficulty and coma (15).

Effects on liver have been investigated in two studies. In one study, male rats were exposed for 4 hours to o-DCB in concentrations ranging from 204 to 774 ppm, and various serum enzymes were measured 24 hours later. Exposed animals showed dose-dependent increases of glutamate dehydrogenase, glutamic-pyruvic transaminase (ALT) and some other enzymes when compared with controls (6). Similar results were obtained in a similar study in which rats were exposed for 4 hours to levels ranging from 245 to 739 ppm. Glutamate dehydrogenase activity in the serum of animals exposed to 374 – 386 ppm for 4 hours was up to 13 times greater than in controls. Glutathione-S-transferase activity in the liver increased at the same time, whereas cytochrome P-450 levels were unaffected (5). A reduction of glutathione in the liver, occurring before the increase of plasma ALT, was

observed after intraperitoneal administration of o-DCB but not after administration of p-DCB (2, 3).

In a 13-week study, rats and mice were given o-DCB by gavage in doses up to 4000 mg/kg body weight/day. Liver damage was noted in the rats at doses of 125 mg/kg or more (23). Tubular degeneration was noted in the kidneys of male mice given 120 mg/kg body weight/day, 5 days/week for 2 years (23). There were no indications that o-DCB was carcinogenic to either rats or mice in this two-year study, in which the daily doses were 60 or 120 mg/kg. The observed kidney damage was probably not mediated by an α_2-micro-globulin complex, as it is with exposure to p-DCB (8).

Laboratory animals exposed to 4796 mg/m^3 (≈ 800 ppm) 7 hours/day, 5 days/week for 69 days weakened and lost weight, and developed tremor and eye irritation (16). Rats, guinea pigs and rabbits showed no harmful effects after six to seven months of exposure to 93 ppm (17).

p-DCB. In two skin sensitization studies (GPMT), p-DCB was found to be slightly sensitizing to skin; it was consequently classified as a Grade II allergen on the Magnusson-Kligman scale (12). Unlike o-DCB, p-DCB (at the same doses) does not seem to be acutely hepatotoxic. The difference was attributed to differences in biotransformation and formation of reactive metabolites (2).

In a 13-week study in which p-DCB was given to rats and mice by gavage 5 days/week, nephropathy (tubular degeneration) was observed in the male rats receiving doses of 300 mg/kg body weight. Rats given 600 mg/kg had elevated relative liver weights (24).

m-DCB. Rats were given m-DCB by gavage in single doses of up to 2800 mg/kg body weight: 24 hours later, centrilobular damage in livers was noted at 129 mg/kg, and liver necrosis and elevated serum enzyme levels at 450 mg/kg (1). Liver cell necrosis, elevated liver weights and elevated concentrations of serum enzymes were noted in male mice given 300 mg/kg by gavage (29).

Mutagenicity, carcinogenicity, teratogenicity

There are four case reports of DCB-related cancers (leukemias) in man, but the data provide no basis for assessing the cancer risk. No exposure levels were given for any of the cases, and the cause-effect relationship between DCB exposure and cancer can not be confirmed (12).

In a study of 26 workers who were accidentally exposed to o-DCB (the air concentration was defined as a ”characteristic strong odor”) for 4 workdays (8 hours/day), examination of peripheral leucocytes showed chromosomal aberrations in about 9% of cells from the exposed workers, compared with 2% in 10 controls. At a follow-up six months later, the exposed group still had a higher frequency of aberrations than unexposed subjects (30). Since there is no information regarding other exposures that may have occurred simultaneously, a definite connection can not be made between the chromosomal aberrations and the exposure to o-DCB.

In vitro tests of o-DCB have generally yielded negative results for mutagenicity and genotoxicity. In vivo studies of chromosome aberrations in bone marrow cells also yielded negative results. It was concluded that o-DCB is not genotoxic (12). Several different in vitro and in vivo genotoxicity tests with p-DCB have also yielded negative results.

The mutagenicity of m-DCB was tested on several different strains of *Salmonella typhimurium*, both with and without metabolizing systems. No mutagenic activity was seen in any of the tests (9).

In a 2-year follow-up study with p-DCB, a dose of 150 mg/kg resulted in kidney tumors (adenocarcinomas) in male rats. Mice given 300 mg/kg developed nephropathy, hyperplasia in adrenal glands, hepatocellular necroses and liver tumors. While there was clear evidence of adenocarcinomas in the renal tubuli of male rats, there was no indication of cancer in female rats. Both male and female mice had hepatocellular carcinomas and adenomas (24). It has been proposed that, in sensitive mouse strains, these tumors are a species-specific response to stimuli that are mitogenic but not genotoxic (10, 11). It should be mentioned, however, that a subsequent Japanese study (original data were not available when this document was produced) reports that mice of both sexes and of another strain (BDF1) developed hepatocellular tumors which could be related to inhalation of p-DCB (EU document, not yet official). At the dose levels that caused renal cancer in the male rats, cell proliferation in the kidneys was elevated: this, together with complex binding and other factors, indicates that the tumor-causing activity of p-DCB is mediated by an α_2-microglobulin complex (8, 11, 28).

Tumor promotion activity was tested using the liver foci method as an indicator: m-DCB showed no tumor promotion activity in rats (15).

The IARC assessed o-DCB and p-DCB in 1987 (18): o-DCB was placed in Group 3 (”not classifiable with regard to its carcinogenicity to humans”), and p-DCB was placed in Group 2B (”possibly carcinogenic to humans”). At that time the IARC assessments did not include consideration of mechanistic studies.

In a teratology study, rats and rabbits were exposed to up to 400 ppm o-DCB during gestation. The mothers in the highest dose group showed some indication of toxicity (lower weight gain), but o-DCB was judged to be neither teratogenic nor fetotoxic (14). Structural changes in testes and effects on spermatogenesis were observed in rats given 800 mg/kg body weight intraperitoneally (21).

In a teratology study with p-DCB, rabbits were exposed to concentrations up to 800 ppm, 6 hours/day on days 6 to 18 of gestation. Their young showed no indications of deformities (14). In a two-generation reproduction study with rats, each generation was exposed to up to 539 ppm, 6 hours/day for 10 – 11 weeks. No effects on reproduction were noted (22). Doses of up to 1000 mg/kg body weight were given to rats by gavage on days 6 to 15 of gestation: slower growth was noted in the mothers at doses of 500 mg/kg or higher. At maternal dose levels of 750 and 1000 mg/kg, an increase of skeletal variations was observed in pups. The embryotoxicity was regarded as a secondary effect of the maternal toxicity, and it was concluded that p-DCB was apparently not teratogenic (13).

Dose-response / dose-effect relationships

Reported data on human exposures to o-DCB and p-DCB are given in Table 1. There are no such data for m-DCB.

Table 1. Effects of o-DCB and p-DCB on humans (from Reference 12).

Concentration	Effect	Ref.
o-DCB		17
15 ppm (1 – 44 ppm) "industrial"	No unpleasant odor	
50 ppm	Discernible odor, but no irritation of eyes or nose	
100 ppm	Irritation of eyes and respiratory passages	
p-DCB		16
15 – 30 ppm	Weak odor	
30 – 60 ppm	Strong odor	
45 ppm (15 – 85 ppm)	No irritation	
80 – 160 ppm	Extremely uncomfortable, even for those accustomed to exposure	
105 ppm (50 – 170 ppm)	Irritation of eyes and nose	
›160 ppm	"Unbreathable" concentration	

Conclusions

The critical effect of occupational exposure to *o-DCB* is irritation of eyes and mucous membranes. A NOAEL of 50 ppm has been reported from industrial environments. The odor can be discerned at concentrations as low as about 15 ppm. The LOAEL for hepatotoxicity reported from animal experiments is 100 mg/kg body weight for rats and 250 mg/kg for mice. There is a case report indicating a connection between exposure to o-DCB and chromosome aberrations, but o-DCB has shown no genotoxic activity in in vitro tests.

The critical effect of occupational exposure to *p-DCB* is irritation of eyes and mucous membranes. A NOAEL of 45 ppm has been reported. The odor is recognizable at concentrations as low as 15 ppm. Tests indicate that p-DCB has no genotoxic activity. Although the substance has induced kidney tumors in male rats, available data indicate that the mechanism behind these tumors is not relevant to humans. The substance has also induced liver tumors in mice. Although it is doubtful that the mechanism behind these tumors is relevant to humans, p-DCB should be regarded as a human carcinogen until the mechanism behind the genesis of the liver tumors is more clearly understood.

The critical effect of occupational exposure to *m-DCB* can not be established. There are no data on which to base a NOAEL/LOAEL.

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Consensus Report for Phosphorus Oxides

February 11, 1998

This document discusses phosphorus trioxide and phosphorus pentoxide.

Chemical and physical data. Uses

phosphorus trioxide

CAS No.:	1314-24-5
Synonym:	diphosphorus trioxide
Formula:	$P_2O_3(P_4O_6)$
Molecular weight:	109.95
Boiling point:	173 °C
Melting point:	23.8 °C
Conversion factors:	1 ppm = 4.56 mg/m^3 (20 °C); 1 mg/m^3 = 0.22 ppm (20 °C)

phosphorus pentoxide

CAS No.:	1314-56-3
Synonyms:	diphosphorus pentoxide, phosphorus(V)oxide, phosphoric acid anhydride
Formula:	P_2O_5 (P_4O_{10})
Molecular weight:	141.94
Boiling point:	605 °C*
Melting point:	562 °C*
Conversion factors:	1 ppm = 5.89 mg/m^3 (20 °C); 1 mg/m^3 = 0.17 ppm (20 °C)

* Values are from Reference 12. Other sources report other boiling and melting points.

Phosphorus trioxide is formed by the oxidation of phosphorus under conditions of low temperature and limited oxygen supply. The substance has the form of colorless crystals that melt at room temperature. It reacts slowly with cold water, producing phosphorous acid, whereas hot water causes a violent reaction producing phosphorus hydrides, red phosphorus and phosphoric acid. Heated in air, phosphorus trioxide ignites at about 70 °C and burns to phosphorus pentoxide (6, 11). Small amounts of phosphorus trioxide can probably be formed in combustion of red and white phosphorus (6, 15).

Phosphorus pentoxide, which is a white solid, is formed by oxidation of phosphorus with an adequate supply of oxygen. It is produced commercially by burning phosphorus in

a current of air. The substance readily absorbs water and transforms through a series of reactions (liberating heat) to phosphoric acid. The smoke formed by burning red or white phosphorus in air is mostly phosphorus pentoxide at first, but in normally humid air it gradually shifts to phosphoric acid (5, 6, 8, 15). Because of its high affinity for water, phosphorus pentoxide is used as a desiccant (5). It is also used in the production of surfactants, phosphoryl chloride and acrylate esters, and as a catalyst in air blowing of asphalt (8).

Uptake, biotransformation, excretion

No studies were found on the uptake, metabolism or excretion of phosphorus trioxide or phosphorus pentoxide. Phosphorus pentoxide is transformed to phosphoric acid on contact with moisture (e.g. on skin and mucous membranes) (15).

It should be mentioned that the phosphate ion is a normal component of the body, and that uptake from normal occupational exposure to phosphoric acid has been considered too small to make a significant contribution to the phosphate pool in the body (7, 9).

