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Scientific Basis for Swedish Occupational Standards XXIII

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(Except for the consensus report on Toluene wich was written in English)

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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 Swedish Work Environment Authority (SWEA). In most cases a scientific basis is written on request from the SWEA. The Criteria Group shall not propose a numerical occupational exposure limit value but, as far as possible, give a dose-response/dose-effect relationship and the critical effect of occupational exposure.

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

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

This is the 23rd volume that is published and it contains consensus reports approved by the Criteria Group during the period July 2001 to June 2002. These and previously published consensus reports are listed in the Appendix (p 57).

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of June, 2002)

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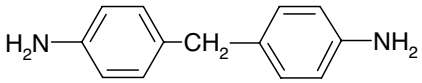
Consensus Report for 4,4´-Methylenedianiline (MDA)

October 3, 2001

This work is an update of the Consensus Report published in 1987 (36).

Chemical and physical data. Uses

CAS No.:	101-77-9
Synonyms:	4,4´-diaminodiphenylmethane bis-(4-aminophenyl)-methane 4,4´-methylenebisaniline 4-(4-aminobenzyl)-aniline
Formula:	$C_{13}H_{14}N_2$
Structure:	
Molecular weight:	198.27
Boiling point:	398 – 399 °C
Melting point:	91.5 – 92 °C
Vapor pressure:	1.2 kPa (9 mm Hg) at 232 °C; calculated 1.33 x 10^{-7} kPa (1 x 10^{-6} mm Hg) at 20 °C (16)
Solubility:	0.1 g/100 g water
Distribution coefficient:	log $P_{octanol/water}$ = 1.6 (22)

Pure 4,4´-methylenedianiline at room temperature is a crystalline powder with a weak amine odor. It dissolves easily in alcohol, benzene and ether, but only slightly in water (1). Industrial grade MDA is a liquid, and typically has the following composition:

4,4´-MDA	60%
MDA polymers	36%
2,4´-MDA	3.5%
2,2´-MDA	< 0.1%
water	< 300 ppm
aniline	< 100 ppm.

MDA is used in the production of various polymers and plastics. Most of it is used in closed systems to make methylenediphenyl diisocyanate (MDI) and

polyisocyanates for use in production of polyurethane. MDA is also added to rubber as an antioxidant and to epoxy products and neoprene as a hardener. Smaller amounts are/were used in rust preventives and azo dyes for leather and hair (36).

Occupational exposure occurs mostly during production of MDA or polymers. However, emissions of MDA and MDI have also been detected around use of finished products – heating polyurethane foam, for example (12, 25, 38). MDA and its metabolites have been found in hydrolyzed urine and plasma from workers exposed to MDI, and exposure to MDI thus implies potential exposure to MDA (50). To measure individual exposure to airborne MDA, samples are taken on acid-treated fiberglass filters and analyzed by liquid chromatography (16).

Uptake, biotransformation, excretion

Uptake

At room temperature MDA occurs almost entirely in aerosol form, and it can be taken up via respiratory passages, skin and digestive tract. In occupational exposures, most MDA enters the body via skin and respiratory passages (9). Several reports describe skin uptake as the primary path of exposure (7, 8, 37). One study reviews several cases of MDA-induced hepatitis in a plastics factory during the years 1966 – 1972. The problems caused by the poor work environment were addressed, and in 1971 the workers had begun using helmets with separate air intakes and the reported MDA concentrations in the air were low: in the range 1.6 to 4.4 $\mu g/m^3$ outside the helmet and 0.6 $\mu g/m^3$ inside the helmet. Despite these improvements, there were more cases of liver damage during 1971 – 72. All the workers who developed hepatitis had been kneading a paste of MDA plastic protected only by cotton gloves, and had worked with their hands in the plastic for several hours per day. Workers with other tasks at the workplace were unaffected (37).

Skin uptake was quantified by Brunmark *et al*.: five volunteers were given patch tests with 0.75 – 2.25 μmol MDA in isopropanol. An average uptake of 28% was calculated from analysis of the MDA remaining in the patch test chamber after 1 hour of exposure (6). Calculations based on this result yield an uptake rate of 0.24 $\mu g/cm^2$/hour.

Biotransformation

Biotransformation has been found to be an important factor in acute toxicity, genotoxicity and elimination of MDA (2, 6, 27, 31). Several metabolites and a few MDA-metabolizing enzymes have been identified, but mapping of MDA metabolism is far from complete.

N-Acetyl MDA has been identified as the primary metabolite in the urine of exposed workers (8). MDA and acetyl-MDA have also been found as hemoglobin adducts (47). Valine adducts in hemoglobin were isolated in order to identify the genotoxic reactive intermediates of MDA. A valine adduct of hemoglobin was

identified, and it was proposed that the reactive intermediate is 1-[(4-imino-2,5-cyclohexadiene-1-ylidene)-methyl]-4-aminobenzene (31). The cytochrome P450 system has been found to be involved, and several reactive intermediates have been identified (2, 27) (see Figure 1). MDA treatment of rats increases enzyme activity in their livers (57).

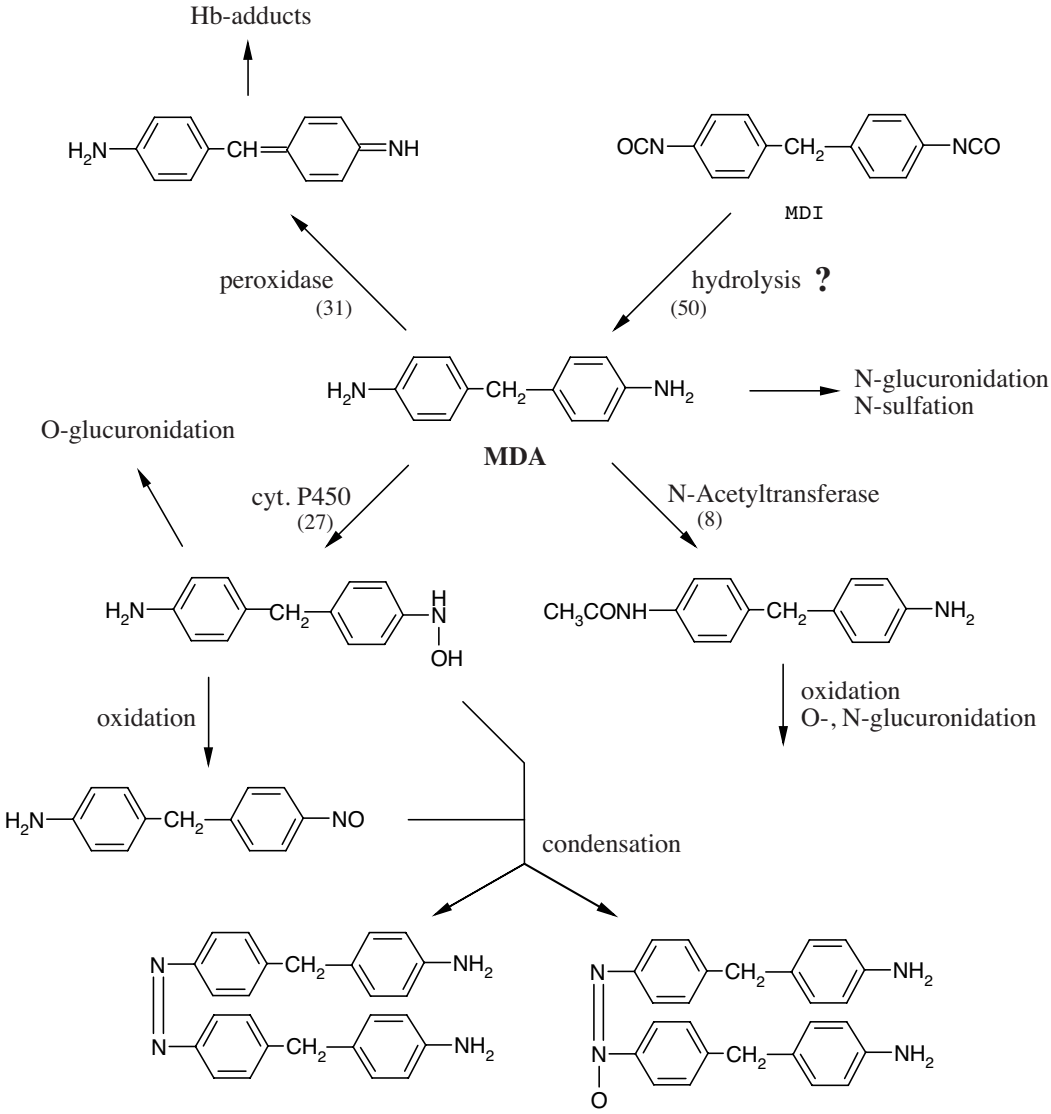


Figure 1. Proposed metabolism of MDA. References are given within parentheses. cyt. P450 = cytochrome P450 monooxygenase; Hb = hemoglobin.

It is important to bear in mind that MDI may be hydrolyzed to MDA *in vivo*. Rats were exposed to an aerosol of MDI for 3 to 12 months, and although no MDA was detected in the exposure chamber both MDA and acetyl-MDA were identified in the rats' urine and the corresponding hemoglobin adducts in their blood (50). MDA and acetyl-MDA have also been detected in urine and as hemoglobin adducts in blood from workers exposed only to MDI (47). The analysis method, however, involves hydrolysis of the plasma or urine, which means that MDI can be transformed to MDA during the sample processing. Figure 1 summarizes the proposed metabolic pathways for MDA.

In a study of elimination and absorption kinetics, 5 volunteers were given 1 hour of epicutaneous exposure to 0.75 – 2.25 μmol MDA. It was found that the plasma concentration was highest 3 to 7 hours later, and the calculated half time for the elimination phase was 9 to 19 hours. The highest levels in urine were noted 6 to 11 hours after the exposure, and the half time in urine was 4 to 11 hours (6). A similar study of workers exposed to heated polyurethane foam showed considerably longer elimination times: the half times were determined to be 10 to 22 days in plasma and 59 to 73 hours in urine (13). The observation that in these two studies the half time for elimination was shorter in urine than in plasma can be explained by assuming that MDA probably exists in at least two compartments with different half times (free and protein-bound MDA, for example), or that the observation time was too brief.

Excretion

MDA is excreted in both urine and feces (16). The distribution between excretion pathways varies with species and method of administration (16).

There are no complete data from human exposures. However, Brunmark *et al*. report that only 16% of absorbed MDA was excreted in urine within 50 hours of exposure and that MDA in urine was subsequently below the detection limit. They conclude that MDA is probably excreted and metabolized in other ways as well, and may be stored in the body (6).

Biological measures of exposure

Since skin uptake accounts for a large portion of total uptake, methods have been developed for biological exposure monitoring. These are gas-chromatographic-mass spectrophotometric analysis of MDA and acetyl-MDA in urine (7), in plasma (13), and as hemoglobin adducts in blood (50). Analysis of MDA concentrations in urine is suitable for estimating exposures during a workshift, but several measurements both post-shift and pre-shift are required if the results are to be reliable (6, 12). For estimating exposures over longer periods, there is a method based on quantitative analysis of MDA and acetyl-MDA in hemoglobin adducts (47, 50). Workers exposed to low levels of MDA or MDI were examined, and acetyl-MDA and MDA were found (after hydrolysis) in the urine and blood of most of them, although in most cases the air concentration was below the detection limit. Biological exposure monitoring is proposed as a sensitive method of assessing exposure to MDA and MDI (47, 50). In order to identify high exposure

during a single workshift, and for quantitative estimates of longer exposures, measurements of MDA in both blood and urine are recommended (47). However, this method can not differentiate between MDA exposure and MDI exposure.

Toxic effects

Human data

Several incidents of MDA poisoning have been reported, after oral intake of contaminated bread or drink as well as after occupational exposure via skin or inhalation. In all cases the amount of MDA taken up is unknown. Regardless of whether the uptake was dermal, oral or via inhalation, the result was liver damage (3, 5, 32, 33, 37, 44, 53). A retrospective study reviews 12 cases of chemical hepatitis that occurred in the 1966-1972 period at a plastics factory where these workers made insulation containing MDA. They kneaded a plastic paste with their hands, and became ill after one to three weeks of work at the factory but one or two days after beginning work with the plastic. All 12 had jaundice and dark urine, and 5 also had skin rashes. In the report it is pointed out that other workers doing the same task did not become ill, and that differences in exposure or in sensitivity to MDA were possible reasons for the difference in risk (37).

Another case report describes floorlayers who developed jaundice and stomach cramps. They used MDA as hardener in an epoxy glue that they mixed on site (3). A third study describes an occupational exposure in a chemical plant where large quantities of MDA were used. A young man was exposed to MDA when the air filtration system broke down, spraying MDA into the air as a yellow dust. While the system was being repaired he took a lunch break and removed the top part of his protective overalls, leaving his upper body covered only by a T-shirt. In addition to stomach pains he developed a skin rash and hepatitis, as well as acute myocardiopathy (5). Yet another study describes a man who drank an unknown amount of MDA dissolved in potassium carbonate and butyrolactone. His vision was affected, and he developed jaundice and temporary heart problems. Eighteen months later his vision had still not recovered (44).

The most remarkable poisoning incident occurred in Epping, U.K, in 1965, when 84 persons developed jaundice and other symptoms after eating bread contaminated with MDA (32). The jaundice lasted for 1.5 to 4 months, and the patients felt unwell for several weeks after the symptoms of jaundice had disappeared. Liver biopsies revealed portal inflammation, eosinophil infiltration, bile duct inflammation, bile stasis and various degrees of cell damage (33). All the victims recovered without further complications within a year (33). A bit of the contaminated bread was analyzed, and the total dose was estimated to have been about 3 mg/kg body weight. It is emphasized, however, that this figure is highly speculative: only one slice of bread was analyzed, it is known that the MDA was unevenly distributed in the contaminated flour, the analysis method is presumably inaccurate, and the total bread intake of each individual is unknown (20, 32).

