SCOEL/SUM/118
September 2006

Recommendation from the Scientific Committee on

Occupational Exposure Limits

for Methyl Isocyanate

8-hour TWA:	-
STEL (15 min):	0,02 ppm
Additional classification:	-

Substance Identity and Properties

CAS No.:	624-83-9
Synonyms:	isocyanic acid methylester
Structure:	H_3C-N=C=O
Molecular weight:	57.06
Boiling point:	39°C
Melting point:	-45°C
Vapour pressure:	46.4 kPa (20°C)
Conversion factors:	1 ppm = 2.4 mg/m^3 1 mg/m^3 = 0.4 ppm

Classification:

F+; R12	Extremely flammable
Repr.Cat.3; R63	Possible risk of harm to the unborn child
T+; R26	Very toxic by inhalation
T; R24/25	Toxic in contact with skin and if swallowed
R42/43	May cause sensitization by inhalation and skin contact
Xi; R37/38	Irritating to respiratory system and skin
R41	Risk of serious damage to eyes

This summary document is based on a consensus document from the Swedish Criteria Group for Occupational Standards (Montelius, 2002).

Methyl isocyanate (MIC) is a monoisocyanate and should be distinguished from the diisocyanates. At room temperature MIC is a clear liquid. It is sparingly soluble in water, although on contact with water it reacts violently, producing a large amount of heat. MIC has a sharp odour with an odour threshold above 2 ppm (Römpp and Falbe, 1997).

Occurrence and Use

Methylisocyanate (MIC) occurs primarily as an intermediate in the production of carbamate pesticides. It has also been used in the production of polymers (Hrhyhorczuk et al., 1992). Photolytic breakdown of N-methyldithiocarbamate releases some MIC, and it can therefore occur in the air around application of the pesticides (Geddes et al., 1995). MIC is found in tobacco smoke: the measured content in the main stream ranges from 1.5 to 5 µg per cigarette (IARC, 1986).

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 (Karlsson et al.,1998, Lilja et al, 1999). Exposure measurements made in foundries indicate that MIC occurs primarily where "hot box" cores are used in chill casting (Lilja et al,. 2000). 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 (Antonsson etal, 2000, Skarping et al., 2001). In a survey of isocyanates in Swedish polyurethane industries, MIC levels of about 3 ppb (moulding), 0.2 ppb (flame lamination) and 0.04 ppb (UV lamination) have been reported (Sennbro et al., 2004).

Health Effects

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 (Dhara and Dhara, 1995). 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 (Bucher, 1987). 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 (Ferguson et al., 1988). 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 at 0.5 ppm. Radioactivity in blood dropped gradually after the exposure 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, foetuses, spleen, uterus and kidneys, and after 24 hours in lungs, spleen and foetuses (Ferguson et al., 1988). 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 (Bhattacharya et al., 1996, 1988).

Sax (1984) mentions, without going into detail, that MIC is absorbed by the skin. No other data on skin uptake were found. The LD50-values in experimental animals are considerably lower by the oral than by the dermal route (see section Animal toxicity data).

MIC has been observed to cause carbamoylation of N-terminal valine in the haemoglobin of rats and rabbit blood both in vivo and in vitro (Ramachandran et al., 1988), 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 (Srimachari and Chandra, 1997). S-(N-methylcarbamoyl)glutathione, another reactive conjugate, has been identified in bile from rats given MIC via a catheter in the portal vein (Pearson et al., 1990). In another experiment, the glutathione conjugate in the form of S-(N-methylcarbamoyl)-N-acetylcysteine was identified in urine of rats given MIC intraperitoneally (Slatter et al., 1991).

MIC reacts readily with water, forming methylamine, which further reacts to dimethylurea (Worthy, 1985). 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.

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) (Avashia et al., 1996). 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 measurements of MIC (the method used is not reported) were made in the 1977-90 period. In 1977 more than 80% of the measurements exceeded 0.02 ppm, whereas only one of 33 measurements made in 1990 was above this level. The groups were compared, using lung function values from the most recent examination and taking smoking habits into account. No effect of MIC on lung function could be discerned, nor was any effect seen when each 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, exact times not given) to MIC (Kimmerle and Eben, 1964) (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 odour was perceived. At 4 ppm the symptoms of irritation were more pronounced, and at 21 ppm they were unbearable.