Toxic effects

Human data

Phosphorus pentoxide in either smoke or powder form is irritating/corrosive to eyes, respiratory passages and skin, and can cause severe burns (8, 10). There are a few unpublished studies that report both exposure levels (smoke) and symptoms of exposed persons. These studies, however, give no analysis data, so the chemical composition of the smoke is not clear. Two older studies (from 1935 and 1944), cited in Reference 8, report that respiratory symptoms were observed in persons exposed to smoke from white phosphorus. One of the studies reports coughing and throat irritation in 108 men who were exposed to 87 – 1770 mg/m^3 for an unspecified period. According to the report, as a result of this experiment exposure to a smoke concentration of 700 mg/m^3 was considered to be uncomfortable for working persons, and 1000 mg/m^3 for resting persons. In the other study, men were exposed in a chamber to 185 – 592 mg/m^3 for 5 to 15 minutes. Throat irritation, coughing, chest tightness and nasal discharge were reported, and it was stated that 15 minutes of exposure to 514 mg/m^3 was near the level at which there was danger of severe (not further described) effects.

According to unpublished information (Rushing, 1957; cited in Reference 1 and elsewhere), exposure to phosphorus pentoxide smoke at a concentration of 100 mg/m^3 was considered unbearable by all subjects except previously exposed workers. It is further stated that an air concentration in the range 3.6 – 11.3 mg/m^3 was tolerable but caused coughing in workers who were not accustomed to it, and that concentrations in the range 0.8 – 5.4 mg/m^3 were noticeable, but not uncomfortable (no exposure times were given). Since there are no further data, this information can not be assessed more closely.

Animal data

LC_{50} values for phosphorus pentoxide smoke from burning red phosphorus are reported in an abstract (4). They reflect large inter-species variation in sensitivity. The calculated LC_{50} values (in mg/m^3) were 61 for guinea pigs, 271 for mice, 1217 for rats and 1689 for rabbits, and the deaths usually occurred during or shortly after the exposures. Many of the rats and rabbits that died had acute inflammations and necroses in the mucous membranes of the larynx and trachea and hemorrhages and edema in lungs, but the guinea pigs that died showed only minor inflammatory changes in the respiratory passages. The surviving guinea pigs were examined 14 days after exposure: they had necrotic areas in the mucous membranes of the larynx and trachea. No exposure-related effects were seen in the airways of surviving animals after exposure to air concentrations of 450 (rats, rabbits), 111 (mice), and ‹ 36 mg/m^3 (guinea pigs).

In another study (6), rats were exposed to smoke probably containing a mixture of partial hydrolysis products of phosphorus pentoxide, including cyclotetraphosphoric acid, formed by combustion of red phosphorus/butyl rubber (95:5) containing minor amounts of mineral oil and talc (the smoke also contained small amounts of phosphene). In the experiment, the animals were exposed to a smoke concentration ranging from 3150 to 8460 mg/m^3 (2720 – 6420 mg/m^3 measured as phosphoric acid, approximately equivalent to 1970 – 4650 mg/m^3 phosphorus pentoxide) for 1 hour, or to 1530 mg/m^3 smoke (1210 mg/m^3 measured as phosphoric acid; about 880 mg/m^3 measured as phosphorus pentoxide) for 4 hours. Damage (including swelling, sores, hemorrhaging, inflammation) to larynx, epiglottis and trachea was noted in the animals that died, and surviving animals had a deformed epiglottis. Pronounced lung changes (including swelling, hemorrhages) were particularly common in animals exposed to concentrations of 5360 mg/m^3 (≈ 3200 mg/m^3 phosphorus pentoxide) or higher. The LC_{50} was reported to be 4330 mg/m^3 (≈ 2920 mg/m^3 phosphorus pentoxide).

Rabbits and rats were exposed for 30 minutes to smoke from two different pyrotechnic mixtures containing red phosphorus (95% phosphorus/5% butyl rubber; 97% phosphorus/3% butadiene styrene). The reported air concentrations were 3200 mg/m^3 and 3100 mg/m^3 respectively (680 mg/m^3 or 670 mg/m^3 expressed as phosphorus; about 1560 mg/m^3 or 1535 mg/m^3 expressed as phosphorus pentoxide). Both mixtures resulted in inflammatory changes in the larynx, trachea and lungs (alveolitis, bronchial pneumonia). Hemostasis was observed in the livers of a few animals that died, but its connection to the exposures is uncertain. No noteworthy histological changes were seen in kidneys, adrenals, spleen or pancreas (13).

Rats were exposed for 2, 4 or 13 weeks (2.25 hours/day, 4 days/week) to smoke generated by burning red phosphorus/butyl rubber (95:5). Concentrations were 300 – 1200 mg/m^3. The highest dose level caused labored breathing (3). Rats exposed to 750 or 1200 mg/m^3 for 13 weeks showed significant reductions in body weight and feed consumption (2). Minimal to severe connective tissue changes were found in the lungs of rats exposed to air concentrations of 750 mg/m^3 or higher. (At a phosphoric acid content of 70%, this is equivalent to about 380 mg/m^3 phosphorus pentoxide or higher.) The frequency/severity of the changes increased with increased dose and exposure time. A few animals exposed for

13 weeks showed slight indications of connective tissue changes at the lowest dose level, 300 mg/m^3 (at a phosphoric acid concentration of 70% this is equivalent to about 150 mg/m^3 phosphorus pentoxide) (3), while 13 weeks of exposure to 50 mg/m^3 on the above schedule reportedly (2, 3) caused no measurable lung fibrosis (no further details of this sub-study are given). At exposures of 300 mg/m^3 or above (13 weeks) there was also significantly reduced (transient) bactericidal activity in the lungs. Minor, transient biochemical changes in alveolar macrophages (ATP levels, 5'-nucleotide activity) were noted at several exposure levels (300 – 1200 mg/m^3) and exposure periods (3).

The effects of exposure to smoke from burning red phosphorus/polyvinyl butyral (95:5) were studied in another experiment with rats, guinea pigs and mice (14). The animals were exposed to an average 128 or 16 mg/m^3 (expressed as phosphorus) 1 hour/day, 5 days/week for 36 weeks (mice) or 40 weeks. These exposure levels, converted to phosphorus pentoxide, were 293 and 37 mg/m^3. (If it is assumed that this smoke is comparable with the smoke in Reference 13, from two different pyrotechnic mixtures containing 95 – 97% red phosphorus, these phosphorus levels can be considered approximately equivalent to 600 mg/m^3 and 75 mg/m^3 smoke). The higher dose level affected survival of both guinea pigs and mice: all of the guinea pigs in this dose group died during or shortly after their initial exposure, and histological examination revealed lung damage. Among the guinea pigs in the low-dose group there was a slightly elevated occurrence of chronic interstitial nephritis ($p < 0.05$), and more deaths than in the control group. Among the rats and mice there was a dose-dependent reduction in growth, but no effects of the exposure were observed in examined organs except a possibly greater (dose-dependent) accumulation of macrophages in the lungs of the mice. It should be mentioned, however, that many of the pathological examinations were made 19 months after the beginning of the study.

In an unpublished study (8) it is reported that effects on the respiratory passages of rats were noted after exposure to smoke from burning white phosphorus 15 minutes/day, 5 days/week for 13 weeks. The reported exposure levels were 1161, 589 and 193 mg/m^3. In the highest dose group, 40% of the animals died; inflammation was observed in the trachea, larynx and bronchi. Minor inflammatory changes were observed in the tracheas of animals in the middle dose group, but in the low-dose group there was only one animal with tracheitis. No systemic effects (clinical chemistry, hematology, body or organ weights) were observed in any dose group. According to the authors, the LOAEL was 193 mg/m^3 (8).

Mutagenicity, carcinogenicity, reproduction toxicity

An unpublished study (8) reports that no mutagenic effects (gene mutations in gametes) could be observed in tests with fruit flies. The flies were given 0.01 – 10% condensed smoke from burning white phosphorus in food for 42 hours. Another unpublished study (8) reports that no mutagenic effect, expressed as significant, dose-related increase in the number of resorbed embryos, was observed in rats after males had been repeatedly

exposed to 500 or 1000 mg/m^3 smoke from white phosphorus (15 minutes/day, 5 days/week, 10 weeks) and mated with untreated females.

No data on carcinogenicity were found in the literature.

In an unpublished reproduction study (8), rats were reported to show effects after exposure to 500 or 1000 mg/m^3 smoke of white phosphorus 15 minutes/day before (males 10 weeks; females 3 weeks), during and after gestation. Although no external deformities or significant effects on litter size were observed, the average body weight of the pups was lower in the high-dose group than in the other groups and these pups also had a significantly lower survival rate than the others. The authors attribute this effect to poor maternal care due to the weakened condition of the mothers after the exposures. In another section of the study, a dose-dependent increase in the incidence of a type of skeletal variation was noted in embryos after maternal exposure to smoke of white phosphorus on days 6 to 15 of gestation (500 or 1000 mg/m^3, 15 minutes/day). Other types of changes (visceral) were also noted in the fetuses in the high-dose group, but the significance of these observations is unclear. No information regarding possible toxicity to the mothers was reported in this part of the study.

Dose-effect / dose-response relationships

There are no data on human exposures that could provide a basis for a dose-effect or dose-response relationship for phosphorus trioxide or phosphorus pentoxide, but unpublished data indicate a concentration-dependent effect on respiratory passages.

Effects on experimental animals that inhaled smoke from burning red phosphorus (probably containing mostly phosphorus pentoxide and/or hydrolysis products) are summarized in Table 1.

Table 1. Effects on laboratory animals exposed by inhalation to smoke from burning red phosphorus.

Exposure	Species	Effects	Ref.
4330 mg/m^3, 1 hour (≈ 2920 mg/m^3 phosphorus pentoxide*)	Rats	LC_{50}, pronounced swelling of larynx, deformed epiglottis	6
3100–3200 mg/m^3, 30 min. (≈1535–1560 mg/m^3 phosphorus pentoxide**)	Rats, rabbits	Inflammatory changes in larynx, trachea and lungs	6
1689 mg/m^3§, 1 hour	Rabbits	LC_{50}	4
1530 mg/m^3, 4 hours (880 mg/m^3 phosphorus pentoxide*)	Rats	2 of 10 animals died; pronounced swelling and inflammation of larynx, deformed epiglottis	6

1217 mg/m^3§, 1 hour	Rats	LC_{50}	4
750 mg/m^3, 2.25 hours/day, 4 days/week; 2, 4, or 13 weeks (380 mg/m^3 phosphorus pentoxide*)	Rats	Minimal to mild connective tissue changes in lungs, reduced bactericidal activity in lungs (13 weeks), reduced body weight (13 weeks)	2, 3
600 mg/m^3, 1 hour/day, 5 days/week; 36 – 40 weeks (293 mg/m^3 phosphorus pentoxide**)	Rats, mice, guinea pigs	Deaths, lung damage, reduced growth, elevated numbers of macrophages in lungs (mice)	14
300 mg/m^3, 2.25 hours/day, 4 days/week; 13 weeks (150 mg/m^3 phosphorus pentoxide*)	Rats	Minimal connective tissue changes in lungs, reduced bactericidal activity in lungs	3
271 mg/m^3§, 1 hour	Mice	LC_{50}	4
75 mg/m^3, 1 hour/day, 5 days/week; 36 – 40 weeks (37 mg/m^3 phosphorus pentoxide**)	Rats, mice, guinea pigs	Deaths, retarded growth, slightly elevated occurrence of nephritis (guinea pigs); increased accumulation of macrophages in lungs (mice)	14
61 mg/m^3§, 1 hour	Guinea pigs	LC_{50}	4

§ reported as phosphorus pentoxide smoke

* the phosphorus pentoxide concentration was calculated from the concentration of phosphoric acid.