Skin

Direct contact with MDA colors the skin, nails and hair yellow (10), and several studies have demonstrated that MDA is a contact allergen. Several case reports describe positive reactions to patch tests with MDA, but it is uncertain whether MDA induced the hypersensitivity or the positive reactions are due to a cross-reaction with similar para-amino compounds (4, 16, 18, 28, 45). Studies by Von Gailhofer and Kanerva, however, indicate that MDA causes skin sensitization. Von Gailhofer and Ludvan (18) found that 39 of 202 patients had positive reactions to MDA only, and their data indicate that workers in chemical laboratories have an elevated risk of developing contact allergy to MDA. Kanerva *et al*. (28) found that MDA was the second most common contact allergen on patch tests given to patients with suspected occupational dermatosis after contact with plastic chemicals. They tested 174 patients with their 'plastic and glue series no. 1,' and 2.9% were positive to MDA. In a previous study the same group had examined 6 patients occupationally exposed to isocyanates: 5 of them had reactions to both MDA and MDI, 3 to an additional 5 isocyanates, and 1 to MDA alone. Primary sensitization to MDA and a cross-reaction to MDI is the most likely explanation, but primary sensitization to MDI is also a possibility (15). One case of photosensitization has been reported (34).

Animal data

MDA is acutely toxic to several animal species, including rats, mice, guinea pigs, rabbits and dogs, when given in oral doses of 100 to 800 mg/kg (23). Cats have been found to be more sensitive, with liver and kidney damage after a single dose of 10 mg/kg (16). Acute toxic effects in all species are liver and kidney damage, and cats also go blind. The LD_{50} for oral administration to Wistar rats was 830 mg MDA/kg body weight (43). Rats exposed to MDA for several weeks developed liver cirrhosis (39, 58) or liver fibrosis and inflammation in the portal area (46). In rats given 1000 ppm MDA in diet for 8 to 40 weeks, there was intraheptic bile duct proliferation in addition to a duration-dependent increase in the previously mentioned types of liver damage (17).

Hypertrophy of adrenals, uterus and thyroid was observed in ovarectomized rats given MDA by gavage in doses of 150 mg/kg/day for two weeks (54). Other effects seen in rats given similar subchronic doses are degeneration of liver, kidneys and spleen (17, 19, 24). In a 13-week study by the National Toxicology Program (NTP), rats and mice were given MDA dihydrochloride (MDA-2HCl) in drinking water, 0 to 800 mg/liter. There were dose-dependent increases in the frequencies of hyperplasias in bile ducts and thyroids, and at the highest dose goiter as well. The highest dose having no observed effect was 100 mg/liter (≈ 6 - 7 mg/kg for rats, 13 - 16 mg/kg for mice) (40). For rats, the toxicity threshold for a single exposure is estimated to be between 25 and 75 mg/kg (2). Recent morphological studies have shown that bile duct epithelial cells are damaged first. Necrosis in intrahepatic bile ducts had become severe within 6 hours after oral administration of MDA (50 mg/kg), and less severe damage was seen in small

peripheral bile ducts (30). Kanz *et al*. found toxic compounds in the bile of rats 4 hours after a single oral dose of 250 mg/kg (29).

Effects on drug-metabolizing enzymes in rat liver were studied, and the lowest single dose that yielded a significant effect was 50 mg/kg (57). Dose-effect relationships observed in studies with rats and mice are summarized in Table 1.

Mutagenicity

Several experiments, both *in vivo* and *in vitro*, have shown that MDA is mutagenic and genotoxic. MDA was found to be mutagenic in *Salmonella typhimurium* strains TA98 and TA100 only after activation with S9. The N-acetylated metabolites were not mutagenic under the same conditions (41, 52). MDA induced DNA repair in rat hepatocytes (38). Exposure to MDA *in vivo* induced sister chromatid exchanges in bone marrow cells and DNA strand breaks in hepatic cells (41, 42). MDA-induced DNA adducts have been detected with the ^{32}P-postlabeling method and by injection of radioactive MDA (48, 55). MDA is clearly mutagenic *in vitro* and genotoxic *in vivo*.

Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified MDA as "possibly carcinogenic to humans" (Group 2B) (25, 26). The European Commission has placed MDA in Category 2, with the risk description "may cause cancer" (R45) (14). The results of cancer studies with rats and mice are summarized in Table 2 and below.

Animal data

The NTP conducted a well controlled cancer study in which Fischer-344 rats and B_6C_3F mice of both sexes, 50 animals per group, were given MDA in drinking water (two different dose levels) for two years. The study showed that MDA caused tumors in liver and thyroid (56). The rats received water containing 0, 150 or 300 mg MDA hydrochloride/liter, corresponding to a daily MDA intake of 0, 9-10 or 16-19 mg/kg. There was no effect on survival. At the highest dose level, the incidences of thyroid carcinomas in male rats and of thyroid adenomas in female rats were significantly higher than in controls. A dose-related increase of hepato-cellular neoplastic noduli was also observed in the male rats (56). The same test protocol was followed with the mice. They were given drinking water containing 0, 150 or 300 mg MDA hydrochloride/liter, corresponding to a daily MDA intake of 0, 19-25, or 43-57 mg/kg. For males, survival was significantly lower in the high-dose group than in the low-dose or control groups. As with the rats, the greatest effects were on liver and thyroid. The incidences of hyperplasia and adenoma in thyroid were significantly higher in both males and females receiving the high dose. A dose-dependent increase in hepatocellular carcinomas was observed in both sexes, and of hepatocellular adenomas in females (56). Smaller

or poorly documented studies also indicate that MDA has a carcinogenic effect (39, 46, 51).

Using the results of the animal experiments made by the NTP, the Dutch Expert Committee on Occupational Standards (DECOS) made a linear extrapolation yielding a calculated increase of cancer risk for MDA exposure: 4×10^{-5} with 40 years of exposure to 0.009 mg MDA/m^3 (21).

Human data

Seldén *et al*. studied 550 Swedish power plant workers probably exposed to MDA and found one case of bladder cancer (expected 0.6) (49). Cragle *et al*. compared 263 chemical process workers with 271 unexposed workers from the same factory and found five cases of bladder cancer among the exposed workers (expected 0.66), a significant increase (11). None of the five had worked with MDA, although there was indirect exposure. All five, however, had been exposed to trichloroethylene (11).

Liss and Guirguis report one case of bladder cancer among 10 former workers in a factory that made epoxy paste, all of whom had been poisoned by MDA at some time during the 1967-1976 period (35).

In a follow-up 24 years after the accident in Epping, where exposure consisted of high doses of MDA in contaminated bread consumed during a fairly short period, no chronic effect of the poisoning could be seen in the 68 victims (81%) that could be traced. This study unfortunately has little value, since the documentation is poor and the investigation was incomplete (20).

In summary, studies of occupational exposure are limited by the small number of cases and the prevalence of mixed exposures. Several aromatic amines similar to MDA can cause bladder cancer in humans.

Reproduction toxicity

A study of uncertain relevance reports that MDA injected into the yolks of fertile eggs reduces hatching frequency and has teratogenic effects (25).

Dose-effect / dose-response relationships

There are no data from which to derive a dose-effect or dose-response relationship for occupational exposure to MDA. An injection of 2-10 mg/kg given to rats resulted in enzyme induction, but no toxic effects (57). In the NTP study, the highest dose without toxic effect was 100 mg MDA-2HCl/liter (≈ 6-7 mg/kg for rats, 13-16 mg/kg for mice) for 13 weeks (40).

Effects on rats and mice are summarized in Tables 1 and 2.

Table 1. Dose-effect relationships observed in laboratory animals exposed to MDA. (i.p = intraperitoneal; p.o. = per os; d.w. = as MDA dihydrochloride in drinking water)

Exposure method, dose (mg/kg b.w.)	Effects	Ref.
Rats		
single dose, *i.p.*		
2 or 10	No effect.	57
50 or 100	Increased enzyme activity in livers.	57
single dose, p.o.		
25	Increased serum-alanine aminotransferase activity and liver weight.	2
50	Six hours after exposure: severe necrosis in intrahepatic bile ducts, moderate damage to smaller ducts.	30
75 or 125 or 225	Increased serum-alanine aminotransferase and γ -glutamyl transferase activity; dose-dependent increases in total serum bilirubin and liver weights; reduced bile flow.	2
100	Necrosis and neutrophil infiltration in bile ducts, hepato-cellular necrosis, neutrophil infiltration in parenchyme.	2
250	4 hours after exposure: severe cellular necrosis in main bile duct, minimal damage in peripheral ducts. 24 hours after exposure: hepatocellular necrosis, cytolysis of cortical thymocytes, bile stasis.	29
multiple doses, i.p.		
2 (daily, 3 days)	Increased enzyme activity in liver.	57
50 (daily, 3 days)	Reduced cytochrome P450 activity, increased enzyme activity in liver.	57
multiple doses, p.o.		
20 or 50 (daily, 3 days)	DNA adducts.	55
8-600 (daily, 10 days)	Necrotic inflammation in gall bladders and bile ducts.	19
150 or 200[1] (daily, 14 days)	Hypertrophy in adrenals, thyroids and uterus of ovarectomized females.	54
0.1% MDA in diet, (8 to 40 weeks)	Time-dependent increase of proliferation, necrosis and fibrosis in bile duct epithelium and infiltration of oval cells. Reduced weight gain.	17
38 (daily, 5 days/week, 17 weeks)	Cirrhosis.	39
50 or 100[2] mg/l, d.w. (13 weeks)	No effect.	40
200 mg/l, d.w. (13 weeks)	Reduced water intake.	40
400 mg/l, d.w. (13 weeks)	Some rats had hyperplasia in bile ducts, hypertrophy in pituitary, hyperplasia in thyroid.	40
800 mg/l, d.w. (13 weeks)	All rats had hyperplasia in bile ducts, hypertrophy in pituitary, hyperplasia in thyroid and reduced weight gain.	40
Mice[3]		
25 or 50 or 100[4] mg/l (13 weeks)	No effect.	40
200 mg/l (13 weeks)	Reduced weight gain.	40
400 mg/l (13 weeks)	Hyperplasia in bile ducts.	40
150-300 mg/l (104 weeks)	Kidney damage with mineralization of renal papillae.	56

[1]the animals were given MDA dihydrochloride.
[2]≈ 6-7 mg/kg.
[3]All exposures in mice are to MDA dihydrochloride in drinking water.
[4]≈13-16 mg/kg b.w.

Table 2. Occurrence of tumors in rats and mice, 50 males or 50 females per group, exposed to MDA dihydrochloride in drinking water for 2 years (56). The numbers in the last two columns give the number of affected animals in the group of 50.

Species, exposure	Tumors	No. affected animals males	females
Rats (Fischer-344)			
Unexposed controls	Liver:		
	hepatocellular neoplastic nodules	1	4
	Thyroid:		
	follicular hyperplasia	1	1
	adenoma	1	0
	carcinoma	0	0
150 mg/l	Liver:		
(9-10 mg/kg/day)	hepatocellular neoplastic nodules	12*	8
300 mg/l	Liver:		
(16-19 mg/kg/day)	hepatocellular neoplastic nodules	25*	8
	Thyroid:		
	follicular hyperplasia	2	3
	adenoma	3	17*
	carcinoma	7*	2
Mice (B_6C_3F)			
Unexposed controls	Liver:		
	hepatocellular adenoma	7	3
	carcinoma	10	1
	Thyroid:		
	follicular hyperplasia	0	0
	adenoma	0	0
	carcinoma	0	0
150 mg/l	Liver:		
(19-25 mg/kg/day)	hepatocellular adenoma	10	9
	carcinoma	33*	6
300 mg/l	Reduced survival		
(43-57 mg/kg/day)			
	Liver:		
	hepatocellular adenoma	8	12*
	carcinoma	29*	11*
	Thyroid:		
	follicular hyperplasia	18*	23*
	adenoma	16*	13*
	carcinoma	0	3

*significant difference from controls; $p < 0.002$.

Conclusions

There are insufficient human data for establishing a critical effect of MDA. Occupational exposure to MDA, where skin absorption plays a major role, has caused liver damage. Judging from animal experiments, the critical effect is liver damage, including liver cancer. MDA is genotoxic *in vitro* and forms DNA adducts *in vivo*. MDA is carcinogenic to experimental animals and should be regarded as carcinogenic to humans. MDA in direct contact with the skin is readily absorbed, and the substance can cause contact allergy.

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Consensus Report for Methylisocyanate (MIC) and Isocyanic Acid (ICA)

December 5, 2001

Chemical and physical data. Occurrence

	methylisocyanate (MIC)	*isocyanic acid (ICA)*
CAS No.:	624-83-9	75-13-8
Synonyms:	isocyanic acid methylester	hydrogen isocyanate
Structure:	H_3C-N=C=O	HN=C=O
Molecular weight:	57.06	43.02
Boiling point:	39 °C	23 °C
Melting point:	- 45 °C	- 80 °C
Vapor pressure:	46.4 kPa (20 °C)	13.3 kPa (- 19 °C)
Conversion factors:	1 ppm = 2.4 mg/m^3	1 ppm = 1.8 mg/m^3
	1 mg/m^3 = 0.4 ppm	1 mg/m^3 = 0.6 ppm

Methylisocyanate (MIC) is a monoisocyanate. At room temperature it is a clear liquid. MIC is sparingly soluble in water, although on contact with water it reacts violently, producing a large amount of heat. The speed of the reaction depends a great deal on temperature, and is accelerated by acids, bases and amines (50). MIC has a sharp odor and an odor threshold above 2 ppm (13). Isocyanic acid (ICA) above 0 °C is an unstable liquid with a tendency to polymerize. The primary polymerization product – which is also generated in gas form – is the trimer, cyanuric acid. Isocyanic acid is soluble in water, but disintegrates both via ionization and by formation of ammonia and carbon dioxide (10). In gas form it has a sharp odor (54).