In chamber study performed by the Mellon Institute (1970), none of the 8 volunteers exposed for 1 min at 1.75 ppm MIC perceived the odour, 3 reported nose or throat irritation, 7 had increased tear flow, and all 8 experienced eye irritation. All effects disappeared within 10 min after the end of exposure, except in one woman who reported "having something in her eye" for 45 min. When six of the subjects were exposed for 10 min at 0.5 ppm MIC, eye irritation was experienced in three of them after 1-2 min in five after 3—5 min and in all after 10 min. Tearing appeared shortly after, whereas throat irritation was somewhat less evident. Only one subject perceived an odour.

Table 2. Effects in volunteers after short-term controlled exposure to MIC.

Exposure level, ppm	Exposure duration	Effects	Reference
21	1-5 min	Unendurable irritation	Kimmerle and Eben, 1964
4	1-5 min	Severe irritation of mucous membranes	Kimmerle and Eben, 1964
2	1-5 min	Tearing, irritation of eyes, nose and throat	Kimmerle and Eben, 1964
1.75	1 min	Eye irritation in all 8 subjects Tearing in 7 subjects Nose or throat irritation in 3 subjects Odour perception by none	Mellon Institute, 1970
0.5	5 min	Eye (5 of 6 subjects), nose (5) and throat (3) irritation, tearing (5) subjects	Mellon Institute, 1970
	2 min	Eye (3 of 6 subjects) and throat (1) irriation	
	1 min	No irritation	
0.4	1-5 min	No irritation	Kimmerle and Eben, 1964

In a survey of isocyanates in foundries in Sweden, the average exposure to MIC was 0.0049 mg/m^3 (0.002 ppm, geometric mean, 298 personal full-shift samples) whereas the level of the related substance isocyanic acid (ICA) was 0.024 mg/m^3 and that of formaldehyde was 0.12 mg/m^3 (64 samples). The Swedish permissible exposure limit for isocyanates (0.01 ppm) was exceeded in 18% and 80% of the samples for MIC and ICA, respectively (Lilja et al., 1999, 2000). Significantly more of the exposed workers reported "cough attacks without cold" (36% of 64 workers versus 16% of 134 non-exposed controls) and "runny, itching eyes" (44% versus 25%). The exposed workers further had slight but significant impairment in lung function (reduced FEV1) prior to shift, as well as a more pronounced impairment during shift, compared to controls. The change in lung function was not significantly correlated to work task or chemical exposure levels (Löfstedt et al., 2003). In view of the lack of exposure-effect correlations and multiple chemical exposures, this study is not useful as a starting point in deriving an OEL for MIC.

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 (Mehta et al.,

1990). 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 OEL. A brief review of some of the studies is nevertheless presented below.

It is estimated that about 2 000 people in the Bhopal disaster died within the first few hours. The reported cause of death was alveolar necroses combined with ulcerations in bronchial mucosa and pulmonary edema (Weill, 1988). In one study, 379 survivors were divided into eight groups on the basis of their degree of exposure, as estimated from the number 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 (Andersson et al., 1988b). Since amines can cause eye damage (Järvinen et al., 1999), the relevance of MIC here can not be assessed with certainty.

Kamat et al. (1992) 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 along with a previous one also presents an analysis of antibodies in serum samples from 99 cases (Karol and Kamat, 1988, Kamat et al., 1992). The initial samples were taken a few months after the disaster. 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. 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 (Vijayan and Sankaran, 1996). 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. Bronchoalveolar lavage 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 (Cullinan et al., 1997). 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 (Andersson et al., 1985). 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 (Andersson et al., 1990b).

One year after the disaster, a study of cognitive function was made on a group of 52 victims (Misra et al., 1997). 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 (Cullinan et al., 1996). 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.

Animal toxicity data

The acute toxicity of MIC appears to follow closely Haber's rule, the LC_{50} in laboratory animals ranging from 171 ppm (rats, 15-min exposure) to 5,4 ppm (guinea pig, 6-h exposure) depending on the exposure duration (Table 2). One study (Smyth et al., 1969) reports LD_{50} values of 71 mg/kg (0.071 ml/kg) in rats by the oral route and 220 mg/kg (0.22 ml/kg) in rabbits by the dermal route, whereas another study (Vernot et al., 1977) reports rat oral and rabbit dermal LD_{50} values of 140 and 1800 mg/kg, respectively. A third study reports higher lethal doses, with calculated LD_{50} and LC_{50} values of 329 mg/kg body weight (subcutaneous route) and 465 ppm (30-min exposure), respectively, in rats (Jeevaratnam et al., 1990).