** the phosphorus pentoxide concentration was calculated from the concentration of phosphorus.

Conclusions

The critical effect of exposure to *phosphorus pentoxide*, judging from data on smoke exposures, is irritation of respiratory passages. There is a possibility that the effects are due to hydrolysis products. The chemical characteristics of phosphorus pentoxide indicate that the substance can also be irritating/corrosive to eyes and skin.

For *phosphorus trioxide*, available data do not allow a critical effect to be established.

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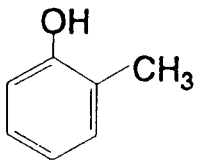
Consensus Report for Cresol

February 11, 1998

This document is based primarily on a criteria document produced in collaboration with the Dutch Expert Committee (14), and treats the three isomers ortho-, meta- and para-cresol.

Chemical and physical data. Uses

ortho-cresol

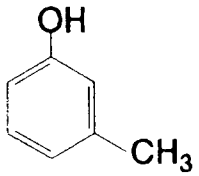
CAS No.:	95-48-7
Synonyms:	o-cresylic acid, 1-hydroxy-2-methylbenzene, 2-hydroxytoluene, 2-methylphenol
Formula:	C_7H_8O;C_6H_4 (OH)CH_3
Structure:	
Molecular weight:	108.14
Boiling point:	191 °C (101.3 kPa)
Melting point:	30.9 °C (101.3 kPa)
Vapor pressure:	0.032 kPa (20 °C)
Distribution coefficient:	log K_{ow} = 1.95
Conversion factors:	1 mg/m^3 = 0.22 ppm (20 °C; 101.3 kPa); 1 ppm = 4.50 mg/m^3

At room temperature o-cresol is either a white crystalline substance or a yellowish liquid. The isomer is soluble in water (26 mg/liter), alcohol, ether, acetone, benzene and chloroform. The odor resembles that of phenol and the reported odor threshold is 0.65 ppm.

The isomer is used as a solvent and disinfectant. It is an intermediate in the manufacture of a large number of products.

meta-cresol

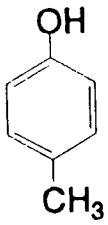
CAS No.:	108-39-4
Synonyms:	m-cresylic acid, 1-hydroxy-3-methylbenzene 3-hydroxytoluene, 3-methylphenol

Formula:	C_7H_8O; $C_6H_4(OH)CH_3$
Structure:	
Molecular weight:	108.14
Boiling point:	202.2 °C (101.3 kPa)
Melting point:	11.5 °C (101.3 kPa)
Vapor pressure:	0.005 kPa (25 °C)
Distribution coefficient:	log K_{ow} = 1.96
Conversion factors:	1 mg/m^3 = 0.22 ppm (20 °C; 101.3 kPa); 1 ppm = 4.50 mg/m^3

At room temperature m-cresol is a clear or yellowish liquid with a phenol-like odor. The reported odor threshold is 0.00028 ppm. The substance is soluble in water (23 mg/liter), alcohol, ether, acetone, benzene and chloroform.

In the production of herbicides and insecticides m-cresol is sometimes used as an intermediate. It is also used in the production of cosmetics.

para-cresol

CAS No.:	106-44-5
Synonyms:	p-cresylic acid, 1-hydroxy-4-methylbenzene, 4-hydroxytoluene, 4-methylphenol
Formula:	C_7H_8O;$C_6H_4(OH)CH_3$
Structure:	
Molecular weight:	108.14
Boiling point:	201.9 °C (101.3 kPa)
Melting point:	34.8 °C (101.3 kPa)
Vapor pressure:	0.005 kPa (25 °C)
Distribution coefficient:	log K_{ow} = 1.94
Conversion factors:	1 mg/m^3 = 0.22 ppm (20 °C; 101.3 kPa); 1 ppm = 4.50 mg/m^3

At room temperature p-cresol is a crystalline substance, but it transforms easily into a yellowish liquid. The odor resembles that of phenol. The reported odor threshold is 0.045 ppm. The isomer is soluble in water (22 mg/liter), alcohol, ether, acetone, benzene and chloroform.

In the cosmetics industry, p-cresol is used to form antioxidants. A mixture of m- and p-cresol is often used in the production of herbicides and as disinfectant and preservative.

Industrial cresol (CAS No. 1319-77-3) is a mixture of all three isomers, and also contains small amounts of phenol and xylenols. This product is a colorless to yellow or pink liquid with a phenol-like odor. Its boiling point is 191 – 203 °C and its melting point is

11 – 25 °C. A 50% solution (v/v) of cresol in a soapy solvent is marketed under the brand name Lysol.

Cresol mixtures are used as degreasers, preservatives in cutting oil, in ore flotation and for wood impregnation.

Uptake, biotransformation, excretion

There are no quantitative data on uptake of cresols by human subjects. Toxicological data indicate that cresols can be absorbed by the skin. In an in vitro study, p-cresol (4 μg/cm^2) was applied to stratum corneum from a mouse (in a diffusion cell). The cumulative permeation was 69% of the applied dose after 6 hours, 74% after 12 hours and 77% after 24 hours (7).

Rabbits given 100 or 200 mg cresol (individual isomers) per kg body weight by gavage excreted 75 to 90% of the dose in urine within 24 hours, indicating almost complete absorption from the digestive tract. Most of the cresol absorbed by the rabbits was excreted as conjugates (60 – 70% of the dose as glucuronides; 10 – 15% as sulfates) (4).

In vitro studies with rat liver microsomes have revealed that the oxidative metabolism of p-cresol differs from that of the other two isomers (15, 16).

The microbial flora in the digestive tract can form p-cresol from tyrosine in food. The urine from ten healthy subjects was reported to contain 51.8 mg p-cresol per day (2, 12).

Toxic effects

Skin contact with cresols can result in severe skin irritation and dermatitis. Cresols are also regarded as potent eye irritants for humans (14). There are several case reports describing the effects of oral intake (intentional or unintentional) of cresols. The effects comprise irritation of mouth and throat, stomach pains, eructation, hemolytic anemia, increased heart rate, liver and kidney damage, headaches, facial paralysis, drowsiness, coma and death. Skin contact has also resulted in effects on the nervous system, liver and kidneys, and caused some human fatalities (9).

When cresol was applied to the eyes of rabbits in the Draize test, it was observed that all three of the isomers were strongly irritating. They were also found to be powerful irritants when applied to shaved rabbit skin (17).

Judging from the calculated LD_{50} values for rats, mice and rabbits, m-cresol seems to be more toxic than the other two isomers, which have LD_{50} values nearly twice as high (14).

ortho-cresol: A criteria document from NIOSH (9) contains a review of a Russian study reporting that a concentrated aerosol of o-cresol (exposure levels and times not given) had an irritative effect on respiratory passages. Brief exposures (not more closely defined) to 1.4 ppm o-cresol caused irritation of mucous membranes in the nose and respiratory passages of 8 of 10 volunteers.

Of 10 patients with dermatitis and contact allergy (phenol-formaldehyde) patch-tested with a solution of 81% o-cresol in ethanol, 4 had a positive response. Three of these had a

positive response to an 8.1% solution, but not to an 0.81% solution. None of the 20 controls had a positive response to the o-cresol solution (5).

In an in vivo mutagenicity study, mice were given intraperitoneal injections of 200 mg o-cresol/kg body weight. Within 21.5 hours the mice became lethargic and developed "gooseflesh" and watery eyes (6). The intraperitoneal dose of o-cresol causing convulsions in 50% of animals was estimated to be 117 mg/kg body weight (1). A total intravenous dose of 50 – 60 mg o-cresol/kg body weight given to rats caused excitation with muscle spasms (8).

In an NTP study (10), groups of rats and mice were given o-cresol in feed (0, 300, 1000, 3000, 10,000 or 30,000 ppm) for 28 days. Three mice died, but none of the rats, and no clinical indications of toxicity were observed. The LOAEL for male rats was reported to be 3000 ppm in feed (≈ 260 mg o-cresol/kg body weight/day), since at this dose the rats had elevated relative liver and kidney weights. The LOAEL for female rats was 10,000 ppm in feed (≈ 880 mg/kg body weight/day). The LOAEL for mice (both sexes) was 3000 ppm in feed, equivalent to a dose of about 550 (males) to 750 (females) mg/kg body weight/day: the effect observed was elevated relative liver weights.

In a similar 13-week study, groups of rats were given 0, 1880, 3750, 7500, 15,000 or 30,000 ppm o-cresol in feed. The LOAEL (both sexes) reported in this study was 7500 ppm in feed (≈ 500 mg/kg body weight/day). As in the previous study, the observed effect was elevated liver weights (10). In an earlier study, cited in Reference 10, groups of rats were given o-cresol (in corn oil) by gavage for 13 weeks. Doses were 0, 35, 175 or 600 mg/kg body weight/day. Animals in the highest dose group showed effects such as lethargy, tremor, labored breathing, convulsions and coma. No histopathological changes could be found. The LOAEL arrived at in this study was 600 mg/kg.

The neurotoxicity of o-cresol was examined in an unpublished study cited in Reference 14. Groups of rats were given o-cresol by gavage in doses of 0, 50, 175, 450 or 600 mg/kg body weight/day for 13 weeks. Four of 10 males and 7 of 10 females in the highest dose group died, and 2 animals in the 450 mg/kg dose group died. No damage to brain or nervous tissue was observed, nor were there any observed effects in behavior tests.

There is also a 13-week study in which groups of mice were given o-cresol in feed (0, 1250, 2500, 5000, 10,000 or 20,000 ppm). For males, a LOAEL of 1250 ppm (the lowest dose tested, equivalent to about 200 mg o-cresol/kg body weight/day) was reported: the observed effect was an increase in relative liver weights. The same effect was seen in females receiving 5000 ppm in feed (≈ 935 mg/kg body weight/day) (10).

meta-cresol. Mice were given 200 mg m-cresol by intraperitoneal injection. Within 21.5 hours the animals became lethargic and had watery eyes (6). The intraperitoneal dose that caused convulsions in 50% of animals was calculated to be 102 mg/kg body weight (1).

In a 28-day study, groups of rats and mice were given m-cresol in feed (0, 300, 1000, 3000, 10,000 or 30,000 ppm). There were no clinical indications of toxicity, and no histopathological changes were found. The LOAEL for rats (both sexes) was 10,000 ppm in feed (≈ 870 mg/kg body weight/day). The effects noted were increased relative liver and kidney weights. For male mice the LOAEL was 3000 ppm in feed (≈ 520 mg/kg body

weight/day). Female mice had elevated relative liver weights at all dose levels (the lowest dose was equivalent to about 60 mg/kg body weight/day) (10).

Groups of rats were given m-cresol by gavage in doses of 0, 50, 150 or 450 mg/kg body weight/day for 13 weeks: the LOAEL for males was 150 mg/kg/day, and for females 450 mg/kg/day (10). In a neurotoxicity study, rats were given 0, 50, 150 or 450 mg/kg body weight /day. In the highest dose group there were elevated incidences of salivation, hypoactivity and rapid breathing. These effects were not seen at lower doses (14).

para-cresol. An 0.5% solution of p-cresol in acetone, applied to shaved mouse skin 3 times a week for 6 weeks, caused depigmentation of both skin and hair (13).