Methylisocyanate occurs primarily as an intermediate in the production of carbamate pesticides. It has also been used in the production of polymers (32). Photolytic breakdown of N-methyldithiocarbamate releases some MIC, and it can therefore occur in the air around application of the pesticides (26). MIC is found in tobacco smoke: the measured content in the main stream ranges from 1.5 to 5 μg per cigarette (33). In the laboratory, MIC has also been identified in emissions from heating of core sand and mineral wool, where it results from breakdown or chemical transformation of the carbamide resin binder (42, 46). Exposure measurements made in foundries indicate that MIC occurs primarily where “hot box” cores are used in chill casting (47). MIC occurs in the isocyanate mixture created by thermal breakdown of TDI- or HDI-based polyurethane

lacquers during welding, cutting and grinding operations in automobile repair shops (7, 59). ICA is usually found along with MIC in welding plumes (and also around chill casting), often in concentrations as much as ten times as high. Most information on the occurrence of MIC and ICA is relatively new, since it has only recently become possible to analyze low-molecular monoisocyanates in mixed chemical exposures such as those resulting from thermal breakdown. A method based on sampling in dibutyl amine followed by analysis with liquid chromatography-mass spectrometry (LC-MS) (42) was published in 1998. Several laboratories have since developed methods for analyzing MIC. In another method that has been found applicable, samples are derivatized with 1-(2-methoxyphenyl)piperazine and analyzed using GC-MS; LC and other detectors have also been used successfully (20). A recently published abstract presents a diffusion sampling method for MIC (48). These methods can also be used for analysis of ICA. Because of its instability, however, ICA is not commercially available – a circumstance that makes its quantification difficult.

Uptake, biotransformation, excretion

Massive exposure to MIC was one of the consequences of the disaster in Bhopal, India, in 1984, when about 27 tons of MIC dispersed into a populated area around a Union Carbide plant. There are no precise air measurements, but concentrations were later estimated to have been in the range 0.12 to 85 ppm (17). In subsequent assessments of the injuries, it has been debated whether they were caused indirectly as a result of reduced respiratory function or directly via respiratory uptake and distribution to other organs (13). The question arises from the fact that MIC is a powerful irritant: it is postulated that this may have inhibited normal respiratory uptake and systemic distribution. After Bhopal, animal experiments with radiocarbon-labeled MIC were conducted to clarify this point.

Mice were exposed by inhalation to 0.5, 5 or 15 ppm ^{14}C-MIC for 1 to 6 hours, and uptake and distribution were studied (24). The radioactivity appeared in the blood within a few minutes, but did not show a linear increase with concentration. This was attributed to the greater irritation of higher doses and the resulting formation of mucus in the respiratory passages, which was assumed to affect the respiratory rate and thus inhibit inhalation and uptake in the blood. The highest radioactivity in blood in relation to air concentration was measured after the exposure to 0.5 ppm. Radioactivity in blood dropped gradually after the exposures and was nearly gone within three days. Radioactivity fell more rapidly in urine than in bile. In male mice, the highest levels of radioactivity after 2 hours were found in the lungs, sternum, digestive tract, spleen and kidneys, and after 24 hours in blood and lungs. In female mice, the highest levels of radioactivity after 2 hours were in lungs, fetuses, spleen, uterus and kidneys, and after 24 hours in lungs, spleen and fetuses (24). The effective uptake and distribution is probably due to the *in vivo* binding of MIC to proteins in tissues, blood plasma and erythrocyte membranes. Protein binding has been experimentally verified in mice after both inhalation and intraperitoneal administration of ^{14}C-labeled MIC (11, 12).

Sax (55) mentions, without going into detail, that MIC is absorbed by the skin. No other data on skin uptake were found.

MIC has been observed to cause carbamoylation of N-terminal valine in the hemoglobin of rats and rabbits both *in vivo* and *in vitro* (53), and 3-methyl-5-isopropyl hydantoin (MIH), the cyclic transformation product of MIC and valine, could then be identified in blood. MIH has also been identified in blood from the Bhopal victims (61). S-(N-methylcarbamoyl)glutathione, another reactive conjugate, has been identified in bile from rats given MIC via a catheter in the portal vein (52). In another experiment, the glutathione conjugate in the form of S-(N-methylcarbamoyl)-N-acetylcysteine was identified in urine of rats given MIC intraperitoneally (60).

MIC reacts readily with water, forming methylamine, which further reacts to dimethylurea (72). It is quite likely that some MIC is also transformed *in vivo* to methylamine. No studies were found in which methylamine or dimethyl urea were measured in blood or urine, however.

There is no information on uptake, biotransformation or excretion of ICA. Patients with uremia have elevated concentrations of carbamoylated hemoglobin, which is the reaction product of hemoglobin and isocyanic acid (45, 73). The isocyanic acid is assumed to result from the endogenous breakdown of urea occurring in cases of acute kidney failure.

Toxic effects

Human data

A study made at an industry producing and using MIC presents an examination of lung function data in employee medical records covering a 10-year period (the dates are not given) (8). The employees were divided by their supervisors into four categories based on their estimated exposure to MIC: none (N = 123), low (N = 103), moderate (N = 138) and high (N = 67). The records also contained information on smoking habits. About 800 monitoring measurements of MIC (the method used is not reported) had been made in the 1977 – 1990 period. In 1977 more than 80% of the measurements had exceeded 0.02 ppm, whereas only one of 33 measurements made in 1990 were above this level. The groups were compared, using lung function values from the most recent examination and taking smoking habits into account, and no effect of MIC on lung function could be discerned. Nor was any effect seen when a worker's first examination was compared with his most recent one. Conclusions should be drawn with caution, however, since individuals who developed health problems may have quit (and thus not been examined after the problem arose) and also because there is considerable room for error in the exposure classifications. The medical records also contained information on exposures due to spills or leakage. The authors do not give the number of these cases, but report that the most common symptoms were eye and skin irritation, and in a few cases respiratory problems. No clear effect on lung function was seen in these cases.

Four volunteers were briefly exposed (1 to 5 minutes) to MIC (44) (see Table 1). No effect was noted at an exposure level of 0.4 ppm, but 2 ppm caused irritation of eyes (notably tear flow) and mucous membranes in nose and throat, although no odor was perceived. At 4 ppm the symptoms of irritation were more pronounced, and at 21 ppm they were unbearable.

There are several studies providing information on the 1984 disaster in Bhopal. About 200,000 persons were acutely exposed to high (> 27 ppm) concentrations of MIC, as well as to other substances including phosgene, methylamine and hydrogen cyanide (50). There is thus some doubt as to whether all the observed effects can be attributed to MIC. Because of the nature of the exposure conditions, and because effects on the lungs may have produced secondary effects on other organs, most of the toxicological information from the disaster is of little value in establishing an occupational exposure limit. A brief review of some of the studies is nevertheless presented below.

The acute effects of the Bhopal disaster have been compiled. It is estimated that about 2000 people died within the first few hours. The reported cause of death is alveolar necroses combined with ulcerations in bronchial mucosa and pulmonary edema (71). In one study, 379 survivors were divided into eight groups on the basis of their degree of exposure, as estimated from the numbers of dead (both humans and animals) near their homes and the hypothetical spread of the toxic cloud. There were 119 controls with similar socioeconomic backgrounds. The number of dead was estimated to be 1850 in an area that was assumed to represent 70% of the total area contaminated by the gas. The symptom most commonly reported on the questionnaire given to the surviving victims was smarting eyes, followed by coughing, persistent tear flow and nausea. The prevalence of eye symptoms showed no correlation to the proportion of deaths nearby, but the reports of coughing did show such a correlation. Redness and superficial sores on corneas and conjunctiva were observed in eye examinations (5). Since amines can cause eye damage (35), the relevance of MIC here can not be assessed with certainty.

Kamat *et al*. (41) followed 113 patients who had been referred to their pulmonary medicine and psychiatric clinics for persistent respiratory symptoms in the three months following the disaster. The patients (with 23 - 50% attrition from the original cohort) were followed up at 3, 6, 12, 18 and 24 months, using a standardized questionnaire, physical examinations, lung x-rays, spirometry etc. The report is difficult to interpret, but it appears that a patient's condition was initially classified on the basis of the number and severity of respiratory symptoms: mild for 30 patients, moderate for 57, and severe for 26. The respiratory symptoms had regressed somewhat at 3, 6, and 12 months, but increased again at 18 and 24 months. Shortness of breath with physical exertion was the most persistent. Neurological symptoms such as muscular weakness and forgetfulness increased. The proportion of patients with depression had increased at 6 months and the proportion with anxiety at 12 months. Other symptoms, such as irritability and concentration difficulty, showed declining trends. Only 2 to 4 percent of the lung x-rays were judged to be completely normal. The others

showed changes in interstitial lung tissue and in the pleural sac. Lung function tests revealed possible reductions in lung function, primarily of a restrictive type.

The above study also presents an analysis of antibodies in serum samples from 99 cases (41). These results are more fully described in an earlier report from the same study (43). The initial samples were taken a few months after the disaster, and MIC-specific antibodies were found in 11 subjects: IgM in 7, IgG in 6 and IgE in 4. The antibody titers of some of the subjects were followed for up to a year after the disaster. The rises in antibodies were small, and in most cases later samples were negative. The small elevations in IgE antibodies were seen only on the first sampling occasion (41, 43). The data on antibodies are difficult to assess, since the documentation is poor and the articles contain inconsistencies.

Another research group made similar examinations of lung function in Bhopal victims one to seven years after the disaster (70). The material consisted of 60 persons, 6 of whom were judged to have had low exposure (slight irritation of eyes and respiratory passages on the day of the disaster), 13 moderate exposure (respiratory symptoms, eye irritation that did not require hospitalization), and 41 high exposure (respiratory and eye symptoms severe enough to require hospitalization and/or death of a family member as a result of the exposure). There was also an unexposed control group. The most commonly reported symptoms were shortness of breath on physical exertion and coughs. BAL samples taken one to seven years (average 2.8 years) after the disaster showed elevations of total cell counts, macrophages and lymphocytes in the high-exposure group, statistically significant when compared with the low-exposure group and controls.

Permanent damage to the respiratory passages was reported in a follow-up study made 10 years after the disaster (16). Questionnaires were distributed to 454 persons chosen on the basis of residence within a radius of 2, 4, 6, 8 or 10 kilometers from the plant. The control group comprised persons of the same socioeconomic background who lived in an area outside the city. From the cohort, 20% were randomly chosen for spirometry tests; this group ultimately contained 74 persons. The occurrence of specific respiratory symptoms – mucus formation, cough, rales etc. – could be clearly related to the exposure level derived from the distance between the victim's home and the site of the disaster (from 0-2 km to >10 km). The symptoms were equally prevalent among men and women, and more common among persons below 35 years of age (median value for the entire group) and among smokers than non-smokers. The same trend could be discerned in the results of lung function tests, which showed mild obstructive reductions in lung function that increased with proximity to the plant. This trend became a bit less clear when smoking habits and socioeconomic factors were included in the calculations.

In a follow-up study of effects on eyes, no cases of blindness or impaired vision were found 2 months after the event (6). Of a total of 131 examined cases, six had unilateral scars on the cornea, three had corneal edema and one complained of constantly running eyes. After 3 years, 463 were examined, 99 of whom were controls. Compared with controls, the victims of the Bhopal disaster had higher

frequencies of eye irritation, eyelid infections, cataracts, trachoma and loss of visual acuity, which increased with increasing exposure (4).

One year after the disaster, a study of cognitive function was made on a group of 52 victims (51). They were grouped into three exposure classes on the basis of symptoms and distance from the plant. Compared with controls, normal performance values were seen in the least-exposed group, whereas in the other two groups the values deviated significantly for "associate learning" and motor ability. In the most exposed group there were also lower values on the Standard Progressive Matrix (SPM), a test that measures ability to think logically. Clinical indications of central, peripheral and vestibular neurological damage, as well as impaired short-term memory, were also seen in another study of the Bhopal victims (15). In interviews, they reported more psychological symptoms such as headaches, fatigue, concentration difficulty and irritability than controls. The symptoms did not always increase with exposure. The exposure estimates can be questioned in both these studies of CNS effects, and in the latter article there is some discussion of the difficulty of taking socioeconomic differences into account in assessing the results. The authors also suggest that persistent depressions may be a factor contributing to the other symptoms.

Asthma resulting from exposure to MIC has not been reported.

For ICA, there are no data regarding toxic effects on humans.

Animal data

The calculated LD_{50} for rats given MIC subcutaneously is 329 mg/kg body weight. The LC_{50} for 30 minutes of exposure was 465 ppm (1080 mg/m^3) (38). The LC_{50} for 15 minutes of exposure to MIC has been reported to be 171 ppm for rats and 112 ppm for guinea pigs (19). The reported LC_{50} for 3 hours of exposure is 26.8 ppm for mice (68).

The RD_{50} for mice (the dose that causes a 50% decline in respiratory rate), a measure of sensory irritation (effects on the trigeminus nerve via the upper respiratory passages), was estimated to be 1.3 ppm in one study (23), and 2.9 ppm in another (34). The RD_{50} for pulmonary irritation (stimulation of the vagus nerve cells via type J receptors in the alveoli) was 1.9 ppm for mice exposed via tracheal catheters (23).

Irritation of the upper and lower respiratory passages is the most commonly reported effect in all animal experiments. When rats were exposed to 0, 3, 10 or 30 ppm MIC for 2 hours, effects on lung function increased with concentration. No abnormal changes of lung function were observed at exposure to 3 ppm MIC, but exposure to 10 ppm caused obstructive changes in respiratory passages which did not regress during the following 13 weeks (62). Lung damage was seen in rats exposed to 3 or 10 ppm MIC for 2 hours and examined 4 and 6 months later. At 4 months there were ECG changes in both dose groups, and right ventricular hypertrophy was also seen in the high-dose group (not examined at 6 months). The authors suggest that the hypertrophy and the ECG changes were probably secondary effects of the lung damage with pulmonary hypertension (63). A LOAEL (Lowest Observed Adverse Effect Level) of 3.1 ppm for damage to

respiratory epithelium was reported in a study in which rats were exposed by inhalation to 0, 0.15, 0.6 or 3.1 ppm MIC 6 hours/day for 4 + 4 days. The NOAEL (No Observed Adverse Effect Level) in this study was 0.6 ppm (18).

Six hours of high exposure – above 4.4 ppm for guinea pigs, above 4.6 ppm for rats and above 8.4 ppm for mice – resulted in damage to the upper respiratory passages of all three species: necrosis and erosion of epithelial cells in the larynx and trachea, and alveolitis, hemorrhages and inflammation in lungs (25). The changes disappeared within a week. When rats were exposed to 128 ppm (320 mg/m^3) MIC 8 minutes/day for 10 days, the exposure induced progressive cellular inflammation with increase of eosinophils, neutrophils and mononuclear cells (28). Guinea pigs exposed for 3 hours to 19 or 37 ppm MIC had lung changes of the same types reported earlier in the victims at Bhopal (22).