The RD_{50} for mice (the concentration 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 (Ferguson et al., 1986), and 2.9 ppm in another (James et al., 1987). 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 (Ferguson et al., 1986).

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 (Stevens et al., 1987). 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 (Tepper et al., 1987). A LOAEL 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 h/d for 4 + 4 days. The NOAEL in this study was 0.6 ppm (Dodd et al., 1987a).

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, haemorrhages and inflammation in lungs (Fowler and Dodd, 1987). The changes disappeared within a week. When rats were exposed to 128 ppm (320 mg/m^3) MIC during 8 min/d for 10 days, the exposure induced progressive cellular inflammation with increase of eosinophils, neutrophils and mononuclear cells (Gupta et al., 1993). 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 (Ferguson and Alarie, 1991).

In one study (Bucher and Uraih, 1989), F344 rats and $B6C3F_1$ 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.

In a National Toxicology Program (NTP) study (Hong et al., 1987), mice were exposed to 1 or 3 ppm MIC 6 h/d 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 further 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.

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 (Uraih et al., 1987).

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

Exposure, duration	Species	Effect	Reference
171 ppm, 15 min 121 ppm, 15 min	Rat Guinea pig	LC_{50}	Dodd et al., 1987b
12.2 ppm, 6 h 6.1 ppm, 6 h 5.4 ppm, 6 h	Mouse Rat Guinea pig	LC_{50}	Fowler and Dodd, 1987
10 ppm, 2 h	Rat	Proliferation of connective tissue below respiratory epithelium with intrusion into respiratory lumen	Bucher and Uraih, 1989
10 ppm, 2 h	Rat	Right ventricular hypertrophy, ECG changes secondary to lung damage	Tepper et al., 1987
9 ppm, 3 h, day 8 or 9 of gestation	Mouse, rat	Over 80% of foetuses resorbed, reduced placenta weights	Varma, 1987
3.1 ppm, 6 h/d, 8 d	Rat	Damage to respiratory epithelium, weight loss, pulmonary edema, increase in Hb (males)	Dodd et al., 1987a
3 ppm, 6 h/d, 4 d	Mouse	Bronchial fibrosis, damage to olfactory epithelium, bone marrow depression	Hong et al., 1987
3 ppm, 2 h	Rat	ECG changes due to lung damage	Tepper et al., 1987
3 ppm, 2 h	Rat	No changes in lung function	Stevens et al., 1987
2.9 ppm, 30 min	Mouse	RD_{50} (sensory irritation)	James et al., 1987
2.4 ppm, 6 h	Mouse, rat,	Retarded weight gain	Fowler and

	guinea pig		Dodd, 1987
1.9 ppm, 90 min[1] 1.3 ppm, 90 min	Mouse	RD_{50} (pulmonary irritation) RD_{50} (sensory irritation)	Ferguson et al., 1986
1 ppm, 6 h/d, 4 d	Mouse	Unspecified damage to respiratory epithelium, transient bone marrow depression	Hong et al., 1987
0.6 ppm, 6 h/d, 8 d 0.15 ppm, 6 h/d, 8 d	Rat	No effect on respiratory passages, body weight or Hb Idem	Dodd et al., 1987a

[1] Via tracheal catheter.

Immunological effects of MIC have been examined in some studies (Karol and Kamat, 1988, Tucker et al., 1987). A slight increase of immunoglobulin levels was measured in rats after exposure to MIC (Saxena et al., 1991). MIC demonstrated a slight immunosuppressive effect in an NTP study with mice (Tucker et al., 1987). Mice were exposed to 1 or 3 ppm MIC 6 h/d 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 in 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 (Bhattacharya et al., 1996, Jeevaratnam et al., 1993, 1990). Exposure of mice or rats to MIC concentrations, either intraperitoneally or via inhalation in the range 3 to 30 ppm, has caused temporary degenerative changes in blood cells and cells in liver parenchyma (Gupta and Amma, 1993). In a study with mice, intraperitoneal injections of 293-1170 mg MIC per 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 (Gupta and Prabha, 1996). In vitro studies have shown that MIC affects both brain and muscle cells, but the clinical relevance of this finding is not clear (Andersson et al., 1988a, 1990a).

There are only a few studies on 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 (Jeevaratnam and Vidya, 1994, Jeevaratnam et al., 1992). 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 (Troup et al., 1987). MIC also exerts a dose-dependent inhibition of acetylcholinesterase activity in vitro in erythrocytes from humans, rats and guinea pigs (Jeevaratnam and Vaidynathan, 1992, Troup et al., 1987). The relevance of these mechanisms is questionable at the much lower concentrations of MIC expected at workplaces.