Patch tests with p-cresol were given to the same 10 subjects who were tested with o-cresol (see above). One person had a positive response to an 81% solution (in ethanol) (5).

Mice given 75 mg p-cresol/kg body weight intraperitoneally became lethargic and developed watery eyes within 21.5 hours (6). The intraperitoneal dose causing convulsions in 50% of the mice was calculated to be 110 mg/kg body weight (1).

In a 28-day study, groups of rats and mice were given feed containing p-cresol (0, 300, 1000, 3000, 10,000 or 30,000 ppm). All the mice in the highest dose group died. The rats showed histopathological changes in bone marrow and nasal epithelia, in addition to the effects noted with the other isomers. The damage to nasal epithelium was assumed to result from its direct contact with the feed. For the rats, the LOAEL was 3000 ppm (≈ 250 mg/kg body weight/day). The effects noted were bone marrow hypocellularity and elevated relative liver weights. Elevated relative liver weights were observed in the mice at a LOAEL of 3000 ppm in feed (≈ 500 mg/kg body weight/day) (10).

In a 13-week study, groups of rats were given p-cresol by gavage in doses of 0, 50, 175 or 600 mg/kg body weight/day. The females in the two highest dose groups developed a dose-related anemia. Males in the highest dose groups had elevated serum protein. There were indications of chronic nephropathy (unspecified) in all dose groups. In addition, minimal metaplasias were found in tracheal epithelia in the high-dose groups of both sexes. The LOAEL was determined to be 175 mg/kg body weight /day (10).

In a neurotoxicity study, groups of rats were given 0, 50, 150, or 600 mg p-cresol/kg body weight/day for 13 weeks. Histological examinations revealed no damage to brain or nervous tissue, and no exposure-related effects were discernible in behavior tests. In the highest dose group there were increased incidences of salivation, hypoactivity and panting (14).

meta-+ para-cresol (60:40). The cresol mixture was given to groups of rats and mice in feed (0, 300, 1000, 3000, 10,000 or 30,000 ppm) for 28 days. Irritation was seen in nasal epithelia, esophagus and forestomach of both rats and mice. For male rats, the LOAEL was 3000 ppm (≈ 260 mg/kg body weight/day). At that dose, animals had elevated relative liver weights and histopathological changes in thyroids. For female rats, the effects at the LOAEL, 1000 ppm in feed (≈100 mg/kg body weight/day), were elevated relative and absolute liver weights. For male mice, the LOAEL was 1000 ppm in feed (≈160

mg/kg/day), and for female mice 3000 ppm (≈ 600 mg/kg/day). For both sexes the observed effect was elevated liver weights (10).

The same cresol mixture was also used in a 13-week study with rats and mice. The rats were given feed containing 0, 1880, 3750, 7500, 19,000 or 30,000 ppm. Clinical data from the two highest dose groups indicated disturbances in hepatocellular function. Males in these dose groups also had thyroid damage. Uterine atrophy was observed in females in the highest dose group. For both sexes, the LOAEL (elevated liver weights) was 3750 ppm (≈ 240 mg/kg body weight/day) (10). The mice in this study were given feed containing 0, 625, 1250, 2500, 5000 or 10,000 ppm of the cresol mixture. The observed effects were limited to elevated relative liver weights and nasal irritation (hyperplasia in epithelial tissue). The LOAEL for females was 5000 ppm (≈ 775 mg/kg/day) and for males 10,000 ppm (≈ 900 mg/kg/day) (10).

Mutagenicity, carcinogenicity, teratogenicity

The results of several unpublished genotoxicity studies are presented in Reference 14. Briefly, it can be said that o-cresol and p-cresol have been negative in mutagenicity tests with bacteria, whereas m-cresol was negative in tests with *Salmonella typhimurium* but positive in tests with *E. coli*. On the other hand, m-cresol was negative in mammalian cell systems, whereas o-cresol and p-cresol showed clastogenic activity in some mammalian cell systems (e.g. CHO cells). There is no indication that any of the isomers has genotoxic activity in vivo (14).

No long-term cancer studies with experimental animals were found in the literature, but a cancer study with o-cresol and a mixture of m- and p-cresol is planned by the NTP (11).

After application of a single initiation dose of 9,10-dimethyl-1,2-benzanthracene, each isomer (dissolved in acetone) was applied to the skin of mice twice a week for 11 weeks. After 12 weeks, 17 of 27 mice treated with o-cresol were still alive, as were 14 of 29 treated with m-cresol and 20 of 28 treated with p-cresol. Average numbers of papillomas per surviving mouse were 1.35 for o-cresol, 0.93 for m-cresol and 0.55 for p-cresol. There were no papillomas in the control group, which after initiation was treated with acetone alone. No carcinomas were seen (3). It has been shown that o-cresol influences the carcinogenic effect of benzo(a)pyrene in the forestomachs of mice. Simultaneous administration (gavage) of 1 mg o-cresol and 1 mg benzo(a)pyrene twice a week (20 doses in all) increased the number of tumors and reduced the latency time in comparison to treatment with benzo(a)pyrene alone. If the o-cresol was given to the animals before the benzo(a)pyrene treatment was begun, the number of malignant tumors was lower and the latency time longer. If the substances were given in reverse order, all the resulting tumors were benign (18).

In the above-described NTP study (10) in which groups of rats and mice were given cresol in feed for 28 days or 13 weeks, reproductive organs were also examined. The o-cresol had no effect on tissue weights in the rats, and no histopathological changes were seen. The m-cresol resulted in uterine atrophy in female rats in the highest dose group (about 2300 mg/kg body weight/day, 28 days). With p-cresol, histopathological changes

were seen in uteri at a daily dose (28 days) of about 2050 mg/kg body weight. Mice in the 28-day study had histopathological changes in uteri and ovaries at a daily dose of about 5000 mg o-cresol/kg body weight. The other two isomers yielded the same results.

Several unpublished reproduction toxicity studies are reviewed in Reference 14. In all cases cresol was given in diet, and maternal toxicity was observed at doses lower than those affecting reproduction or young. Rats showed indications of maternal toxicity at daily doses of 175 mg/kg body weight or higher, whereas no indications of toxicity appeared in young at daily doses below 450 mg/kg body weight. For rats, the NOAEL for maternal toxicity was 30 mg/kg body weight/day (all three isomers), and for rabbits 5 mg p-cresol/kg body weight/day and 100 mg/kg/day for the other two isomers. There is also a mouse study reporting a NOAEL of 263 mg/kg body weight/day.

Dose-response / dose-effect relationships

There are no data on which to base a dose-response or dose-effect relationship for humans. Brief exposures to 1.4 ppm o-cresol caused irritation of mucous membranes. Long-term studies with rats which report a LOAEL and the observed effects are summarized in Table 1.

As for studies with other animal species, it can be mentioned that 60 mg/kg body weight m-cresol given in diet for 28 days resulted in elevated relative liver weights in females of mice. Intraperitoneal injections of 75 mg p-cresol/kg body weight given to mice caused lethargy and watery eyes, and about 100 mg/kg caused convulsions, regardless of which cresol isomer was used. In 13-week studies in which o-cresol was given to mice in feed, it was found that daily doses of 200 mg/kg body weight resulted in elevated relative body weights.

Conclusions

The critical effect of occupational exposure to cresols is irritation of skin, mucous membranes and eyes. Skin uptake can be a major factor in occurrence of systemic effects. One study indicates that o-cresol may have tumor-promoting activity.

Table 1. Summary of results from long-term studies with rats. Details are given in the section on Toxic Effects.

Isomer	LOAEL mg/kg/day	Type of study	Effect	Ref.
ortho-cresol	600	13 weeks, gavage	CNS depression, death	10
	510	13 weeks, in diet	Increased relative liver weights	10
	450	13 weeks, gavage; 2-generation study	CNS depression, death, toxicity in F1 generation	14
	450	13 weeks, gavage; neurotoxicity study	Indications of toxicity	14
	175	13 weeks, gavage; 2-generation study	Indications of toxicity in F0 generation	14
meta-cresol	450	13 weeks, gavage; 2-generation study	CNS depression, death, indications of toxicity in F1 generation	14
	450	13 weeks, gavage; neurotoxicity study	Indications of toxicity	14
	450	13 weeks, gavage	Indications of toxicity in females	10
	175	13 weeks, gavage; 2-generation study	Indications of toxicity in F0 generation	14
	150	13 weeks, gavage	Retarded weight gain	10
para-cresol	600	13 weeks, gavage; neurotoxicity study	Indications of toxicity	14
	450	13 weeks, gavage; 2-generation study	CNS depression, death, indications of toxicity in F1 generation	14
	175	13 weeks, gavage	Elevated total protein in serum of males, mild anemia in females	10
	175	13 weeks, gavage; 2-generation study	Indications of toxicity in F0 generation	14

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Consensus Report for Hydrogen Bromide

February 11, 1998

Chemical and physical data. Uses

CAS No.:	10035-10-6
Synonyms:	hydrogen bromide, hydrobromic acid
Formula:	HBr
Molecular weight:	80.92
Boiling point:	- 67 °C
Melting point:	- 88.5 °C
Vapor pressure:	2198 kPa (20 °C); 28 kPa (20 °C) (aqueous solution)
Saturation concentration:	2.1% in air (20 °C)
Solubility in water:	193 g/100 ml (25 °C)
Conversion factors:	1 ppm = 3.36 mg/m^3 (20 °C); 1 mg/m^3 = 0.30 ppm (20 °C)

Hydrogen bromide at room temperature is a colorless gas with a sharp odor (8). One study (3) reports the odor threshold to be 2 ppm. The gas is much heavier than air and forms a fog in damp air, since it takes up enough water to form droplets (4, 9). Hydrogen bromide dissolves readily in water, creating a strong acid. Hydrobromic acid is a clear, fuming liquid that turns brown on exposure to air and light. Hydrogen bromide is also soluble in acetic acid, alcohol, toluene etc. (6).

Hydrobromic acid/hydrogen bromide are found only in industrial processes. Hydrobromic acid can be produced by a direct reaction between bromine and hydrogen, from seawater, or as a by-product in bromization of organic compounds (6). Hydrobromic acid may be used in bromization of aliphatic and aromatic compounds and in the production of inorganic bromides. These compounds may be used as fireproofing agents, in pharmaceuticals etc. (6). Hydrogen bromide may be emitted from pyrolysis of fire-extinguishing chemicals or disinfectants containing bromine (7, 10, 14).

Uptake, biotransformation, excretion

No information was found.

Toxic effects

Human data

The chemical characteristics of hydrogen bromide make it extremely irritating to the upper respiratory passages. At high air concentrations, the substance has been reported to cause deaths due to cramps/inflammation in the larynx, inflammation in the upper respiratory passages, and/or pulmonary edema (4, 8). Exposure to the substance in either gas or liquid form has also been reported to cause severe irritation (sometimes corrosion) of eyes and skin (2, 4, 8) .