In one study (14), F344 rats and $B_6C_3F_1$ mice were exposed by inhalation to 0, 1, 3 or 10 ppm MIC for 2 hours, and then observed for 2 years. Survival and weight gain were normal in all exposure groups. Definite effects on the lungs, particularly proliferation of the connective tissue layer below the respiratory epithelium and connective tissue invasion in the lumen of the respiratory passages, were observed in the rats exposed to 10 ppm. Similar damage was seen in another group of rats exposed to 10 ppm MIC and examined one year later.

Rats and mice exposed to 10 or 30 ppm MIC for 2 hours had severe necrosis and damage on most of the nasal mucosa, including the olfactory cells. Both epithelial and olfactory cells regenerated rapidly, however, and had returned to normal within 3 months (66).

In a National Toxicology Program (NTP) study (31), mice were exposed to 1 or 3 ppm MIC 6 hours/day for 4 days. Histopathological examination after the exposure to 3 ppm revealed pronounced fibrosis in bronchi, with intraluminal fibrosis and damage to olfactory epithelium. The 1 ppm exposure caused damage to respiratory epithelium (not more fully described). Myelotoxic effects on stem cells were also observed at both exposure levels, but they were judged to be a secondary effect of the damage to the respiratory system.

Immunological effects of MIC have been examined in some studies (43, 65). A slight increase of immunoglobulin levels was measured in rats after exposure to MIC (56). MIC demonstrated a slight immunosuppressive effect in an NTP study with mice (65). Mice were exposed to 1 or 3 ppm MIC 6 hours/day for 4 days, and slightly reduced mitogen-stimulated lymphocyte proliferation was observed at both doses; at the higher dose there was also a significantly lower response on MLR (Mixed Leukocyte Response) tests. The reduction was temporary and had disappeared after 120 days. The authors regard these effects as secondary, resulting from toxic effects on the lungs or general toxicity, rather than a direct effect of MIC on the immune system.

Systemic effects of MIC observed in exposed rats are severe hyperglycemia, metabolic acidosis and uremia (11, 36, 38). Exposure of mice or rats to MIC concentrations in the range 3 to 30 ppm, either intraperitoneally or via inhalation, has caused temporary degenerative changes in blood cells and cells in liver parenchyma (29). In a study with mice, intraperitoneal injections of 293-1170 mg

MIC/kg body weight had effects on amino acid concentrations (stimulating on glutamate and aspartate, inhibiting on GABA) in the brain and plasma. This was regarded as an indication of neurotoxic and systemic effects (30). *In vitro* studies have shown that MIC affects both brain and muscle cells, but the clinical relevance of this finding is not clear (2, 3).

There are only a few studies of the toxic mechanisms of MIC. *In vitro* and *in vivo* studies with cells from hepatic and nervous tissue of rats indicate that MIC can inhibit the respiratory chain in mitochondria, and thus induce histotoxic hypoxia (39, 40). This effect was also observed in another study, in which guinea pigs were exposed to 25, 125 or 225 ppm and rats to 100, 600 or 1000 ppm MIC for 15 minutes (64). MIC also exerts a dose-dependent inhibition of acetylcholinesterase activity *in vitro* in erythrocytes from humans, rats and guinea pigs (37, 64).

There are no data from animal studies on toxic effects of ICA.

Mutagenicity, carcinogenicity, teratogenicity

MIC showed no mutagenic activity in standard Ames' tests (58). Negative results were also obtained in Ames' tests with urine from rats exposed to MIC (1) and in a sex-linked recessive lethal test with *Drosophila* (58). In the same study, positive results were obtained for point mutations in the mouse lymphoma test. The authors conclude that MIC may be genotoxic by binding to nuclear proteins. MIC has induced chromosome aberrations and polyploidy in hamster fibroblasts both with and without metabolizing systems (49). Persons exposed to MIC and other substances during the Bhopal disaster had higher frequencies of chromosome aberrations than unexposed controls (27).

No neoplastic changes in respiratory organs were observed in a study (14) in which F344 rats and $B_6C_3F_1$ mice were exposed by inhalation to 0, 1, 3 or 10 ppm MIC for 2 hours and subsequently observed for up to 2 years. In the male rats exposed to 3 or 10 ppm there were elevated incidences of pheochromocytomas in adrenal cortex and acinous tumors in pancreas. This study is not a conventional cancer study, and the authors point out that the correlation to exposure is weak and that no conclusions should be drawn on the basis of their observations.

Judging from structure-activity correlations, the carcinogenic potency of MIC should be low (21). There are no mutagenicity, carcinogenicity or teratogenicity studies with long-term exposures to MIC.

A dose-dependent absorption of fetuses was observed in mice exposed to 2, 6, 9 or 15 ppm MIC for 3 hours on the eighth day of gestation. There was total resorption in more than 75% of the females exposed to the two highest doses, and reduced fetus and placenta weights were observed at all dose levels. The authors suggest that the maternal toxicity (weight loss, reduced weight gain) may have caused the observed effects (67). In a later study it was shown that treatment with hormones that counteract certain effects of the maternal toxicity (but not e.g. weight loss) did not counteract the effects on the fetuses (69). In another study, mice were exposed to 1 or 3 ppm MIC 6 hours/day on days 14 to 17 of gestation.

There were significant increases in the numbers of dead fetuses in both groups, and lower neonatal survival in the high-dose group. The authors caution against drawing conclusions on whether the fetotoxicity was a direct effect of MIC or was secondary to the effects on the lungs of the mothers (57).

Studies of victims of the Bhopal disaster revealed that mothers exposed to MIC had higher numbers of miscarriages, but not stillbirths, than unexposed controls (9). In a controlled study, Cullinan *et al.* (15) reported an increase in stillbirths (exposed 9%, unexposed 4%) and miscarriages (year of disaster 7%, later years 1%), but the study covered few cases.

There are no data on mutagenicity, carcinogenicity or teratogenicity for ICA.

Dose-effect / dose-response relationships

Despite the Bhopal disaster and the facts that MIC is chemically related to more thoroughly studied substances such as toluene diisocyanate and is an extremely toxic substance, the literature on which to base a critical effect or a dose-response relationship is scanty. No reliable studies on the relationship between occupational exposure to MIC and effects on health were found. There is only one study on dose-response relationships for humans. Results from animal studies suggest that dose-effect and dose-response curves are steep.

Irritation of eyes and mucous membranes has been described in human subjects after short-term exposures to MIC. In one study, volunteers were exposed to MIC for 1 to 5 minutes: at 0.4 ppm no irritation was reported, but irritation of eyes and mucous membranes increased markedly at 2 and 4 ppm, and was unacceptable at 21 ppm (see Table 1).

Irritation of upper and lower respiratory passages has been described in studies with rats, mice and guinea pigs. Permanent lung damage has been reported at higher doses (Table 2). The exposure-effect relationships observed in laboratory animals exposed by inhalation to MIC are summarized in Table 2.

There are no data on which to base an estimate of dose-effect or dose-response relationships for ICA.

Table 1. Effects on four volunteers exposed to MIC in an exposure chamber for 1 to 5 minutes (44).

MIC concentration	Effects
21 ppm	Unendurable irritation
4 ppm	Severe irritation of mucous membranes
2 ppm	Tear flow, irritation of eyes, nose and throat
0.4 ppm	No irritation

Table 2. Effects on laboratory animals exposed by inhalation to MIC.

Exposure	Species	Effect	Ref.
171 ppm, 15 min.	rat	LC_{50}	19
121 ppm, 15 min.	guinea pig	LC_{50}	19
12.2 ppm, 6 hours	mouse	LC_{50}	25
10 ppm, 2 hours	rat	Proliferation of connective tissue below respiratory epithelium with intrusion into respiratory lumen	14
10 ppm, 2 hours	rat	Right ventricular hypertrophy, ECG changes secondary to lung damage	63
9 ppm, 3 hours day 8 or 9 of gestation	mouse, rat	Over 80% of fetuses resorbed, reduced placenta weights	67
6.1 ppm, 6 hours	rat	LC_{50}	25
5.4 ppm, 6 hours	guinea pig	LC_{50}	25
3.1 ppm, 6 hours/day, 4 + 4 days	rat	Damage to respiratory epithelium, weight loss, pulmonary edema, increase in hemoglobin (males)	18
3 ppm, 6 hours/day, 4 days	mouse	Bronchial fibrosis, damage to olfactory epithelium	31
3 ppm, 2 hours	rat	ECG changes due to lung damage	63
3 ppm, 2 hours	rat	No changes in lung function	62
2.9 ppm, 30 min.	mouse	RD_{50} (sensory irritation)	34
2.4 ppm, 6 hours	mouse, rat, guinea pig	Retarded weight gain	25
1.9 ppm, 90 min. (via tracheal catheter)	mouse	RD_{50} (pulmonary irritation)	23
1.3 ppm, 90 min.	mouse	RD_{50} (sensory irritation)	23
1 ppm, 6 hours/day 4 days	mouse	Damage to respiratory epithelium	31
0.6 ppm, 6 hours/day 4 + 4 days	rat	No effect on respiratory passages, weight or hemoglobin levels	18

Conclusions

Judging from the data from brief exposures of human subjects, the critical effect of exposure to MIC is irritation of eyes and mucous membranes, which occurs at 2 ppm. In animal experiments exposure to similar levels for up to 6 hours results in severe damage to mucous membranes in respiratory passages. At somewhat higher levels there is a steep increase in mortality.

There are no data which would serve to establish a critical effect for ICA.

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Consensus Report for Methylisoamylketone

February 6, 2002

This report is an update of the Consensus Report published in 1992 (6).

Chemical and physical data. Uses

CAS No.:	110-12-3
Synonyms:	5-methylhexane-2-one 5-methyl-2-hexanone isoamylmethylketone isopentylmethylketone methyl isoamyl ketone MIAK
Formula:	$CH_3COCH_2CH_2CH(CH_3)_2$
Molecular weight:	114.19
Boiling point:	144 °C
Melting point:	- 73.9 °C
Flash point (closed cup):	43 °C
Density:	0.813 g/ml
Vapor pressure (20 °C):	0.2 kPa (6); 0.6 kPa (10)
Saturation concentration:	5900 ppm (20 °C)
Solubility in water:	5.4 g/liter
Conversion factors (20 °C):	1 mg/m^3 = 0.211 ppm 1 ppm = 4.74 mg/m^3

MIAK is a clear, flammable liquid with a sharp, sweetish odor. The odor threshold has been reported to be 0.01 (11) and 0.18 ppm (3). The latter value was calculated with QSAR (Quantitative Structure-Activity Relationship). The substance is soluble in alcohol and ether and somewhat soluble in water (10). It is used as a solvent for nitrocellulose, cellulose acetate, and acrylic and vinyl copolymers (11).

Uptake, biotransformation, excretion

Uptake of MIAK via inhalation and oral administration has been studied in rats. With six hours of inhalation exposure to 1950 ppm, the highest concentration in blood (138 μg/ml) was measured after 4 hours, and with single oral doses of 1830 mg/kg body weight (b.w.) the highest blood concentration (94 μg/ml) was seen

after 1 hour. The half time in blood was 0.7 hours after the inhalation exposure and 5.3 hours after the oral dose (5). Skin uptake is indicated by an LD_{50} for dermal exposure (8), but this study provides no uptake data. The water/air distribution coefficient for MIAK is reported to be 240 (1) and that for octanol/water is given as 52.5 in one work (3) and as 75.9 in another (9).

Toxic effects

MIAK has fairly low acute toxicity. The reported LD_{50} for oral administration to rats and mice is in the range 2542 – 4760 mg/kg b.w. (8, 9, 11), and the reported LD_{50} for skin application to rabbits is 8130 mg/kg b.w. (8). An LC_{50} somewhere between 2000 and 4000 ppm is reported in an inhalation study with rats (4 hours of exposure: 0/6 rats died at 2000 ppm; 6/6 died at 4000 ppm) (8). An unpublished study with rats (cited in Reference 10) gives a calculated LC_{50} of 3813 ppm for 6-hours of exposure. The same study reports that 6-hour exposures resulted in eye irritation, narcosis, reduced respiratory rates and a death (1/4) at 3200 ppm, effects on the central nervous system (reduced response to noise) at 1600 ppm, and no discernible effects at 800 ppm (10).

The RD_{50} (50% reduction of respiratory rate due to sensory irritation in the upper respiratory passages) for mice exposed to MIAK by inhalation is reported in one study to be 1232 ppm for 5 minutes (Muller & Greff 1984, cited in Reference 7). In another study, inhalation of 416 to 1515 ppm MIAK for 15 minutes was found to reduce the respiratory rates of mice by 27 to 61%, and the RD_{50} was calculated to be 1222 ppm (2). The reported nasal irritation threshold for people exposed to MIAK, calculated with QSAR, is 2042 ppm (3).

Effects on the nervous system, measured as reduction in total duration of inactivity during 3 minutes of swimming (the“behavioral despair swimming test”), were reported in mice after 4 hours of whole-body exposure to 270 – 637 ppm MIAK. The lowest exposure level (270 ppm) yielded a 26% reduction in the total duration of inactivity, and the ID_{50} (the air concentration causing a 50% deterioration in test performance) was calculated to be 446 ppm (2). The relevance of this swimming test in assessing toxicity, however, is unclear (11).