Mutagenicity and carcinogenicity

MIC showed no mutagenic activity in standard Ames' tests (Shelby et al., 1987). Negative results were also obtained in Ames' tests with urine from rats exposed to MIC (Andersson et al., 1986) and in a sex-linked recessive lethal test with Drosophila (Shelby et al., 1987). 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 (McConnell et al., 1987). Persons exposed to MIC and other substances during the Bhopal disaster had higher frequencies of chromosome aberrations than unexposed controls (Ghosh et al., 1990).

No neoplastic changes in respiratory organs were observed in a study (Bucher and Uraih, 1989) in which F344 rats and B6C3F$_1$ 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.

There are no mutagenicity or carcinogenicity studies with long-term exposures to MIC. Judging from structure-activity correlations, the carcinogenic potency of MIC should be low (Ennever and Rosenkranz, 1987).

Reproductive toxicity

A dose-dependent absorption of foetuses 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 foetus 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 (Varma, 1987). 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 foetuses (Varma et al., 1990). In another study, mice were exposed to 1 or 3 ppm MIC 6 h/d on days 14 to 17 of gestation. There were significant increases in the numbers of dead foetuses in both groups, and lower neonatal survival in the high-dose group. The authors caution against drawing conclusions on whether the foetotoxicity was a direct effect of MIC or was secondary to the effects on the lungs of the mothers (Schwetz et al., 1987).

Studies of victims of the Bhopal disaster revealed that mothers exposed to MIC had higher numbers of miscarriages, but not stillbirths, than unexposed controls (Bajaj et al., 1993). In a controlled study, Cullinan et al. (1996) reported an increase in stillbirths (exposed 9%, unexposed 4%) and miscarriages (year of disaster 7%, later years 1%), but the study covered few cases.

Recommendation

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 are two studies on dose-response relationships for humans, but these cover exposure durations of only up to a few minutes. Results from animal studies suggest that dose-effect and dose-response curves are steep.

Irritation of upper and lower respiratory passages has been described in studies with rats, mice and guinea pigs after short-term (0.5 – 1.5 h) exposures at 1.3- 2.9 ppm MIC. Permanent lung damage is reported at slightly higher exposure levels (3 – 3.1 ppm, 6 h/d, 4 - 8 d). No adverse effects were seen in rats exposed to MIC at 0.6 ppm (6 h/d, 8 d) in one study, whereas the mouse NTP study reported unspecified damage to respiratory epithelium accompanied by bone marrow depression at 1 ppm and pronounced bronchial fibrosis at 3 ppm (6 h/d, 4 d). At somewhat higher levels there is a steep increase in mortality, with 6-h LC_{50}-values of 5-12 ppm in different animal species. The only systemic effect observed, bone marrow depression, was thought to be a secondary effect of the lung damage.

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. In another study, eye irritation started to appear after 1-2 min and tearing after 3-5 min at 0.5 ppm MIC.

The available data are not sufficient to determine an 8-h OEL for MIC. In view of the short exposure duration (irritation at 0.5 ppm after a few minutes) and small number of subjects in the human experimental studies and the serious effects seen in animals acutely exposed at 1 ppm and higher levels, SCOEL proposes a STEL of 0.02 ppm, equivalent to 20 ppb. This value is well below the RD50 for sensory irritation in mice (1.3 ppm) and the NOEL in rats (0.6 ppm). MIC is a highly reactive chemical and, as supported by animal experiments, long-term systemic effects are unlikely at the recommended level even after prolonged exposure. It should be noted that no odour is present at the recommended STEL.

Unlike the diisocyanates, there is no convincing data showing that MIC is a respiratory or skin sensitizer. Asthma resulting from exposure to MIC has not been reported

Considering the more than tenfold higher dermal than oral LD_{50}-value in experimental animals and that the critical effects of MIC are exerted at the points of contact (eyes, airways) and not via systemic exposure, a skin notation is not warranted.

No measurement difficulties are foreseen at the recommended levels. For example, a recent paper reports detection limits of 3 and 0.2 $\mu g/m^3$, (1.2 and 0.08 ppb) for 15-min and 8-h sampling periods, respectively (Henneken et al., 2003). The method is based on diffusive sampling on a glass fiber filter impregnated with 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole (NBDPZ) followed by analysis of the urea derivative by high-performance liquid chromatography with fluorescence detection.

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