There is a case report (11) of a person who was splashed with a mixture of hydrogen bromide and phosphorus tribromide, especially on the face and hair. She suffered local burns, dizziness, cough and slight throat irritation. She probably breathed gas containing bromine for at least 5 to 10 minutes after the accident, and during the subsequent weeks she developed chemical pneumonia. No air concentrations are given in this report. Another report (5) describes acute symptoms including burning sensations in the eyes, throat and chest, shortness of breath, hoarseness and coughing in two persons who on different occasions had bathed for 5 – 10 minutes in a hot tub in a closed 8 x 11-foot room. The facility had been using ”bromine tablets” which on hydrolysis release HBrO and other substances. Reaction with microorganisms can produce bromide ions and hydrobromic acid, which when heated evaporate to bromine gas and hydrogen bromide gas, respectively. Both persons had noticed a sharp odor while bathing, but no air concentrations are given in the report. Some symptoms, including coughing, hoarseness, shortness of breath and a burning sensation in the chest with physical exertion, persisted for several months, and a metacholine test was strongly positive. One of the patients also suffered hair loss and intermittent bleeding from the anus for a week or two after the exposure.

There are a few reports containing both information on air concentrations of hydrogen bromide and effects on exposed persons, but the data given are usually quite sparse. Two reference works (4, 8) state that a few minutes of exposure to air concentrations around 1300 – 2000 ppm have caused death. One of them (4) also states that 30 – 60 minutes of inhalation exposure to concentrations in the range 1000 – 1300 ppm is ”dangerous.” According to the same source, the highest concentration tolerable for 60 minutes is about 50 – 100 ppm, and the maximum tolerable for several hours is in the range 10 – 50 ppm. This work also reports that brief exposure (not more precisely defined) to about 35 ppm has caused throat irritation. There is a published report (14) describing severe irritation to eyes, nose, throat and skin of persons exposed to hydrogen bromide in a house recently fumigated with methyl bromide gas (and unintentionally heated). The concentration of hydrogen bromide was not measured, but was estimated to have been roughly 72 ppm. In an unpublished study cited in the American threshold limit document (1), irritation of nose and throat is reported at exposure to 3 – 6 ppm for ”several minutes” (6 volunteers). It is also reported that the odor of hydrogen bromide was discernible at exposures as low as 2 ppm (Table 1).

Chronic exposure to hydrogen bromide has been associated with catarrh in upper respiratory passages, digestive disturbances, minor changes in reflexes and lower erythrocyte counts (2), but there are no data on air concentrations, exposure times, other simultaneous exposures etc., and this information can therefore not be evaluated.

Animal data

The LC_{50} for rats exposed to hydrogen bromide has been reported to be 2858 ppm for 1 hour of exposure and 3000 ppm for 30 minutes (12, 15). For mice, the reported LC_{50} with 1 hour of exposure is 814 ppm (15).

Severe tissue damage (massive necroses, inflammation) in the anterior portion of the nose was observed in rats exposed by inhalation to 1300 ppm hydrogen bromide for 30 minutes; the same inhalation exposure via the mouth (pseudo-mouth breathing) caused changes in the trachea (necrosis, inflammation). Inhalation via the nose was also associated with significant weight loss after 24 hours. Mortality in the two exposure groups was 8% and 19%, respectively (16).

A 1.7% solution of hydrogen bromide in water (10 ml/kg body weight) was given orally to 4 rats twice a week for 17 weeks: the rats developed liver changes (hydropic degeneration, various degrees of fatty livers). There were no observed effects on behavior, appetite, weight or coat quality (13).

Table 1. Dose-response relationships for 6 volunteers exposed by inhalation to hydrogen bromide gas (unpublished study cited in Reference 1).

Response	Number of subjects showing response				
	2 ppm	3 ppm	4 ppm	5 ppm	6 ppm
Nose irritation	0	1	3	6	6
Throat irritation	0	1	1	1	1
Eye irritation	0	0	0	0	0
Odor recognition	6	6	6	6	6

Mutagenicity, carcinogenicity, reproduction toxicity

No studies were found in the literature.

Dose-effect / dose-response relationships

Dose-dependent effects on the upper respiratory passages have been reported in human subjects exposed briefly to air concentrations of 3 ppm or above; see Table 1. This information is based on unpublished data.

The dose-effect relationships observed in laboratory animals are summarized in Table 2.

Table 2. Exposure-effect relationships for hydrogen bromide reported from animal experiments.

Exposure	Species	Effect	Ref.
3000 ppm, inhalation; 30 min.	Rats	LC_{50}	12
2858 ppm, inhalation, 1 hour	Rats	LC_{50}	15
1300 ppm, inhalation via nose or mouth, 30 min.	Rats	Severe tissue damage in nose/ trachea; weight loss, deaths	16
814 ppm, inhalation, 1 hour	Mice	LC_{50}	15
10 ml/kg body weight, 1.7% solution, per os; twice a week for 17 weeks	Rats	Liver changes	13

Conclusions

The critical effect of short-term exposure to hydrogen bromide is irritation of the upper respiratory tract. The chemical characteristics of the substance make it irritative/corrosive to eyes and skin.

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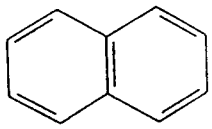
Consensus Report for Naphthalene

May 27, 1998

Chemical and physical data. Uses

CAS No.:	91-20-3
Name:	naphthalene
Formula:	$C_{10}H_8$
Molecular weight:	128.2
Boiling point:	217.9 °C
Melting point:	80.2 °C
Vapor pressure:	0.0072 kPa (20 °C)
Saturation concentration:	530 mg/m^3 (100 ppm) (25 °C)
Conversion factors:	1 mg/m^3 = 0.188 ppm; 1 ppm = 5.327 mg/m^3



At room temperature, naphthalene usually occurs as white flakes. It has a tarry odor, and the reported odor threshold is 0.084 ppm (4). At 20 °C, naphthalene is virtually insoluble in water (30 mg/liter), sparingly soluble in methanol and ethanol (42 g/liter), soluble in benzene (402 g/liter) and readily soluble in ether, chloroform and carbon disulfide (500 g/liter).

Naphthalene is produced from mineral oil or coal tar. It is used mostly in the chemical industry for production of phthalic acid anhydride. It is also used in production of insecticides. Naphthalene in the form of mothballs or flakes was previously used in homes. It is a component of exhausts containing PAHs.

Uptake, biotransformation, excretion

Naphthalene can be absorbed via the respiratory passages and digestive tract, but quantitative data are generally lacking. When 43 µg radioactively labeled naphthalene was applied to rat skin (13 cm^2 surface), about 50% of the dose was excreted in urine within 12 hours. The main metabolites in urine were 1,2- and 2-7-dihydroxynaphthalene (63).

Radioactively labeled naphthalene was injected into rat intestines: thirty minutes later about 85% was found in the portal vein as unchanged naphthalene and only a small amount as metabolites, primarily 1,2-dihydrodiol and 1-naphthol (8). Radioactively labeled naphthalene given by gavage to chickens, pigs and dairy cows, either as single doses or as daily doses for 31 days, was recovered primarily in kidneys, lungs and fatty tissue (chickens), in fatty tissue (pigs) and in liver (cows). The single doses were 0.44 mg for

chickens, 2.46 mg for pigs and 30.7 mg for cows, and the daily doses in the 31-day study were 0.036 mg for chickens, 0.112 mg for pigs, and 5.115 mg for cows. In all cases the recovered amounts of naphthalene and metabolites were low (17).

Mice were given radioactively labeled naphthalene (200 mg/kg body weight) intraperitoneally: four hours later the highest concentrations of covalent-bound metabolites were in liver, kidneys and lungs (66).

In Clara cells from mouse lungs, naphthalene is biotransformed to an epoxide. The process is mediated by cytochrome P-450. The epoxide undergoes spontaneous enzymatic transformation (epoxide hydrolase) to dihydrodiol, which is oxidized to 1,2-naphthohydroquinone; an alternative pathway is transformation to 1-naphthol, which is then hydroxylated to 1,2-naphthohydroquinone (see Figure 1). This is further oxidized to 1,2-naphthoquinone, which forms covalent bonds to protein in the Clara cells (70). Biotransformation of naphthalene to 1,2-dihydroxynaphthalene has also been observed in rabbit eyes. This metabolite auto-oxidizes to 1,2-naphthoquinone, which has a yellow color (28).

When naphthalene was incubated with glutathione and microsomes from mice, rats, hamsters or monkeys, the most rapid metabolism was measured in lung and liver tissues from mice. The rate for rats was 12%, for hamsters 37% and for monkeys 1% of that for mice. The metabolites were 1,2-dihydro-1,2-dihydroxynaphthalene and three glutathione conjugates (11, 12). The three conjugates are diastereomers of 1-hydroxy-2-glutathionyl-1,2-dihydronaphthalene (13). Metabolism is stereo-selective in mice, but not in rats and hamsters. The reaction to epoxide is catalyzed by cytochrome P-450 2F2 (14).

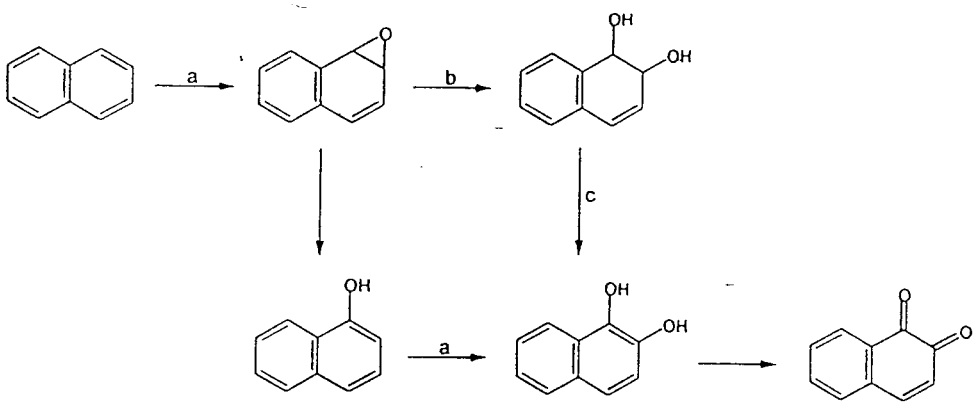


Figure 1. Biotransformation of naphthalene to 1,2-naphthoquinone in Clara cells. (a = cytochrome P-450, b = epoxide hydrolase, c = dihydrodiol dehydrogenase) (From Reference 70).

Human liver microsomes can metabolize naphthalene to epoxide, which is rapidly detoxified by epoxide hydrolase (61). Hydrolysis of naphthalene-1,2-epoxide in different species was compared in in vitro studies with liver microsomes. The degree of hydrolysis was 0.9 in human liver microsomes, 0.8 in rabbits, 0.6 – 0.7 in hamsters and dogs, and 0.3 in rats and mice, indicating inter-species differences in biotransformation (34).

Workers exposed to naphthalene have 1-naphthol in their urine. Concentrations of 0.4 to 34.6 mg/liter were measured in the urine of naphthalene distillers after a shift. Coking plant workers exposed to naphthalene and other aromatic and polycyclic hydrocarbons had urine concentrations of 0.89 to 4.86 mg/liter. Air concentrations of naphthalene were not reported. Unexposed persons have on average 0.12 mg 1-naphthol/liter urine (7).

After a shift of working with creosote-impregnated wood, workers had urine concentrations of 1-naphthol averaging 20.5 μmol/liter (≈ 2.75 mg/liter). Measured naphthalene concentrations in air averaged 1.5 mg/m^3 (27).