In an inhalation experiment, rats were exposed 6 hours/day, 5 days/week (12 exposures in 16 days) to 970 or 2090 ppm MIAK. CNS effects – slight lethargy and lower aural response – were observed during the higher exposure. There were also dose-dependent increases in absolute (not significant in males) and relative liver weights, higher relative kidney weights (not significant in females at 2090 ppm), and, in males, histopathological changes (hyalin degeneration or hyalin droplet formation) in epithelial cells in renal ducts. No indications of liver or kidney damage were seen in clinical/chemical analysis, however (5). When rats were exposed on the same schedule to 210, 1030 or 2080 ppm MIAK for 96 days (69 exposures) a dose-dependent CNS effect was initially seen at the two higher dose levels. Slight lethargy and lower aural response were observed later, but only at the highest air concentration. Porphyrin-like discolorations around the eyes, nose and mouth (regarded as indications of slight irritation), as well as significant,

dose-dependent increases of absolute and relative liver weights, were also seen at the two higher dose levels. Histopathological examinations revealed dose-dependent liver changes, including minimal to moderate hypertrophy of hepatocytes and, in males, also minimal to mild necrosis. Effects on kidneys were seen primarily in males. Indications of mild/moderate regeneration of epithelium in renal tubules were seen at the two higher dose levels, though at 1030 ppm only in males. Males in the highest dose group also showed indications of possible increase in hyalin drop degeneration in the proximal convoluted tubules. Significantly higher absolute and relative kidney weights were reported in males at the two higher doses, and increased relative kidney weights in females at the highest dose, although clinical-chemical examination revealed no indications of liver or kidney damage. The NOEL in this study was 210 ppm (5).

An unpublished inhalation study reports that no exposure-related effects were seen in rats after exposure to 400 ppm MIAK 6 hours/day, 5 days/week (12 exposures). The same report describes effects observed when the animals were given MIAK by gavage in doses of 1000, 2000 or 4000 mg/kg body weight, 5 days/week for 3 weeks. The highest dose resulted in CNS depression and all the animals died within 1.5 hours. Effects seen at 2000 mg/kg included chronic irritation of stomach lining, hypertrophy of hepatic cells and hyalin drop formation in kidneys. The only observed effect at 1000 mg/kg was slight irritation of the stomach lining. It is also reported that oral administration of 2000 mg/kg b.w./day to rats 5 days/week for 13 weeks resulted in somewhat elevated levels of hepatic enzymes, increased absolute and relative liver and adrenal weights, higher relative kidney weights and histopathological changes in the liver (degeneration, hypertrophy, hyperplasia) and stomach lining (chronic irritation) (10).

Undiluted MIAK applied to the skin of rabbits caused no irritation within 24 hours: changes were ranked 1 on a 10-point scale. In the same study, MIAK applied to eyes of rabbits was ranked 2 (8).

Mutagenicity, carcinogenicity, effects on reproduction

No data were found in the literature.

Dose-effect / dose-response relationships

Kane *et al*. (4), in a study of various irritating substances (not including MIAK), found that the RD_{50} levels for mice often produce intolerable irritation in the eyes and upper respiratory passages of humans, and that an air concentration equivalent to 10% of the RD_{50} for mice usually causes some irritation in humans. A good agreement has also been shown between the ACGIH threshold limit values (1991) based on sensory irritation and air concentrations equivalent to 3% of the RD_{50}, i.e. the value midway between 1% and 10% of the RD_{50} on a logarithmic scale (7). Dose-effect relationships documented in experimental animals exposed to MIAK by inhalation are summarized in Table 1. The RD_{50} for mice is reported to be about 1200 ppm, and a 27% reduction in respiratory rate is observed at about

Table 1. Effects observed in experimental animals exposed to MIAK by inhalation.

Exposure	Species	Effects	Ref.
2090 ppm, 6 hours/day, 5 days/week (12 exposures)	Rat	Slight lethargy, reduced aural response; somewhat elevated liver and kidney weights; histopathological changes in kidneys of males.	5
2080 ppm, 6 hours/day, 5 days/week (69 exposures)	Rat	Lethargy, reduced aural response; somewhat elevated liver and kidney weights; histopathological changes in liver and kidneys; slight irritation of eyes and respiratory passages.	5
1232 ppm, 5 minutes	Mouse	RD_{50}	7
1222 ppm, 15 minutes	Mouse	RD_{50}	2
1030 ppm, 6 hours/day, 5 days/week (69 exposures)	Rat	Slight lethargy, initially reduced aural response; somewhat elevated liver and kidney weights; histopathological changes in liver, and in males also in kidneys. Slight irritation of eyes and respiratory passages.	5
970 ppm, 6 hours/day, 5 days/week (12 exposures)	Rat	Somewhat elevated liver and kidney weights; histopathological changes in kidneys of males.	5
416 ppm, 15 minutes	Mouse	27% reduction in respiratory rate.	2
210 ppm, 6 hours/day, 5 days/week (69 exposures)	Rat	No exposure-related effects.	5

400 ppm (2, 7). In a relatively large study with effects on liver, kidneys and CNS as well as irritation, the NOEL was reported to be 210 ppm (5).

Conclusions

There are no data for human exposures on which to base a critical effect for occupational exposure to MIAK. Limited data from animal experiments indicate that the critical effect of short-term exposure is irritation of mucous membranes in respiratory passages.

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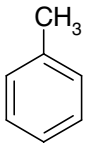
Consensus Report for Toluene

February 6, 2002

This report is based primarily on a criteria document from the Nordic Expert Group (162). The Criteria Group has previously published a consensus report for toluene in 1981 (137).

Chemical and physical data. Uses.

CAS No.:	108-88-3
Synonyms:	methyl benzene, phenyl methane, toluol, methyl benzol, methacide
Molecular formula:	C_7H_8
Structure:	
Molecular weight:	92.13
Boiling point:	110.6 °C
Melting point:	-95 °C
Density:	0.876 g/ml (20 °C)
Vapour pressure:	3.73 kPa (20 °C)
Saturation concentration:	142,000 mg/m^3 (25 °C)
Conversion factors (25 °C):	1 ppm = 3.75 mg/m^3 1 mg/m^3 = 0.267 ppm

Toluene is a high production volume substance, and millions of tonnes are used yearly. Toluene at room temperature is a clear colourless liquid with unpleasant aromatic odour. The odour thresholds reported in various studies range from 1.5 to 262.5 mg/m^3 (2, 43, 121). The reason for the variability in the reported odour threshold is unknown. However, toluene can be detected in air in concentrations at the lower end of the reported odour threshold range. In a volunteer study, increased odour level was perceived at the lowest concentration tested, 37.5 mg/m^3 (3). Toluene is only slightly soluble in water, approximately 6.5 mmol/l at 20 °C. Toluene is soluble in acetone and carbon disulphide, and miscible with most ethers, ketones, alcohols, esters, and aliphatic and aromatic hydrocarbons. Toluene forms azeotropic mixtures with many of the solvents mentioned above. Toluene is used as a solvent in a number of products such as bitumen, tar, paints, lacquers, greases, and natural and synthetic resins. Workers in the chemical industry and paint industry, and workers using products containing toluene (e.g.

painters) may be occupationally exposed. The main exposure to toluene occurs by inhalation of vapours and liquid aerosols and via dermal exposure to liquids. Within production of toluene in the chemical industry, a reasonable worst case short term exposure level is 100 mg/m^3, while the typical full shift exposure level is low, 3 mg/m^3. For production of toluene-containing products, a reasonable worst case short term exposure level is 200 mg/m^3, while the typical full shift exposure level is low, 4 mg/m^3. Occupational use of toluene-containing products can lead to high exposure levels. For use of toluene-containing adhesives and inks the typical full shift exposure level is 75 mg/m^3. These values derive from the EU risk assessment of toluene (24).

Uptake, biotransformation, excretion

The major route of exposure to toluene is inhalation of vapour. Data from experimental exposure of voluntary study subjects show that physical work results in increased toluene uptake (16, 146). Using a 50 W work load, exposure to 300 mg/m^3 (80 ppm) toluene for 2 hours did not result in steady state of the blood concentration of toluene in 12 study subjects. The toluene uptake was 2.4 times higher than the uptake at rest. During the work, lung ventilation increased 2.8 times. Concentrations of toluene in alveolar air and blood increased with increasing work loads (0-150 W in periods of 30 minutes) (16). However, at higher workloads the proportion of toluene taken up decreased (only 29% at 150 W compared with 52% at rest), indicating that the uptake is limited by the rate of removal of toluene from the lungs via blood (77). The amount of toluene absorbed increased with larger amounts of body fat (17). In nine male volunteers exposed to 200 mg/m^3 (53 ppm) toluene for 2 hours during a workload of 50 W the total uptake of toluene was 50% of that inhaled (78).

The steady state dermal penetration rate of neat toluene has been reported to be 14.5 nmol/cm^2/min (80 μg/cm^2/h) (145) using human skin *in vitro*. Similar values of 8.5 and 12.5 nmol/cm^2/min have been reported from animal experiments (140, 141). Applying the ECETOC criteria for skin notation (26), i.e. exposure of 2,000 cm^2 of skin (approximately corresponding to the skin of the hands and forearms) for 1 hour (equivalent to exposure of 250 cm^2 skin or 70% of one hand for 8 h) and using the above human data a dermally absorbed dose of 1.7 mmol toluene is obtained. This corresponds to 16% of the amount absorbed during 8-h inhalatory exposure at 50 ppm (10.8 mmol). The inhalation uptake was calculated assuming exposure at the present Swedish OEL (50 ppm, 8-h TWA), 10 m^3 inhaled air during 8 hours and a pulmonary retention of 50%. In conclusion, dermal exposure to liquid toluene may result in significant systemic exposure.

Experiments with volunteers indicate that upon whole body exposure to toluene vapour, the dermal route contributes to about 1-2% of the systemic exposure (10, 103, 116).

Toluene appears to be well absorbed after oral exposure (162).

Toluene is widely distributed in body tissues, including the placenta, and has high affinity to adipose tissue. In humans the adipose tissue/blood partition coefficient of toluene is 81-83 (123, 124).

Biotransformation of toluene occurs mainly by oxidation in the liver. About 20% of the absorbed toluene is eliminated unchanged in the expired air. Of the remaining 80%, approximately 99% is oxidised via benzyl alcohol and benzaldehyde to benzoic acid. The remaining 1% is oxidised in the aromatic ring, forming ortho-, meta- and para-cresol (157, 158). Benzoic acid is linked to glycine forming hippuric acid, which is excreted in the urine.

Elimination curves for toluene in blood from exposed workers was found to contain at least three exponential components with median half-lives of 9 minutes, 2 hours, and 90 hours, the latter value reflecting the decline of toluene in adipose tissue (94). The half-life of toluene in human adipose tissue is about 3 days (17). The time period during which accumulation occurs can be calculated by multiplying the half-life by 5, i.e. about 15 days, after which steady-state is reached. The conclusion therefore is that although there is some accumulation of toluene it is not an accumulative substance as such compared with, e.g. PCBs, which have a half-life of several years.

Biological measures of exposure

Measurement of toluene in blood, urine and exhaled air provide reliable markers of exposure to toluene. Measurement of toluene metabolites is also utilised for monitoring toluene exposure in humans. Hippuric acid is formed in the body when toluene is metabolised. High performance liquid chromatography (HPLC) with ultraviolet detection is usually used for detection of hippuric acid in urine. Other metabolites such as o-cresol, benzylmercapturic acid, or S-p-toluylmercapturic acid may also be measured (143). A good correlation was found between toluene exposure (air concentration multiplied by time) and concentration of hippuric acid in post exposure urine. However, a background level of hippuric acid is present in human urine, as a product of endogenous metabolism, and of metabolism of substances present in food. In the Western part of the world, at exposure levels below 100 ppm (375 mg/m^3) hippuric acid in post exposure urine cannot be used to separate an exposed person from an unexposed one because the difference between the background level and the toluene-generated level is too small (74). However, hippuric acid background levels in urine vary geographically. In some countries (e.g. Taiwan and Croatia) a low urinary hippuric acid background level is found. Thus, in these parts of the world it is possible to use this metabolite as a biological marker for toluene exposure even at exposure levels lower than 100 ppm (19, 143, 147, 149).

Toxic effects

Human data

Toluene has a degreasing effect on the skin. After repeated exposures, irritative contact dermatitis may develop (11, 38, 153). A five-minute exposure to 1.5 ml toluene on a skin surface area of 3.1 cm^2 caused marked erythema and increased blood flow measured by laser Doppler flowmetry (151). Studies in human volunteers exposed at rest show that deterioration in the air quality and increased odour level is perceived around 10 ppm (37.5 mg/m^3), while complaints of eye irritation start at air concentrations around 100 ppm (375 mg/m^3) (3, 27). Kidney damage has been described as a consequence of high exposure levels in relation to workplace accidents or abuse (114, 120, 143). Three older occupational studies did not show a relation between toluene exposure and kidney damage (4, 34, 93). In a recent longitudinal study of 92 photogravure printers and 74 referents, it was concluded that toluene at 50 ppm (187.5 mg/m^3) was not related to detectable renal dysfunction assessed on the basis of various markers in blood and urine (131).

Acute neuropsychological effects of toluene has been investigated in a number of studies in volunteers (3, 12, 13, 20, 27, 28, 53, 58, 112, 154). Headache, dizziness, feeling of intoxication, irritation and sleepiness were reported in several of the studies at toluene concentrations in the range of 75-150 ppm (281 mg/m^3-562.5 mg/m^3). In one study, headache, eye irritation and increased number of sleeping episodes occurred at 75 ppm (281 mg/m^3) and above (27). At 150 ppm in the same study, function in performance tests was impaired. As concentrations below 75 ppm were not tested, this study does not provide a NOAEL (no observed adverse effect level). Because of various limitations and uncertainties in design and reporting, this study is not considered for further use.

Another study (3) reports that concentrations up to 40 ppm did not result in any adverse effects. In this study, 100 ppm was a LOAEL (lowest observed adverse effect level) for irritation of the eye and nose, headache, dizziness, feeling of intoxication, and a feeling that performance tests were more strenuous. Six out of 16 subjects did not report any irritation during the 100 ppm exposure, i.e. 10 subjects did experience irritation. The highest individual estimation was 64 on a scale with a maximum value called strong irritation (=100). The irritation was felt just after the exposure began and was constant throughout the exposure day.

Disruption of performance of complex tests and increased response time in simple tests following exposure to 100 ppm for 6 hours (mostly at rest, 30 minutes of moderate exercise during the exposure) was found in six healthy adults in a two-period cross-over experiment where each subject served as his/her own control (112). Effects of lower exposure levels were not studied.

The subjective experience and performance effects of a 6 h toluene-exposure were studied in 43 printers and 43 subjects without previous history of chemical exposure (12). Half of each group of subjects were exposed to air, half were exposed to 100 ppm toluene at rest. Fatigue, irritation of eyes, nose and throat was increased by toluene. Manual dexterity, colour discrimination and visual perception were impaired.