Toxic effects

Human data

Naphthalene has been reported to be irritating to eyes and skin. Inhalation of naphthalene in gas form can cause headaches, nausea, vomiting, tremor, perspiration and in severe cases convulsions, coma and death. The lethal dose for adults is on the order of 5 – 15 g naphthalene; for children about 2 g (20).

A case of exfoliative erythrodermy was suspected to be due to naphthalene in clothing treated with moth repellent. The patient had a positive reaction to a patch test with naphthalene, but there were no controls (19). Eye irritation has been reported to occur when concentrations of naphthalene in workplace air exceed about 15 ppm. No further information on the irritation is given in this report of air monitoring at a workplace (53).

Acute hemolytic anemia due to naphthalene has been identified in several cases in children and adults who accidentally ate mothballs. Individuals with reduced glucose-6-phosphate dehydrogenase activity were more sensitive than others. The anemia was marked by formation of Heinz bodies, hemoglobinuria and reduced erythrocyte counts. Other symptoms are nausea, pallor, dark urine and alubuminuria. Anemia has also been observed in children who have come into contact with naphthalene in clothing (6, 15, 16, 37, 41, 44, 48, 55, 57, 58, 64, 71). These studies imply that the causative factor is the biotransformation product naphthol rather than the naphthalene itself. A case of aplastic anemia was reported in a woman exposed for two workdays to about 180 – 460 ppm naphthalene in combination with para-dichlorobenzene (24).

A pharmacist who ingested 5 g naphthalene (in castor oil) as medication developed bilateral cataracts resulting in blindness (39). Occupational exposure to naphthalene dust caused cataracts and retinal hemorrhages in two workers; no exposure levels are given (30). Cataracts were reported in 8 of 21 persons occupationally exposed to naphthalene for about five years; no exposure levels are given (23).

Animal data

The calculated LD_{50} with intraperitoneal administration of naphthalene is 380 mg/kg body weight for mice. The LD_{50} with oral administration has been determined to be 533 mg/kg body weight for male mice, 710 mg/kg for female mice, and 2200 – 2400 mg/kg for rats. The LD_{50} for mice given the substance by gavage was 353 mg/kg body weight (21, 49, 59, 66).

Groups of mice were exposed to 0, 10 or 30 ppm naphthalene 6 hours/day, 5 days/week for 103 weeks: there were dose-dependent increases in chronic pneumonia, metaplasias in olfactory epithelium, hyperplasias in respiratory epithelium in the nose, and chronic rhinitis in both sexes (1, 46).

Mice were given naphthalene per os in doses of 27, 53 or 267 mg/kg body weight/day for 14 days: higher mortality, reduced growth, lower thymus weights and elevated lung weights were observed in the highest dose group. No immunotoxicity could be demonstrated. Mice were given oral doses of 5.3, 53 or 133 mg naphthalene/kg body weight/day for 90 days. According to the authors, no biologically relevant naphthalene-related effects could be observed (59).

Intraperitoneal injections of naphthalene (in peanut oil) were given to mice; doses were in the range 0.5 – 3.0 mmol/kg body weight (≈ 64 – 384 mg/kg), and the animals were sacrificed 6 hours to 14 days later. The first indication of toxicity, in Clara cells in bronchial epithelium, could be seen after 6 hours at all dose levels. Toxicity to liver and kidneys was minimal (51).

Rats were given naphthalene (in corn oil) in single oral doses of 1100 mg/kg body weight. This dose is half the LD_{50} value. Urine samples and tissue samples from livers and brains were taken after 12, 24, 48 and 72 hours. After 24 hours, there was a twofold increase in lipid peroxidation in liver and brain mitochondria and a threefold increase of single-strand DNA breaks in liver tissue. The authors concluded that naphthalene induces oxidative stress and tissue damage, which was less severe if the animals were pre-treated with vitamin E (65). Rats given oral doses of naphthalene for 9 weeks (total dose 750 mg/kg body weight) had a 20% weight loss. The treatment increased peroxidation in the liver with reduced glutathione peroxidase activity. This type of peroxidation was not observed in lungs, eyes or hearts (22).

Histological examination of mice 24 hours after intraperitoneal injections of 200 mg naphthalene/kg body weight revealed extensive necrosis in epithelial tissue in bronchi and bronchioles. No tissue damage was observed in livers or kidneys for up to 72 hours after intraperitoneal doses of up to 375 mg naphthalene/kg body weight (66). Mice were given single intraperitoneal doses of 225 mg naphthalene/kg body weight: an effect on microsomal monooxygenase activity was observed in lungs (but not in livers), and morphological changes were seen in Clara cells in the lungs (62). Intraperitoneal injection of 200 mg naphthalene/kg body weight caused a large drop in reduced glutathione in the lungs of mice (31).

A single intraperitoneal dose of 50 mg naphthalene/kg body weight given to mice caused swelling of Clara cells in half the treated animals. At 100 mg/kg there were a few necrotic cells, and at 200 mg/kg a larger number. If the animals had been given 7 daily doses of 50,

100 or 200 mg/kg their airways were not much different from those of controls. If they were subsequently given a dose of 300 mg/kg, some protection against epithelial cell necrosis was observed. At a dose of 200 mg/kg/day for 7 days, but not less, a selective reduction in the rate of formation of 1,2-naphthalene oxide was observed in the lungs, but not the livers, of mice (47). In mice that had become more "tolerant" of naphthalene in a similar manner, bronchiolar epithelia were much like those in controls: the expression of P-450 protein was lower and monooxygenase activity was lower, but covalent binding between protein and reactive metabolites was no lower than in controls (38).

In a comparative study, mice were given intraperitoneal doses of up to 400 mg naphthalene/kg body weight, hamsters up to 800 mg/kg, and rats up to 1600 mg/kg. The animals were sacrificed after 24 hours and their respiratory passages were examined. In the mice, 50 mg/kg caused Clara cell toxicity, 100 mg/kg caused an increase in the number of vacuolizations, and at doses above 200 mg/kg virtually all non-ciliated cells were necrotic. No effects were seen in bronchiolar cells of the rats even at the highest dose, and the hamsters receiving the highest dose (800 mg/kg) had only minor changes in Clara cells. Olfactory epithelium was necrotic in mice at 400 mg/kg, in hamsters at 400 mg/kg, and in rats at 200 mg/kg and higher (50).

In a study of PNEC (pulmonary neuroendocrine cells), mice were given 300 mg naphthalene/kg body weight intraperitoneally – a dose that selectively destroys Clara cells after the naphthalene has been metabolized to epoxide. Within 5 days the damage had caused hyperplasias characterized by an elevated number of neuroepithelial bodies (cell aggregations) (60).

Single intraperitoneal doses of naphthalene were given to mice 7 and 14 days old. The lowest dose, 25 mg/kg, caused massive damage to bronchial epithelium in the younger group. In the older group the effect was strongest at 50 mg/kg, and in adult mice 100 mg/kg caused only moderate damage (19).

Reversible hemolytic anemia was observed in three dogs given 3 – 9 grams of naphthalene per os (70).

When naphthalene (in corn oil) was given to C57BL/6 mice intraperitoneally, the animals developed cataracts. The doses were from 500 to 2000 mg/kg body weight, and the cataract development was dose-dependent. The incidence of cataracts was reduced if the animals were pre-treated with cytochrome P-450 inhibitors or vitamin E, and increased if the animals were pre-treated with phenobarbital (a P-450 inducer) and dimethyl maleate. A dose of 2000 mg/kg body weight given to another strain of mice (DBA/2) caused no cataracts (67). Dose-dependent cataracts have also been demonstrated in rats (43). The cataracts can be prevented if the animals are given an aldose reductase inhibitor; this was interpreted as indicating that the metabolism from naphthalene dihydrodiol to 1,2-dihydroxynaphthalene, the active metabolite, is inhibited (40). In tests in which five different strains of rats were given naphthalene by gavage (1 g/kg body weight) every other day, only minor changes were seen in the lenses of the two albino strains whereas the three pigmented strains developed cataracts (36). On the other hand, albino and pigmented rabbits seem to be equally sensitive (29).

Rabbits given naphthalene by gavage in doses of 1 mg/kg body weight/day developed cloudy lenses and retinal degeneration. At dissection, a brown color was noted in the lens and aqueous humor, blue fluorescence in the vitreous humor, crystals in the retina and glassy bodies and reduction of ascorbic acid in the aqueous humor. The metabolite 1,2-dihydroxynaphthalene was considered the primary toxic substance (28).

Mutagenicity, carcinogenicity, teratogenicity

Naphthalene was tested on three different strains of *Salmonella typhimurium*, both with and without metabolic activation: no positive results were obtained (5, 9, 42, 46, 54). In tests with Chinese hamster ovary (CHO) cells, naphthalene induced sister chromatid exchanges both with and without the addition of metabolizing systems. In the presence of the metabolizing systems it also induced chromosomal aberrations (46).

There is a report of a high incidence of larynx cancer. Four of 15 naphthalene refiners had carcinomas in the larynx, and three of the others had some form of cancer. They may have been exposed to other substances (68, 69). In a survey of 11 cases of colorectal cancer in young people, the authors suggest that the cause of the cancers may have been a preparation containing naphthalene that was used to treat intestinal problems, but the study has no control group (3).

Mice were exposed to 10 or 30 ppm naphthalene, 6 hours/day, 5 days/week for 6 months. There was no significant increase in lung adenomas or carcinomas in any of the exposed groups (2). Groups of mice were exposed to 0, 10 or 30 ppm naphthalene 6 hours/day, 5 days/week for 103 weeks. No increase in the incidence of adenomas was seen in males, but in the females there was an increase of alveolar/bronchiolar adenomas and carcinomas. The incidence of adenomas was significantly ($p < 0.01$) greater in the high-dose group than in controls (1, 46).

Rats were given naphthalene per os 6 days/week for 700 days; the total dose was 10 g. No cancer activity was observed. There is no control group in this experiment (56). Tumors were observed in 9 of 25 mice that had their skins painted with naphthalene in benzene 5 days/week during their lifetimes. Four of the animals had leukemia, three had lung adenomas and one had lymphosarcoma, and one tumor was unspecified. Tumors also occurred in 3 of 21 animals treated with benzene alone. Rats (38 per group) were given naphthalene in sesame oil subcutaneously, 500 mg/kg body weight, twice a week for a total of 7 doses, with a subsequent observation period of 18 months: the tumor incidences were 15% for naphthalene and 2% for sesame oil alone. The tumors were uterine and lymphatic sarcomas (35).

Naphthalene pellets were implanted in the bladders of mice and they were examined 30 weeks later for occurrence of adenomas and/or papillomas. One of 23 animals had carcinoma. The authors concluded that the naphthalene pellets disintegrate fairly quickly and that the exposure time was therefore shortened (10).

Naphthalene was tested in an in vitro system using virus-infected embryo cells: no activity was observed (52). Naphthalene has also been tested in an in vitro pre-implantation embryotoxicity test. No toxic effects were seen in a medium with up to 0.78 mM

naphthalene. The addition of a metabolizing system resulted in concentration-dependent embryotoxicity and mortality, with an LC_{50} of 0.18 mM (33).

Mice were given naphthalene by intraperitoneal injection, 14 or 56 mg/kg body weight, on day 2 of gestation. The embryos were removed on day 3 and cultivated in vitro for 72 hours. Naphthalene inhibited survival and implantation capability. Both doses inhibited growth of the embryos, and the higher dose retarded development (32). In a similar test, mice were given 300 mg/kg body weight/day by gavage on days 6 to 13 of gestation. The number of living pups born per mother was lower than in controls. Ten of 50 mothers died during the naphthalene treatment (25).