Humans exposed to very high levels of toluene as a result of toluene abuse or industrial accidents may experience serious nervous system effects including fatal CNS depression. Other effects include cerebellar, pyramidal and cognitive dysfunction such as tremor, ataxia and memory impairment. Brain atrophy attributed to toluene exposure has been identified in heavy abusers (8, 32, 74, 75, 122, 143).

A number of cross-sectional studies, in which a toluene-exposed group of workers have been compared with a matched control group, have been published. Unfortunately, exposure data covering the subjects' entire exposure history are generally lacking in these studies, with only recent exposure being reasonably well documented. As the effects observed in these cross-sectional studies may be viewed as the accumulation of effects induced during the entire period of occupational exposure, which is often many years, it is necessary to have information about the whole period in order to identify LOAELs and NOAELs for the effects. It must be assumed that the exposure levels have changed during the years because of changes in industrial operations and hygiene measures. These studies have reported increased prevalence of subjective complaints (fatigue, recent memory failure, concentration difficulty, mood lability, depressive feelings, irritability, headache, dizziness, sleep disturbances, paresthesia, chest oppression, sexual problems) (75, 161), neuropsychological impairments (6, 30, 35, 57), electrophysiological changes (1, 148), and increased prevalence of neurasthenic complaints, short-term memory complaints, and chronic toxic encephalopathy (CTE) (72, 161) in the toluene-exposed group. In the latter study (161), exposure levels in the two rotogravure plants concerned were estimated retrospectively based on personal interviews, previous hygienic measurements and other written reports concerning the working environment (Table 1). These estimates show that irreversible effects may be induced at exposure during many years at concentrations ranging from 40 to 1700 mg/m^3. Even higher concentrations may have been present in previous years.

Table 1. Estimated retrospective exposure levels for toluene at two Swedish rotogravure plants, from Ørbæk and Nise (161).

Year	Retrospective exposure level (mg/m^3)	
	Company A	Company B
-1955	570[a]	1,710
1956-57	1,710	1,710
1958-68	1,710	1,710
1969	950	1,710
1970-72	950	950
1973-74	610	950
1975-76	610	380
1977	610	250
1978-79	300	250
1980-	43	157

[a]Mixed Stoddard solvent exposure in letterpress printing

Two cross-sectional studies in workers indicate that occupational exposure to toluene increases the risk of developing occupational noise-related high-frequency hearing loss (83, 84). In the first study (83) four groups of workers were studied: unexposed (noise level <85 dB(A) and no toluene), noise exposed (noise level 88-97 dB(A) and no toluene); noise plus toluene exposed (noise level 88-98 dB(A) and toluene concentration 281-2250 mg/m^3), and organic solvent mixture exposed (noise level <85 dB(A) and exposure to four solvents). In the second study (84), a group of workers exposed to varying levels of noise and a mixture of toluene, ethyl acetate, and ethanol were studied. The toluene concentration was 0.14 to 919 mg/m^3, and noise levels were in the range of 71-93 dB(A).

In two cross-sectional studies of workers occupationally exposed to toluene the leukocyte count in peripheral blood has been measured (56, 142). A slight positive correlation to toluene exposure was found in one of the studies (142), however, the leukocyte count in the exposed group was within the range of normal values. The other study did not show an association between increased number of leukocytes and toluene exposure.

Animal data

Toluene was found slightly irritating to the skin in rabbits (41), and moderately to severely irritating to the eyes, also in rabbits (42, 132). Toluene-induced skin oedema following repeated topical administration has been measured in rabbits and guinea pigs (150). The mean increase in guinea pig skin-fold thickness was 225% after 10 daily applications. The response in rabbits was similar. No published data have been found regarding skin sensitisation by toluene.

Data from mice suggest that toluene can cause irritation to the respiratory tract at high concentrations (25, 85, 92).

Toluene has low acute toxicity via inhalation and the oral route. In rats, inhalatory LC_{50} values in the range of 20,000-50,000 mg/m^3/6 h (7, 14) and oral LD_{50} values of 5.5-7.5 g/kg have been reported (65, 128, 144, 156, 159). A dermal LD_{50} of 12.4 g/kg has been determined in the rabbit (128). Via the intraperitoneal route LD_{50} values were found to be approximately 2 g/kg for rats and mice (29, 55, 67, 76).

The effect of repeated inhalation has been examined in a number of studies in rats and mice with exposure durations ranging from 15 weeks to 2 years (40, 51). The most relevant studies for the prediction of effects of long-term exposure in man are the 2-year studies. The major effect of toluene identified in rats exposed for 2 years to 600 or 1200 ppm (2250 or 4500 mg/m^3), was toxicity to the olfactory and respiratory epithelium and was found in both males and females at both exposure levels (51).

In other studies specifically examining the effects on the nervous system after inhalation exposure in rats, various changes were found, including brain region volume changes and neurochemical changes. The dose levels varied between 100 and 1500 ppm (375-5625 mg/m^3) (49, 68, 70, 126, 127).

Auditory impairment of toluene-exposed rats has been demonstrated in a number of studies as behavioural and electrophysiological changes at inhalatory

exposure concentrations between 900 and 1400 ppm 14 h/day, 7 days/week, for 5-14 weeks (109, 110, 111, 113). A LOAEL of 1000 ppm (14 h/day, 2 weeks) and a NOAEL of 700 ppm (14 h/day, 16 weeks) was found. Studies on combined exposure to toluene and noise strongly indicate that a synergistic toxic effect of toluene and noise (1000 ppm toluene + 100 dB Leq (62); or 2000 ppm toluene + 92 dB SPL (73)) on auditory functions may exist (62). In rats exposed to toluene plus hexane, each solvent in a concentration of 1000 ppm (3750 mg/m^3 toluene), a synergistic loss of auditory sensitivity was observed after 3 months (97). Toluene exposure causes a progressive severe loss of hair cells in the cochlea (15, 60, 61, 73, 133).

Repeated oral dosing by gavage for 13 weeks caused neurone cell death in the brain in rats that received 2500 or 1250 mg/kg/day (51).

Mutagenicity Carcinogenicity

Toluene is not mutagenic in *Salmonella typhimurium* (9, 21, 47, 52, 59, 88, 89, 130).

Toluene has not been found to induce DNA repair mediated toxicity to any of several bacteria strain tested, gene conversion in the yeast Saccharomyces cerevisiae or genotoxic effects in *Drosophila melanogaster* (59, 79, 80, 81, 87, 88, 117, 118, 155).

Toluene does not appear to induce biologically significant increases in mutations, sister chromatid exchanges, micronuclei or DNA damage *in vitro* in mammalian cells at non-cytotoxic doses (18, 39, 59, 115, 125, 129, 160).

Positive results have been obtained in three cytogenetic studies performed in the former USSR in the 1970's (54). It has, however, been implied that these significant cytogenetic responses might be due to benzene contamination. In more recent studies, toluene has not induced biologically significant increases in micronuclei and chromosomal aberrations in the bone marrow of mice and rats or DNA damage in peripheral blood cells, bone marrow, and liver of mice (37, 59, 81, 82, 105, 119). Toluene can be considered to be adequately tested and is considered non-genotoxic *in vivo*.

Equivocal results were obtained in a multitude of studies with biological monitoring of various genotoxic effects in peripheral blood lymphocytes from workers exposed to toluene in the occupational environment (5, 33, 36, 44, 45, 64, 71, 86, 95, 102, 104, 107). In most cases confounding due to coexposure to ink, other solvents and various genotoxic substances in the environment cannot be excluded. Smoking, estimated to increase chromosomal aberrations by 10-20% and sister chromatid exchange by 5-8% (96), was not considered in some older studies (33, 36), and matching for this confounding factor was inadequate in other studies (95, 102). A clear synergistic effect between toluene exposure and smoking was demonstrated in one study, that is, the genotoxic effect of smoking was enhanced by toluene (45).

Toluene was not carcinogenic in rats or mice exposed via inhalation for two years (40, 51).

Toluene has been used as vehicle control in a number of dermal cancer studies in mice. No clear increase of skin tumours attributable to toluene was noted (54).

The carcinogenic potential of toluene has been evaluated by IARC (54). IARC has evaluated toluene as not classifiable as to its carcinogenicity to humans (IARC Group 3). In the evaluation, four case-control studies involving several anatomical sites of cancer are mentioned. The results could not be evaluated with regard to toluene itself, because the exposure was to mixtures of solvents and not to pure toluene.

A cohort of 1020 rotogravure printers exposed to toluene and employed for a minimum period of three months in eight plants during 1925-85 was studied. Based on the measurements in the 1940's and 1950's the maximum toluene concentration was about 450 ppm, but it was only about 30 ppm in the mid 1980's. Exposure to benzene occurred until the beginning of the 1960's. Compared with the regional rates, total mortality was not increased during the observation period 1952-86. There was no increase in mortality from non-malignant diseases of the lungs, nervous system, or gastrointestinal and urinary tracts. There was no overall excess of tumours in the years 1958-85. Among the specific cancers, those of the respiratory tract increased significantly. However, statistical significance was not attained, when only subjects with an exposure period of at least five years and a latency period of at least 10 years were considered, and no dose-response relationship could be established (135).

The mortality from various cancer forms in a cohort of 6830 male and 751 female workers in the German rotogravure industry has been investigated. Mortality causes were based on death certificates. Because death certificates are removed after five years in many German federal states, the true number of cause-specific deaths was estimated mathematically based on the information on available causes of death. The number of deaths was 466. Total mortality from cancer (100 deaths observed, resulting in 122.7 estimated deaths) did not differ substantially from the expected level of 127.7 deaths. A significantly higher mortality due to bone and connective tissue tumours was identified, based on a low number of cases (7 deaths observed, resulting in 7.9 estimated deaths versus 4.2 deaths expected). Also mortality due to lung+trachea+bronchus tumours (35 deaths observed, resulting in 43.6 estimated deaths versus 35.4 expected deaths), and brain tumours and tumours of the nervous system was increased (6 deaths observed, resulting in 9.1 estimated deaths versus 4.1 deaths expected), but not to a level reaching statistical significance. Exposure information was very limited and based on work area (152).

Reproductive effects

Human data

In two independent studies in rotogravure printers, effects on male hormones were studied. The observed effects were rather small with most hormone levels being within the reference limit. A correlation with present exposure concentrations was found for the levels of some hormones. Although the effects cannot be regarded as

directly adverse, the studies do give evidence that toluene might interfere with endocrine mechanisms (134, 136).

The possible influence of toluene exposure on fertility was examined by retrospective interviews in a German cross sectional study of 150 male and 90 female workers. The findings of the study indicate reduced female fecundity in relation to low-level toluene exposure. The women worked exclusively in the stacking and bookbinding process, and their estimated overall exposure (based on measurements in previous years) was classified as low (<10 ppm) (106). However, due to various limitations, clear conclusions cannot be drawn from this study. Limitations in the study include potential for recall bias, i.e. persons with undesirable outcome may have recall of exposure, which is different from those who do not experience the outcome. More than one pregnancy per woman could be included in the study, and such pregnancies cannot be regarded as independent observations. Furthermore, the study suffered from an unvalidated low participation rate (39% for women). Reasons for non-participation were not investigated.

No evidence of menstrual disorders were found in female workers exposed to toluene at a mean concentration of 88 ppm (330 mg/m^3), range 50-150 ppm, in a factory manufacturing audio speakers compared with an internal (exposed to 0-25 ppm toluene) and an external control group (90).

There have been several case reports of mothers giving birth to children with so-called toluene embryopathy as a result of toluene sniffing during pregnancy. Microcephaly, narrow bifrontal diameter, short palpebral fissures, deep-set eyes, small midface, low-set prominent ears, micrognathia, spatulate fingertips, small fingernails, hypotonia, and hyperreflexia were found in the children. In total about 45 cases have been described in the literature (101). These cases all very much resemble the foetal alcohol syndrome, and there might be a common mechanism.

Among women working in laboratories, spontaneous abortions and congenital malformations and birth weights of the children were examined in a retrospective case-referent study (138). Significant associations with spontaneous abortions were found for frequent exposure to toluene. No association with congenital malformation was found, however, the number of persons in the malformation study was too small for drawing final conclusions.

Rates of spontaneous abortions were determined using a reproductive questionnaire in 55 women with 105 pregnancies exposed to toluene as the only solvent (mean 88 ppm, range 50-150 ppm). 31 women (68 pregnancies) working in the same factory in departments where little or no exposure to toluene occurred (0-25 ppm) answered the same questionnaire. An external community control group of 190 working class women who were receiving routine antenatal and postnatal care in public maternal health clinics with 444 pregnancies were also studied. The workers were exposed to fairly constant concentrations of toluene during the workshift. Exposure to toluene was assessed by passive personal sampling (31, 91). Only abortions from curettage after a diagnosis by a medical practitioner were determined, and spontaneous and induced abortions were clearly distinguished by probing questions as to the reasons for the curettage. Spontaneous abortion was defined by its occurrence after 12 weeks and before 28

weeks of pregnancy. Significantly higher rates for spontaneous abortions were noted in the toluene exposed women compared with those in the internal and external control groups (12.9% vs. 2.9-4.5%). The rate differences between groups were not likely to be confounded by classical risk factors such as maternal age, order of gravidity, smoking, or alcohol, which were taken into account both in the study design and the analysis (91). A weakness in the study is that a few women contributed with a large fraction of all spontaneous abortions (four women contributed with 9 out of 13 spontaneous abortions in the high toluene exposure group), but the employed (fixed effect) statistical models do not account for this dependence between the observations. Use of a fixed effect model leads to an underestimation of the uncertainty of the effect estimates in this context. A more feasible approach would be to use a random effect logistic regression model. However, the difference in spontaneous abortion rates between the high toluene exposure group and the women receiving care at the maternal health clinic is likely to stay significant with the random effect model.

Animal data

In a 15-week inhalation study no toluene-related effects on sperm morphology and vaginal cytology in rats exposed to 100, 625, and 1250 ppm toluene 6.5 h/day, 5 d/week, were found. Significantly and dose-related decreased sperm count and reduced epididymal weight was found in rats exposed via inhalation to a concentration of 2000 ppm (7500 mg/m^3) during 6 h/day for 90 days. The NOAEL was 600 ppm (2250 mg/m^3) (99). Inhalation of high concentrations of toluene (4000-6000 ppm) for 2 h/day for 5 weeks caused reduced sperm count and quality, and reduced *in vitro* egg penetration ability. The exposure was also associated with narcotic effect, lacrimation, ataxia and tremor and reductions in body weight gain (98).