Mice were given 300 mg naphthalene/kg body weight/day on days 7 to 14 of gestation: there was a significant reduction in the number of living pups, and maternal mortality was also high (49). Rats were given 0, 50, 150 or 450 mg naphthalene/kg body weight/day on days 6 to 15 of gestation: the treatment caused transient CNS effects in the mothers in all dose groups. Growth was slower in the two highest dose groups. The litter sizes and the incidence of deformities were about the same as in controls, and it was concluded that the NOAEL for effects on fetal development was greater than 450 mg/kg (45).

Rats were given intraperitoneal injections of 395 mg naphthalene/kg body weight/day on days 1 to 15 of gestation: pups had later ossification of the skull and later heart development than controls (26).

Dose-effect / dose-response relationships

There are no data on human exposures that can serve as a basis for identifying a dose-effect or dose-response relationship. The LOAEL for eye irritation is about 15 ppm (53). Inhalation data from experiments with laboratory animals indicate that 10 ppm (2 years of exposure) is the LOAEL for inflammations in respiratory organs of mice (46). For effects of single oral or intraperitoneal doses, the LOAEL for effects on lung epithelia of mice is 50 mg/kg body weight (47, 50). There are differences between species, however, since the LOAEL for the same effect is 800 mg/kg in hamsters and over 1600 mg/kg in rats. Regarding effects on olfactory epithelium, the LOAEL is 400 mg/kg for mice and hamsters and 200 mg/kg for rats (50).

Conclusions

Exposure to naphthalene can irritate eyes and mucous membranes and cause cataracts and hemolytic anemia. The anemia is associated primarily with accidental oral intake or contact with moth repellents containing naphthalene. Naphthalene was found in one study to have carcinogenic activity in female mice.

The critical effect of occupational exposure to naphthalene is eye irritation.

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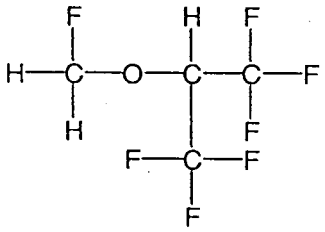
Consensus Report for Sevoflurane and Desflurane

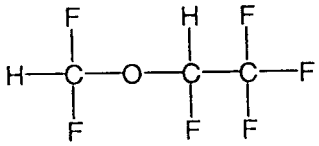
May 27, 1998

Chemical and physical data. Uses

sevoflurane

CAS No.:	28523-86-7
Chemical name:	1,1,1,3,3,3-hexafluoro-2-fluoromethoxypropane
Synonym:	Sevorane
Formula:	$C_4H_3F_7O$
Structure:	
Molecular weight:	200
Boiling point:	58.6 °C (101.3 kPa)
Vapor pressure:	157 kPa (20 °C)
Distribution coefficients:	blood/gas = 0.68 blood/brain = 1.70 blood/fat = 47.50
Conversion factors:	1 mg/m^3 = 0.12 ppm; 1 ppm = 8.3 mg/m^3

desflurane

CAS No.:	57041-67-5
Chemical name:	2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane
Synonym:	Suprane
Formula:	$C_3H_2F_6O$
Structure:	
Molecular weight:	168
Boiling point:	23.5 °C (101.3 kPa)
Vapor pressure:	669 kPa (20 °C)
Distribution coefficients:	blood/gas = 0.42 blood/brain = 1.29 blood/fat = 27.20
Conversion factors:	1 mg/m^3 = 0.14 ppm; 1 ppm = 7.0 mg/m^3

Sevoflurane and desflurane are modern inhalation anesthetics introduced into clinical practice during the 1990s. They are used with both children and adults. They neither burn nor explode.

Sevoflurane is a halogenated methylisopropyl ether. At room temperature it is a clear, colorless, volatile liquid that smells much like chloroform. The odor has been described as pleasant.

Desflurane is a halogenated methylethyl ether. At room temperature it is a clear, colorless volatile liquid with an ether-like odor. The odor has been described as unpleasant.

Exposure levels for medical personnel depend on the method of administering the anesthetic. During endotracheal anesthesia with local exhaust, measured levels of sevoflurane have been in the range 0.5 – 2.1 ppm with occasional peaks around 17 ppm (2, 3, 5, 6, 9, 10). Levels of desflurane measured in similar situations have been below 0.3 ppm (4). When the anesthetic is used on children, and without local exhaust, levels of sevoflurane around 50 ppm, with peaks exceeding 100 ppm, have been measured (9).

Uptake, biotransformation, excretion

Both sevoflurane and desflurane are rapidly taken up by the body and rapidly eliminated. In vivo transformation is independent of dose. About 1 to 5% of inhaled sevoflurane is metabolized, compared with about 0.2% of desflurane. The substances are metabolized in the liver, mostly by cytochrome P-450 (CYP) 2E1, with liberation of inorganic fluorine and carbon dioxide. Inorganic fluoride is excreted in urine (8).

Toxic effects

No data were found for either human or animal exposures at levels relevant in an occupational context. For sevoflurane, there is a reported LD_{50} for oral administration to rats and mice of 108,000 – 37,200 mg/kg body weight, and an LC_{50} for one hour of inhalation (rats and mice) of 58,000 – 83,000 ppm (product information from the manufacturer). There are no data on desflurane.

Like other anesthetics, sevoflurane and desflurane affect the central nervous system, heart, blood vessels, airways and neuromuscular activity. Published studies have been made with levels around 1 or 2 MAC (Minimum Alveolar Concentration), where MAC is the alveolar concentration that results in immobility in 50% of those exposed. The MAC level is 3 to 10% for desflurane and 2% for sevoflurane (8, 11).

Both sevoflurane and desflurane in extremely high doses (above 1 MAC) can be fetotoxic (1).

Conclusions

There is no scientific information on either sevoflurane or desflurane that can be used as a basis for identifying a critical effect relevant to occupational exposures.

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Summary

Lundberg P (ed). Scientific Basis for Swedish Occupational Standards. XIX. *Arbete och Hälsa* 1998:25, pp 1-78.

Critical evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish National Institute for Working Life between July, 1997 and June, 1998.

Key Words: Butyl Acetates, Cresol, Desflurane, Dichlorobenzenes, Dimethyl Amine, Flour Dust, Graphite, Hydrogen Bromide, Naphthalene, Occupational Exposure Limit (OEL), Phosphorus Oxides, Scientific Basis, Sevoflurane.

Sammanfattning

Lundberg P (ed). Vetenskapligt underlag för hygieniska gränsvärden. XIX. *Arbete och Hälsa* 1998:25, s 1-78.

Sammanställningar baserade på kritisk genomgång och värdering av de vetenskapliga fakta, vilka är relevanta som underlag för fastställande av hygieniskt gränsvärde. Volymen omfattar de underlag som avgivits från Kriteriegruppen för hygieniska gränsvärden under perioden juli 1997 - juni 1998.

Nyckelord: Butylacetater, Desfluran, Diklorbensener, Dimetylamin, Fosforoxider, Grafit, Hygieniskt gränsvärde, Kresol, Mjöldamm, Naftalen, Sevofluran, Vetenskapligt underlag, Vätebromid.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 1998:24.

APPENDIX

Consensus Reports in previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	
Acetaldehyde	February 17, 1987	1987:39	(VIII)
Acetamide	December 11, 1991	1992:47	(XIII)
Acetic acid	June15, 1988	1988:32	(IX)
Acetone	October 20, 1987	1988:32	(IX)
Acetonitrile	September 12,1989	1991:8	(XI)
Acrylamide	April 17, 1991	1992:6	(XII)
Acrylates	December 9, 1984	1985:32	(VI)
Acrylonitrile	April 28, 1987	1987:39	(VIII)
Aliphatic amines	August 25, 1982	1983:36	(IV)
Aliphatic hydrocarbons, C_{10}-C_{15}	June 1, 1983	1983:36	(IV)
Aliphatic monoketons	September 5, 1990	1992:6	(XII)
Allyl alcohol	September 9, 1986	1987:39	(VIII)
Allylamine	August 25, 1982	1983:36	(IV)
Allyl chloride	June 6, 1989	1989:32	(X)
Aluminum	April 21, 1982	1982:24	(III)
revised	September 14, 1994	1995:19	(XVI)
p-Aminoazobenzene	February 29, 1980	1981:21	(I)
Ammonia	April 28, 1987	1987:39	(VIII)
Amylacetate	March 23, 1983	1983:36	(IV)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
Arsenic, inorganic	December 9, 1980	1982:9	(II)
revised	February 15, 1984	1984:44	(V)
Arsine	October 20, 1987	1988:32	(IX)
Asbestos	October 21, 1981	1982:24	(III)
Barium	June 16, 1987	1987:39	(VIII)
revised	January 26, 1994	1994:30	(XV)
Benzene	March 4, 1981	1982:9	(II)
revised	February 24, 1988	1988:32	(IX)
Benzoyl peroxide	February 13, 1985	1985:32	(VI)
Beryllium	April 25, 1984	1984:44	(V)
Borax	October 6, 1982	1983:36	(IV)
Boric acid	October 6, 1982	1983:36	(IV)
Boron Nitride	January 27 1993	1993:37	(XIV)
Butadiene	October 23, 1985	1986:35	(VII)
1-Butanol	June 17, 1981	1982:24	(III)
Butanols	June 6, 1984	1984:44	(V)
Butyl acetate	June 6, 1984	1984:44	(V)
Butylamine	August 25, 1982	1983:36	(IV)
Butyl glycol	October 6, 1982	1983:36	(IV)
Cadmium	January 18, 1980	1981:21	(I)
revised	February 15, 1984	1984:44	(V)
revised	May 13, 1992	1992:47	(XIII)
Calcium nitride	January 27, 1993	1993:37	(XIV)
Caprolactam	October 31, 1989	1991:8	(XI)
Carbon monoxide	December 9, 1981	1982:24	(III)
Cathecol	September 4, 1991	1992:47	(XIII)