Lower foetal weight, lower birth weight and delayed postnatal development have been reported in a number of studies (23, 46, 48, 50, 100, 139). The LOAELs are in the range of 1000-2000 ppm (3750-7500 mg/m^3). The NOAELs are in the range of 400-750 ppm (1500-2812 mg/m^3). A NOAEL for effects on birth weight and postnatal development of 600 ppm (2250 mg/m^3) can reasonably be set.

Increased spontaneous activity and impairments of cognitive functions (learning and memory) after exposure to toluene during brain development have been found in two studies in rats. In one study, the dams were exposed at 0 or 1200 ppm (4500 mg/m^3) from gestational day 7 to postnatal day 18 (46). In the other study, the dams were exposed to 0 or 1800 ppm (6750 mg/m^3 on gestational day 7-20 (48, 100, 139). In both studies, the behaviour of the offspring was studied. The LOAEL for the behavioural effects is 1200 ppm (4500 mg/m^3) and a NOAEL cannot be established since lower exposure levels were not investigated.

In mice, Courtney *et al*. (22) found some signs of foetotoxicity of toluene at 400 ppm (1500 mg/m^3), the only dose level in this study. Jones and Balster (63) exposed pregnant mice to air, 200, 400, or 2000 ppm toluene on gestational days 12-17 and found lower birth weight, decreased postnatal weight gain, and delayed

reflex development in the absence of maternal toxicity at 2000 ppm toluene (7500 mg/m^3). The NOAEL was 400 ppm (1500 mg/m^3), but the daily exposure periods were limited to 3 hours. Effects on behaviour in the absence of maternal or general toxicity have been reported in mice after perinatal dosing via drinking water with approximately 60 mg toluene/kg/day (69).

In rabbits equivocal effects were found in a study comprising two teratology tests (66). In the first part of the study (n=14) slight delays in skeletal development were registered at 500 ppm (1875 mg/m^3). No effect was observed in the second part of the study at the same exposure level (n=20).

Dose-effect / dose-response relationships

The effects of toluene have been extensively studied in humans and laboratory animals. The key studies for evaluation of the important effects of toluene are listed in Table 2 (human data) and Table 3 (animal data).

Liquid toluene is irritating to the skin and eyes in animals, while toluene vapours in concentrations at and above 100 ppm causes complaints of the eye, and nose and throat irritation in humans.

In the rat, a NOAEL for clinical and morphological signs of toxicity of 300 ppm for repeated exposure via inhalation was identified in a 2-year study. In another 2-year study higher exposure levels (600 ppm) resulted in nasal toxicity and increased incidence of stomach ulcers. For the dermal route, no data on clinical and morphological signs of toxicity have been found.

Toluene has been shown to affect the central nervous system and the inner ear.

In humans exposed at rest under experimental conditions to 100 ppm toluene (375 mg/m^3) headache, dizziness, feeling of intoxication, and irritation were recorded to occur with significantly increased frequency. At 150 mg/m^3 (40 ppm) and below the effects have not been recorded to occur with increased frequency. For these subjective symptoms a LOAEL of 375 mg/m^3 (100 ppm) and a NOAEL of 150 mg/m^3 (40 ppm) can be established.

Experimental chamber inhalation of 375 mg/m^3 (100 ppm) toluene for 6 hours at rest has in two studies been shown to cause disruption of performance of psychological performance tests, and in another study a feeling of tests being more difficult and strenuous. In the latter study, a NOAEL of 40 ppm was found. For acute neuropsychological effects, 100 ppm can be regarded as a LOAEL.

Chronic toxic encephalopathy (CTE) may be induced by toluene exposure during many years at concentrations ranging from 40-1700 mg/m^3. In the study concerned, it is possible that even higher levels were present in earlier years.

Toluene is ototoxic in the rat and causes a progressive severe loss of hair cells in the cochlea accompanied by hearing loss. The LOAEL in rats is around 1000 ppm (3750 mg/m^3), and the NOAEL around 700 ppm (2625 mg/m^3). In humans, occupational exposure to toluene increases the risk of developing noise-related hearing loss. The exposure concentrations in the studies where this has been

Table 2. LOAELs (lowest observed adverse effect levels) and NOAELs (no observed adverse effect levels) from human studies.

Concentration	Exposure duration	Effects	Ref.
40-1700 mg/m^3 10-450 ppm possibly even higher concentrations in years preceding exposure estimation	workplace, > 4-43 years, median 29 years	fatigue, recent short-term memory problems, concentration difficulties, mood lability, reduced psychometric performance	(161)
375-1125 mg/m^3 average exposure levels 1978-1980: 140-600 ppm 1990: 75-365 ppm	Workplace	Increased incidence of high-frequency bilateral hearing loss (in the presence of noise) (51 noise+toluene-exposed, 50 unexposed, 50 noise-exposed, 39 organic solvent mixture exposed)	(83)
375 mg/m^3 100 ppm	6h	LOAEL for impaired function performance of psychological performance tests	(12, 112)
375 mg/m^3 100 ppm	6h	LOAEL for irritation of eyes, nose and throat	(12)
375 mg/m^3 100 ppm	6h	LOAEL for irritation of the eyes and nose, headache, dizziness, and feeling of intoxication NOAEL for psychometric performance (however tests felt more difficult and strenuous) (16 experimentally exposed subjects, serving as their own control)	(3)
300 mg/m^3 range 50-150 ppm (mean 88 ppm)	workplace	Increased rate of spontaneous abortion (55 exposed, 31 internal controls, 190 external controls)	(91)
150 mg/m^3 40 ppm	6h	NOAEL for irritation of the eyes and nose, headache, dizziness, and feeling of intoxikation (16 experimentally exposed subjects, serving as their own control)	(3)
37,5 mg/m^3 10 ppm	6h	LOAEL for deterioration in the perceived air quality and increased odour level (16 experimentally exposed subjects, serving as their own control)	(3)

Table 3. LOAELs (lowest observed adverse effect levels) and NOAELs (no observed adverse effect levels) from animal studies.

Concentraion	Exposure duration	Species and effects	Ref.
30 mg/m^3 8000 ppm	4-6.5h	Rat, lethal (LD_{50})	(7, 14, 108, 128)
3750 mg/m^3 1000 ppm	2 weeks	Rat, LOAEL for auditory toxicity	(111)
3750 mg/m^3 1000 ppm	gestation day 9-21	Rat, LOAEL for reduced birth weight and retarded postnatal development	(139)
2625 mg/m^3 700 ppm	16 weeks	Rat, NOAEL for auditory toxicity	(111)
2250 mg/m^3 600 ppm	2 years	Rat, LOAEL for nasal toxicity and clinical and morphological signs of toxicity (nasal toxicity and stomach ulcers)	(51)
2250 mg/m^3 600 ppm	gestation day 9-21	Rat, NOAEL for reduced birth weight and retarded postnatal development	(139)
1125 mg/m^3 300 ppm	2 years	Rat, NOAEL for clinical and morphological signs of toxicity	(40)

shown were relatively high (in the first study 281-2250 mg/m^3; in the second study up to 919 mg/m^3). The data cannot be used to identify a human NOAEL.

In toluene-exposed female workers a significantly higher rate of spontaneous abortions was found. The mean toluene concentration was 88 ppm (333 mg/m^3) with a range of 50-150 ppm (188-563 mg/m^3). At higher concentrations in animal studies, toluene has been found to cause lower foetal and birth weight with a LOAEL of around 1000 ppm (3800 mg/m^3), and NOAEL around 600 ppm (2280 mg/m^3). Long-lasting developmental neurotoxicity (impairment of learning ability) has been demonstrated in offspring exposed prenatally or pre- and postnatally with a LOAEL of 1200 ppm (4560 mg/m^3). In male rats exposed to 2000 ppm (7600 mg/m^3), reduced sperm count was found with a NOAEL of 600 ppm (2250 mg/m^3).

Conclusions

The critical effects of toluene exposure are acute CNS effects, irritation and spontaneous abortions. Headache, dizziness, feeling of intoxication, irritation of the eyes, nose and throat and impaired function in neuropsychological tests have been reported after experimental exposure of volunteers at rest for 6 h at 100 ppm (LOAEL). A NOAEL of 40 ppm (irritation) has been reported in healthy volunteers. For spontaneous abortion (studied epidemiologically) the dose-response relationship is not well known in terms of concentrations and duration

of exposure. In one study an increased risk for spontaneous abortion was found at concentrations varying between 50-150 ppm (average 88 ppm).

Other effects of concern are ototoxicity and chronic toxic encephalopathy. Ototoxicity has been studied epidemiologically, and the dose-response relation is not well known. However, ototoxicity has been thoroughly investigated in experimental animals, and a LOAEL of 1000 ppm and a NOAEL of 700 ppm has been identified. Chronic toxic encephalopathy has been studied epidemiologically, and the dose-response relation is not well known. However, it is believed that an individual must be exposed for many years before chronic toxic encephalopathy occurs. In the study concerned, exposure concentrations ranged from 40-1700 mg/m^3 (10-500 ppm), and it is possible that even higher levels were present in earlier years.

Dermal exposure to liquid toluene may result in significant systemic exposure.

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Summary

Montelius J (ed). *Scientific Basis for Swedish Occupational Standards*. XXIII. Arbete och Hälsa 2002:19, pp 1-63. National Institute for Working Life, Solna.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish National Institute for Working Life from July, 2001 through June, 2002.

Key Words: Isocyanic Acid (ICA), 4,4´-Methylenedianiline (MDA), Methylisoamylketone, Methylisocyanate (MIC), Occupational exposure limit (OEL), Risk assessment, Scientific basis, Toluene, Toxicology.

Sammanfattning

Montelius J (ed). *Vetenskapligt underlag för hygieniska gränsvärden*. XXIII. Arbete och Hälsa 2002:19, s 1-63. Arbetslivsinstitutet, Solna.

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 2001 - juni 2002.

Nyckelord: Hygieniskt gränsvärde, Isocyansyra (ICA), 4,4´-Metylendianilin (MDA), Metylisoamylketon, Metylisocyanat (MIC), Riskvärdering, Toluen, Toxikologi, Vetenskapligt underlag.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2002:18.

APPENDIX

Consensus reports in this and previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	(No.)
Acetaldehyde	February 17, 1987	1987:39	(VIII)
Acetamide	December 11, 1991	1992:47	(XIII)
Acetic acid	June15, 1988	1988:32	(IX)
Acetone	October 20, 1987	1988:32	(IX)
Acetonitrile	September 12, 1989	1991:8	(XI)
Acrylamide	April 17, 1991	1992:6	(XII)
Acrylates	December 9, 1984	1985:32	(VI)
Acrylonitrile	April 28, 1987	1987:39	(VIII)
Aliphatic amines	August 25, 1982	1983:36	(IV)
Aliphatic hydrocarbons, C_{10}-C_{15}	June 1, 1983	1983:36	(IV)
Aliphatic monoketons	September 5, 1990	1992:6	(XII)
Allyl alcohol	September 9, 1986	1987:39	(VIII)
Allylamine	August 25, 1982	1983:36	(IV)
Allyl chloride	June 6, 1989	1989:32	(X)
Aluminum	April 21, 1982	1982:24	(III)
revised	September 14, 1994	1995:19	(XVI)
p-Aminoazobenzene	February 29, 1980	1981:21	(I)
Ammonia	April 28, 1987	1987:39	(VIII)
Amylacetate	March 23, 1983	1983:36	(IV)
revised	June 14, 2000	2000:22	(XXI)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
Antimony + compounds	December 8, 1999	2000:22	(XXI)
Arsenic, inorganic	December 9, 1980	1982:9	(II)
revised	February 15, 1984	1984:44	(V)
Arsine	October 20, 1987	1988:32	(IX)
Asbestos	October 21, 1981	1982:24	(III)
Barium	June 16, 1987	1987:39	(VIII)
revised	January 26, 1994	1994:30	(XV)
Benzene	March 4, 1981	1982:9	(II)
revised	February 24, 1988	1988:32	(IX)
Benzoyl peroxide	February 13, 1985	1985:32	(VI)
Beryllium	April 25, 1984	1984:44	(V)
Borax	October 6, 1982	1983:36	(IV)
Boric acid	October 6, 1982	1983:36	(IV)
Boron Nitride	January 27 1993	1993:37	(XIV)
Butadiene	October 23, 1985	1986:35	(VII)
1-Butanol	June 17, 1981	1982:24	(III)
Butanols	June 6, 1984	1984:44	(V)
Butyl acetate	June 6, 1984	1984:44	(V)
Butyl acetates	February 11, 1998	1998:25	(XIX)
Butylamine	August 25, 1982	1983:36	(IV)
Butyl glycol	October 6, 1982	1983:36	(IV)
Cadmium	January 18, 1980	1981:21	(I)
revised	February 15, 1984	1984:44	(V)
revised	May 13, 1992	1992:47	(XIII)
Calcium hydroxide	February 24, 1999	1999:26	(XX)

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

Dimethylethylamine	June 12, 1991	1992:6	(XII)
Dimethylformamide	March 23, 1983	1983:36	(IV)
Dimethyl glutarate	December 9, 1998	1999:26	(XX)
Dimethylhydrazine	January 27, 1993	1993:37	(XIV)
Dimethyl succinate	December 9, 1998	1999:26	(XX)
Dimethylsulfide	September 9, 1986	1987:39	(VIII)
Dimethylsulfoxide, DMSO	December 11, 1991	1992:47	(XIII)
Dioxane	August 25, 1982	1983:36	(IV)
revised	March 4, 1992	1992:47	(XIII)
Diphenylamine	January 25, 1995	1995:19	(XVI)
4,4'-Diphenylmethanediisocyanate (MDI)	April 8, 1981	1982:9	(II)
reviderat	May 30 2001	2001:20	(XXII)
Dipropylene glycol	May 26, 1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12, 1990	1992:6	(XII)
Disulfiram	October 31, 1989	1991:8	(XI)
Enzymes, industrial	June 5, 1996	1996:25	(XVII)
Ethanol	May 30, 1990	1991:8	(XI)
Ethanolamine	September 4, 1991	1992:47	(XIII)
Ethylacetate	March 28, 1990	1991:8	(XI)
Ethylamine	August 25, 1982	1983:36	(IV)
Ethylamylketone	September 5, 1990	1992:6	(XII)
Ethylbenzene	December 16, 1986	1987:39	(VIII)
Ethylchloride	December 11, 1991	1992:47	(XIII)
Ethylene	December 11, 1996	1997:25	(XVIII)
Ethylene chloride	February 29, 1980	1981:21	(I)
Ethylene diamine	August 25, 1982	1983:36	(IV)
Ethylene glycol	October 21, 1981	1982:24	(III)
Ethylene glycol methylether + acetate	June 2, 1999	1999:26	(XX)
Ethyleneglycol monoisopropylether	November 16, 1994	1995:19	(XVI)
Ethyleneglycol monopropylether + acetate	September 15, 1993	1994:30	(XV)
Ethylene oxide	December 9, 1981	1982:24	(III)
Ethylenethiourea	September 27, 2000	2001:20	(XXII)
Ethylether	January 27, 1993	1993:37	(XIV)
Ethylglycol	October 6, 1982	1983:36	(IV)
Ferbam	September 12, 1989	1991:8	(XI)
Ferric dimethyldithiocarbamate	September 12, 1989	1991:8	(XI)
Flour dust	December 10, 1997	1998:25	(XIX)
Formaldehyde	June 30, 1979	1981:21	(I)
revised	August 25, 1982	1983:36	(IV)
Formamide	December 12, 1989	1991:8	(XI)
Formic acid	June 15, 1988	1988:32	(IX)
Furfural	April 25, 1984	1984:44	(V)
Furfuryl alcohol	February 13, 1985	1985:32	(VI)
Gallium + Gallium compounds	January 25, 1995	1995:19	(XVI)
Glutaraldehyde	September 30 1998	1999:26	(XX)
Glycol ethers	October 6, 1982	1983:36	(IV)
Glyoxal	September 13, 1996	1996:25	(XVII)
Grain dust	December 14, 1988	1989:32	(X)
Graphite	December 10, 1997	1998:25	(XIX)
Halothane	April 25, 1985	1985:32	(VI)
2-Heptanone	September 5, 1990	1992:6	(XII)
3-Heptanone	September 5, 1990	1992:6	(XII)
Hexachloroethane	September 15, 1993	1994:30	(XV)
Hexamethylenediisocyanate (HDI)	April 8, 1981	1982:9	(II)

revised	May 30,	2001	2001:20	(XXII)
Hexamethylenetetramine	August 25,	1982	1983:36	(IV)
n-Hexane	January 27,	1982	1982:24	(III)
2-Hexanone	September 5,	1990	1992:6	(XII)
Hexyleneglycol	November 17,	1993	1994:30	(XV)
Hydrazine	May 13,	1992	1992:47	(XIII)
Hydrogen bromide	February 11,	1998	1998:25	(XIX)
Hydrogen cyanide	February 7	2001	2001:20	(XXII)
Hydrogen fluoride	April 25,	1984	1984:44	(V)
Hydrogen peroxide	April 4,	1989	1989:32	(X)
Hydrogen sulfide	May 4,	1983	1983:36	(IV)
Hydroquinone	October 21,	1989	1991:8	(XI)
Indium	March 23,	1994	1994:30	(XV)
Industrial enzymes	June 5,	1996	1996:25	(XVII)
Isocyanic Acid (ICA)	December 5	2001	2002:19	(XXIII)
Isophorone	February 20,	1991	1992:6	(XII)
Isopropanol	December 9,	1981	1982:24	(III)
Isopropylamine	February 7,	1990	1991:8	(XI)
Isopropylbenzene	June 2,	1982	1982:24	(III)
Lactates	March 29,	1995	1995:19	(XVI)
Lactate esters	June 2,	1999	1999:26	(XX)
Lead, inorganic	February 29,	1980	1981:21	(I)
revised	September 5,	1990	1992:6	(XII)
Lithium boron nitride	January 27,	1993	1993:37	(XIV)
Lithium nitride	January 27,	1993	1993:37	(XIV)
Maleic anhydride	September 12,	1989	1991:8	(XI)
Manganese	February 15,	1983	1983:36	(IV)
revised	April 17,	1991	1992:6	(XII)
revised	June 4,	1997	1997:25	(XVIII)
Man made mineral fibers	March 4,	1981	1982:9	(II)
revised	December 1,	1987	1988:32	(IX)
Mercury, inorganic	April 25,	1984	1984:44	(V)
Mesityl oxide	May 4,	1983	1983:36	(IV)
Metal stearates, some	September 15,	1993	1994:30	(XV)
Methacrylates	September 12,	1984	1985:32	(VI)
Methanol	April 25,	1985	1985:32	(VI)
Methyl acetate	March 28	1990	1991:8	(XI)
Methylamine	August 25,	1982	1983:36	(IV)
Methylamyl alcohol	March 17,	1993	1993:37	(XIV)
Methyl bromide	April 27,	1988	1988:32	(IX)
Methyl chloride	March 4,	1992	1992:47	(XIII)
Methyl chloroform	March 4,	1981	1982:9	(II)
Methylene chloride	February 29,	1980	1981:21	(I)
4,4'-Methylene dianiline	June 16,	1987	1987:39	(VIII)
revised	October 3	2001	2002:19	(XXIII)
Methyl ethyl ketone	February 13,	1985	1985:32	(VI)
Methyl ethyl ketone peroxide	February 13,	1985	1985:32	(VI)
Methyl formate	December 12,	1989	1991:8	(XI)
Methyl glycol	October 6,	1982	1983:36	(IV)
Methyl iodide	June 30,	1979	1981:21	(I)
Methylisoamylamine	September 5,	1990	1992:6	(XII)
Methylisoamylketone	February 6	2002	2002:19	(XXIII)
Methylisocyanate (MIC)	December 5	2001	2002:19	(XXIII)
Methyl mercaptane	September 9,	1986	1987:39	(VIII)
Methyl methacrylate	March 17,	1993	1993:37	(XIV)

Methyl pyrrolidone	June 16, 1987	1987:39	(VIII)
α-Methylstyrene	November 1 2000	2001:20	(XXII)
Methyl-t-butyl ether	November 26, 1987	1988:32	(IX)
revised	September 30, 1998	1999:26	(XX)
Mixed solvents, neurotoxicity	April 25, 1985	1985:32	(VI)
Molybdenum	October 27, 1982	1983:36	(IV)
Monochloroacetic acid	February 20, 1991	1992:6	(XII)
Monochlorobenzene	September 16,1993	1993:37	(XIV)
Monomethylhydrazine	March 4, 1992	1992:47	(XIII)
Mononitrotoluene	February 20, 1991	1992:6	(XII)
Monoterpenes	February 17, 1987	1987:39	(VIII)
Morpholine	December 8, 1982	1983:36	(IV)
revised	June 5, 1996	1996:25	(XVII)
Naphthalene	May 27, 1998	1998:25	(XIX)
Natural crystallinic fibers (except asbestos)	June 12, 1991	1992:6	(XII)
Nickel	April 21, 1982	1982:24	(III)
Nitroethane	April 4, 1989	1989:32	(X)
Nitrogen oxides	December 11, 1985	1986:35	(VII)
Nitroglycerin	February 13, 1985	1985:32	(VI)
Nitroglycol	February 13, 1985	1985:32	(VI)
Nitromethane	January 6, 1989	1989:32	(X)
Nitropropane	October 28, 1986	1987:39	(VIII)
2-Nitropropane	March 29, 1995	1995:19	(XVI)
Nitroso compounds	December 12, 1990	1992:6	(XII)
Nitrosomorpholine	December 8, 1982	1983:36	(IV)
Nitrotoluene	February 20, 1991	1992:6	(XII)
Nitrous oxide	December 9, 1981	1982:24	(III)
Oil mist	April 8, 1981	1982:9	(II)
Organic acid anhydrides, some	September 12, 1989	1991:8	(XI)
Oxalic acid	February 24, 1988	1988:32	(IX)
Ozone	April 28, 1987	1987:39	(VIII)
Paper dust	February 7, 1990	1991:8	(XI)
Pentaerythritol	November 16, 1994	1995:19	(XVI)
1,1,1,2,2-Pentafluoroethane	February 24, 1999	1999:26	(XX)
Pentyl acetate	June 14, 2000	2000:22	(XXI)
Peroxides, organic	February 13, 1985	1985:32	(VI)
Phenol	February 13, 1985	1985:32	(VI)
Phosphorous chlorides	September 30, 1998	1999:26	(XX)
Phosphorous oxides	February 11, 1998	1998:25	(XIX)
Phthalates	December 8, 1982	1983:36	(IV)
Phthalic anhydride	September 12, 1989	1991:8	(XI)
Piperazine	September 12, 1984	1985:32	(VI)
Plastic dusts	December 16, 1986	1987:39	(VIII)
Platinum	June 4, 1997	1997:25	(XVIII)
Polyaromatic hydrocarbons	February 15, 1984	1984:44	(V)
Polyisocyanates	April 27, 1988	1988:32	(IX)
Potassium aluminium fluoride	June 4, 1997	1997:25	(XVIII)
Potassium cyanide	February 7 2001	2001:20	(XXII)
Potassium dichromate	May 24, 2000	2000:22	(XXI)
Potassium hydroxide	Marsh 15, 2000	2000:22	(XXI)
2-Propanol	December 9, 1981	1982:24	(III)
Propene	September 13, 1996	1996:25	(XVII)
Propionic acid	November 26, 1987	1988:32	(IX)
Propylacetate	September 14, 1994	1995:19	(XVI)
Propylene glycol	June 6, 1984	1984:44	(V)

Propylene glycol-1,2-dinitrate	May 4,	1983	1983:36	(IV)
Propylene glycol monomethylether	October 28,	1986	1987:39	(VIII)
Propylene oxide	June 11,	1986	1986:35	(VII)
Pyridine	May 13,	1992	1992:47	(XIII)
Quartz	March 13,	1996	1996:25	(XVII)
Resorcinol	September 4,	1991	1992:47	(XIII)
Selenium	December 11,	1985	1986:35	(VII)
revised	February 22,	1993	1993:37	(XIV)
Sevoflurane	May 27,	1998	1998:25	(XIX)
Silica	March 13,	1996	1996:25	(XVII)
Silver	October 28,	1986	1987:39	(VIII)
Sodium cyanide	February 7	2001	2001:20	(XXII)
Sodium hydroxide	August 24,	2000	2000:22	(XXI)
Stearates, metallic, some	September 15,	1993	1994:30	(XV)
Stearates, non-metallic, some	November 17,	1993	1994:30	(XV)
Strontium	January 26,	1994	1994:30	(XV)
Styrene	February 29,	1980	1981:21	(I)
revised	October 31,	1989	1991:8	(XI)
Sulfur dioxide	April 25,	1985	1985:32	(VI)
Sulfur fluorides	March 28,	1990	1991:8	(XI)
Synthetic inorganic fibers	March 4,	1981	1982:9	(II)
revised	December 1,	1987	1988:32	(IX)
Synthetic organic and inorganic fibers	May 30,	1990	1991:8	(XI)
Talc dust	June 12,	1991	1992:6	(XII)
Terpenes, mono-	February 17,	1987	1987:39	(VIII)
Tetrabromoethane	May 30,	1990	1991:8	(XI)
Tetrachloroethane	June 4,	1997	1997:25	(XVIII)
Tetrachloroethylene	February 29,	1980	1981:21	(I)
1,1,1,2-Tetrafluoroethane	March 29,	1995	1995:19	(XVI)
Tetrahydrofuran	October 31,	1989	1991:8	(XI)
Tetranitromethane	April 4,	1989	1989:32	(X)
Thioglycolic acid	June 1,	1994	1994:30	(XV)
Thiourea	December 1,	1987	1988:32	(IX)
revised	June 2,	1999	1999:26	(XX)
Thiram	October 31,	1989	1991:8	(XI)
Thiurams, some	October 31,	1989	1991:8	(XI)
Titanium dioxide	February 21,	1989	1989:32	(X)
Toluene	February 29,	1980	1981:21	(I)
revised	February 6	2002	2002:19	(XXIII)
Toluene-2,4-diamine	November 1,	2000	2001:20	(XXII)
Toluene-2,6-diamine	November 1,	2000	2001:20	(XXII)
Toluene-2,4-diisocyanate	April 8,	1981	1982:9	(II)
revised	May 30,	2001	2001:20	(XXII)
Toluene-2,6-diisocyanate	April 8,	1981	1982:9	(II)
revised	May 30,	2001	2001:20	(XXII)
1,1,1-Trifluoroethane	February 24,	1999	1999:26	(XX)
Trichlorobenzene	September 16,	1993	1993:37	(XIV)
1,1,1-Trichloroethane	March 4,	1981	1982:9	(II)
Trichloroethylene	December 14,	1979	1981:21	(I)
Trichlorofluoromethane	June 2,	1982	1982:24	(III)
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2,	1982	1982:24	(III)
Triethanolamine	August 25,	1982	1983:36	(IV)
Triethylamine	December 5,	1984	1985:32	(VI)
Trimellitic anhydride	September 12,	1989	1991:8	(XI)

Trimethylolpropane	November 16, 1994	1995:19	(XVI)
Trinitrotoluene	April 17, 1991	1992:6	(XII)
Vanadium	March 15, 1983	1983:36	(IV)
Vinyl acetate	June 6, 1989	1989:32	(X)
Vinyl toluene	December 12, 1990	1992:6	(XII)
White spirit	December 16, 1986	1987:39	(VIII)
Wood dust	June 17, 1981	1982:9	(II)
revised	June 25, 2000	2000:22	(XXI)
Xylene	February 29, 1980	1981:21	(I)
Zinc	April 21, 1982	1982:24	(III)
Zinc chromate	May 24, 2000	2000:22	(XXI)
Zinc dimethyl dithiocarbamate	September 12, 1989	1991:8	(XI)
Ziram	September 12, 1989	1991:8	(XI)

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