Chlorine	December 9, 1980	1982:9	(II)
Chlorine dioxide	December 9, 1980	1982:9	(II)
o-Chlorobenzylidene malononitrile	June 1, 1994	1994:30	(XV)
Chlorocresol	December 12, 1990	1992:6	(XII)
Chlorodifluoromethane	June 2, 1982	1982: 24	(III)
Chlorophenols	September 4, 1985	1986:35	(VII)
Chloroprene	April 16, 1986	1986:35	(VII)
Chromium	December 14, 1979	1981:21	(I)
revised	May 26, 1993	1993:37	(XIV)
Coal dust	September 9, 1986	1987:39	(VIII)
Cobalt	October 27, 1982	1983:36	(IV)
Copper	October 21, 1981	1982:24	(III)
Cotton dust	February14, 1986	1986:35	(VII)
Creosote	October 26, 1988	1989:32	(X)
Cumene	June 2, 1982	1982:24	(III)
Cyanoacrylates	March 5, 1997	1997:25	(XVIII)
Cycloalkanes, C_5-C_{15}	April 25, 1984	1984:44	(V)
Cyclohexanone	March 10, 1982	1982:24	(III)
Cyclohexanone peroxide	February 13, 1985	1985:32	(VI)
Cyclohexylamine	February 7, 1990	1991:8	(XI)
Diacetone alcohol	December 14, 1988	1989:32	(X)
1,2-Dibromo-3-chloropropane	May 30, 1979	1981:21	(I)
Dichlorodifluoromethane	June 2, 1982	1982:24	(III)
1,2-Dichloroethane	February 29, 1980	1981:21	(I)
Dichloromethane	February 29, 1980	1981:21	(I)
Dicumyl peroxide	February 13, 1985	1985:32	(VI)
Dicyclopentadiene	March 23, 1994	1994:30	(XV)
Diethanolamine	September 4, 1991	1992:47	(XIII)
Diethylamine	August 25, 1982	1983:36	(IV)
2-Diethylaminoethanol	January 25, 1995	1995:19	(XVI)
Diethylene glycol	September 16,1992	1993:37	(XIV)
Diethyleneglycol ethylether + acetate	December 11, 1996	1997:25	(XVIII)
Diethyleneglycol methylether + acetate	March 13, 1996	1996:25	(XVII)
Diethyleneglycol monobutylether	January 25, 1995	1995:19	(XVI)
Diethylenetriamine	August 25, 1982	1983:36	(IV)
revised	January 25, 1995	1995:19	(XVI)
Diisocyanates	April 8, 1981	1982:9	(II)
revised	April 27, 1988	1988:32	(IX)
Diisopropylamine	February 7, 1990	1991:8	(XI)
N,N-Dimethylacetamide	March 23, 1994	1994:30	(XV)
N,N-Dimethylaniline	December 12, 1989	1991:8	(XI)
Dimethyldisulfide	September 9, 1986	1987:39	(VIII)
Dimethylether	September 14, 1994	1995:19	(XVI)
Dimethylethylamine	June 12, 1991	1992:6	(XII)
Dimethylformamide	March 23, 1983	1983:36	(IV)
Dimethylhydrazine	January 27, 1993	1993:37	(XIV)
Dimethylsulfide	September 9, 1986	1987:39	(VIII)
Dimethylsulfoxide, DMSO	December 11, 1991	1992:47	(XIII)
Dioxane	August 25, 1982	1983:36	(IV)
revised	March 4, 1992	1992:47	(XIII)
Diphenylamine	January 25, 1995	1995:19	(XVI)
4,4'-Diphenylmethanediisocyanate	April 8, 1981	1982:9	(II)
Dipropylene glycol	May 26, 1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12, 1990	1992:6	(XII)
Disulfiram	October 31, 1989	1991:8	(XI)
Enzymes, industrial	June 5, 1996	1996:25	(XVII)

Ethanol	May 30, 1990	1991:8	(XI)
Ethanolamine	September 4, 1991	1992:47	(XIII)
Ethylacetate	March 28, 1990	1991:8	(XI)
Ethylamine	August 25, 1982	1983:36	(IV)
Ethylamylketone	September 5, 1990	1992:6	(XII)
Ethylbenzene	December 16, 1986	1987:39	(VIII)
Ethylchloride	December 11, 1991	1992:47	(XIII)
Ethylene	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)
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)
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)
Formaldehyde	June 30, 1979	1981:21	(I)
revised	August 25, 1982	1983:36	(IV)
Formamide	December 12, 1989	1991:8	(XI)
Formic acid	June 15, 1988	1988:32	(IX)
Furfural	April 25, 1984	1984:44	(V)
Furfuryl alcohol	February 13, 1985	1985:32	(VI)
Gallium + Gallium compounds	January 25, 1995	1995:19	(XVI)
Glycol ethers	October 6, 1982	1983:36	(IV)
Glyoxal	September 13, 1996	1996:25	(XVII)
Grain dust	December 14, 1988	1989:32	(X)
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	April 8, 1981	1982:9	(II)
Hexamethylenetetramine	August 25, 1982	1983:36	(IV)
n-Hexane	January 27, 1982	1982:24	(III)
2-Hexanone	September 5, 1990	1992:6	(XII)
Hexyleneglycol	November 17, 1993	1994:30	(XV)
Hydrazine	May 13, 1992	1992:47	(XIII)
Hydrogen fluoride	April 25, 1984	1984:44	(V)
Hydrogen peroxide	April 4, 1989	1989:32	(X)
Hydrogen sulfide	May 4, 1983	1983:36	(IV)
Hydroquinone	October 21, 1989	1991:8	(XI)
Indium	March 23, 1994	1994:30	(XV)
Industrial enzymes	June 5, 1996	1996:25	(XVII)
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)
Lead, inorganic	February 29, 1980	1981:21	(I)
revised	September 5, 1990	1992:6	(XII)
Lithium boron nitride	January 27, 1993	1993:37	(XIV)
Lithium nitride	January 27, 1993	1993:37	(XIV)

Maleic anhydride	September 12, 1989	1991:8	(XI)
Manganese	February 15, 1983	1983:36	(IV)
revised	April 17, 1991	1992:6	(XII)
revised	June 4, 1997	1997:25	(XVIII)
Man made mineral fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Mercury, inorganic	April 25, 1984	1984:44	(V)
Mesityl oxide	May 4, 1983	1983:36	(IV)
Metal stearates, some	September 15, 1993	1994:30	(XV)
Methacrylates	September 12, 1984	1985:32	(VI)
Methanol	April 25, 1985	1985:32	(VI)
Methyl acetate	March 28 1990	1991:8	(XI)
Methylamine	August 25, 1982	1983:36	(IV)
Methylamyl alcohol	March 17, 1993	1993:37	(XIV)
Methyl bromide	April 27, 1988	1988:32	(IX)
Methyl chloride	March 4, 1992	1992:47	(XIII)
Methyl chloroform	March 4, 1981	1982:9	(II)
Methylene chloride	February 29, 1980	1981:21	(I)
4,4'-Methylene dianiline	June 16, 1987	1987:39	(VIII)
Methyl ethyl ketone	February 13, 1985	1985:32	(VI)
Methyl ethyl ketone peroxide	February 13, 1985	1985:32	(VI)
Methyl formare	December 12, 1989	1991:8	(XI)
Methyl glycol	October 6, 1982	1983:36	(IV)
Methyl iodide	June 30, 1979	1981:21	(I)
Methylisoamylamine	September 5, 1990	1992:6	(XII)
Methyl mercaptane	September 9, 1986	1987:39	(VIII)
Methyl methacrylate	March 17, 1993	1993:37	(XIV)
Methyl pyrrolidone	June 16, 1987	1987:39	(VIII)
Methyl-t-butyl ether	November 26, 1987	1988:32	(IX)
Mixed solvents, neurotoxicity	April 25, 1985	1985:32	(VI)
Molybdenum	October 27, 1982	1983:36	(IV)
Monochloroacetic acid	February 20, 1991	1992:6	(XII)
Monochlorobenzene	September 16,1993	1993:37	(XIV)
Monomethylhydrazine	March 4, 1992	1992:47	(XIII)
Mononitrotoluene	February 20, 1991	1992:6	(XII)
Monoterpenes	February 17, 1987	1987:39	(VIII)
Morpholine	December 8, 1982	1983:36	(IV)
revised	June 5, 1996	1996:25	(XVII)
Natural crystallinic fibers (except asbestos)	June 12, 1991	1992:6	(XII)
Nickel	April 21, 1982	1982:24	(III)
Nitroethane	April 4, 1989	1989:32	(X)
Nitrogen oxides	December 11, 1985	1986:35	(VII)
Nitroglycerin	February 13, 1985	1985:32	(VI)
Nitroglycol	February 13, 1985	1985:32	(VI)
Nitromethane	January 6, 1989	1989:32	(X)
Nitropropane	October 28, 1986	1987:39	(VIII)
2-Nitropropane	March 29, 1995	1995:19	(XVI)
Nitroso compounds	December 12, 1990	1992:6	(XII)
Nitrosomorpholine	December 8, 1982	1983:36	(IV)
Nitrotoluene	February 20, 1991	1992:6	(XII)
Nitrous oxide	December 9, 1981	1982:24	(III)
Oil mist	April 8, 1981	1982:9	(II)
Organic acid anhydrides, some	September 12, 1989	1991:8	(XI)
Oxalic acid	February 24, 1988	1988:32	(IX)
Ozone	April 28, 1987	1987:39	(VIII)

Paper dust	February 7, 1990	1991:8	(XI)
Pentaerythritol	November 16, 1994	1995:19	(XVI)
Peroxides, organic	February 13, 1985	1985:32	(VI)
Phenol	February 13, 1985	1985:32	(VI)
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)
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)
Silica	March 13, 1996	1996:25	(XVII)
Silver	October 28, 1986	1987:39	(VIII)
Stearates, metallic, some	September 15, 1993	1994:30	(XV)
Stearates, non-metallic, some	November 17, 1993	1994:30	(XV)
Strontium	January 26, 1994	1994:30	(XV)
Styrene	February 29, 1980	1981:21	(I)
revised	October 31, 1989	1991:8	(XI)
Sulfur dioxide	April 25, 1985	1985:32	(VI)
Sulfur fluorides	March 28, 1990	1991:8	(XI)
Synthetic inorganic fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Synthetic organic and inorganic fibers	May 30, 1990	1991:8	(XI)
Talc dust	June 12, 1991	1992:6	(XII)
Terpenes, mono-	February 17, 1987	1987:39	(VIII)
Tetrabromoethane	May 30, 1990	1991:8	(XI)
Tetrachloroethane	June 4, 1997	1997:25	(XVIII)
Tetrachloroethylene	February 29, 1980	1981:21	(I)
1,1,1,2-Tetrafluoroethane	March 29, 1995	1995:19	(XVI)
Tetrahydrofuran	October 31, 1989	1991:8	(XI)
Tetranitromethane	April 4, 1989	!989:32	(X)
Thioglycolic acid	June 1, 1994	1994:30	(XV)
Thiourea	December 1, 1987	1988:32	(IX)
Thiram	October 31, 1989	1991:8	(XI)
Thiurams, some	October 31, 1989	1991:8	(XI)
Titanium dioxide	February 21, 1989	1989:32	(X)
Toluene	February 29, 1980	1981:21	(I)
Toluene-2,4-diisocyanate	April 8, 1981	1982:9	(II)
Toluene-2,6-diisocyanate	April 8, 1981	1982:9	(II)

Trichlorobenzene	September 16,1993	1993:37	(XIV)
1,1,1-Trichloroethane	March 4, 1981	1982:9	(II)
Trichloroethylene	December 14, 1979	1981:21	(I)
Trichlorofluoromethane	June 2, 1982	1982:24	(III)
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2, 1982	1982:24	(III)
Triethanolamine	August 25, 1982	1983:36	(IV)
Triethylamine	December 5, 1984	1985:32	(VI)
Trimellitic anhydride	September 12, 1989	1991:8	(XI)
Trimethylolpropane	November 16, 1994	1995:19	(XVI)
Trinitrotoluene	April 17, 1991	1992:6	(XII)
Vanadium	March 15, 1983	1983:36	(IV)
Vinyl acetate	June 6, 1989	1989:32	(X)
Vinyl toluene	December 12, 1990	1992:6	(XII)
White spirit	December 16, 1986	1987:39	(VIII)
Wood dust	June 17, 1981	1982:9	(II)
Xylene	February 29, 1980	1981:21	(I)
Zinc	April 21, 1982	1982:24	(III)
Zinc dimethyl dithiocarbamate	September 12, 1989	1991:8	(XI)
Ziram	September 12, 1989	1991:8	(XI)

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