IDLH

IMMEDIATELY DANGEROUS to LIFE or HEALTH

VALUE PROFILE

Methyl Isocyanate
CAS® No. 624-83-9

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Disease Control and Prevention
National Institute of Occupational Safety and Health

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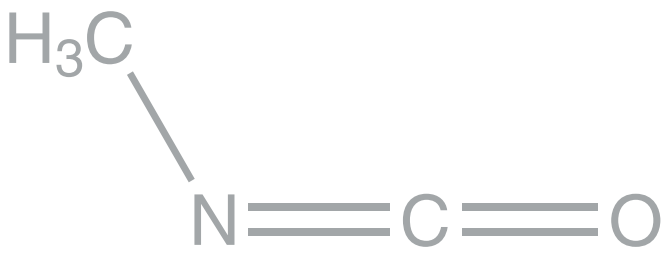
Immediately Dangerous to Life or Health (IDLH) Value Profile

Methyl Isocyanate

[CAS® No. 624-83-9]



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Foreword

Chemicals are a ubiquitous component of the modern workplace. Occupational exposures to chemicals have the potential to adversely affect the health and lives of workers. Acute or short-term exposures to high concentrations of some airborne chemicals have the ability to quickly overwhelm workers, resulting in a spectrum of undesirable health outcomes that may inhibit the ability to escape from the exposure environment (e.g., irritation of the eyes and respiratory tract or cognitive impairment), cause severe irreversible effects (e.g., damage to the respiratory tract or reproductive toxicity), and in extreme cases, cause death. Airborne concentrations of chemicals capable of causing such adverse health effects or of impeding escape from high-risk conditions may arise from a variety of nonroutine workplace situations, including special work procedures (e.g., in confined spaces), industrial accidents (e.g., chemical spills or explosions), and chemical releases into the community (e.g., during transportation incidents or other uncontrolled-release scenarios).

The immediately dangerous to life or health (IDLH) airborne concentration values developed by the National Institute for Occupational Safety and Health (NIOSH) characterize these high-risk exposure concentrations and conditions [NIOSH 2013]. IDLH values are based on a 30-minute exposure duration and have traditionally served as a key component of the decision logic for the selection of respiratory protection devices [NIOSH 2004].

Occupational health professionals have employed these values beyond their initial purpose as a component of the *NIOSH Respirator Selection Logic* to assist in developing risk management plans for nonroutine work practices governing operations in high-risk environments (e.g., confined spaces) and the development of emergency preparedness plans.

The approach used to derive IDLH values for high-priority chemicals is outlined in the *NIOSH Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health Values* [NIOSH 2013]. CIB 66 provides (1) an update on the scientific basis and risk assessment methodology used to derive IDLH values, (2) the rationale and derivation process for IDLH values, and (3) a demonstration of the derivation of scientifically credible IDLH values, using available data resources.

The purpose of this technical report is to present the IDLH value for methyl isocyanate (CAS® # 624-83-9). The scientific basis, toxicologic data and risk assessment approach used to derive the IDLH value are summarized to ensure transparency and scientific credibility.

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Safety and Health
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Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AEGLs	Acute Exposure Guideline Levels
AIHA®	American Industrial Hygiene Association
BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower confidence limit
C	ceiling value
°C	degrees Celsius
CAS®	Chemical Abstracts Service, a division of the American Chemical Society
ERPGs™	Emergency Response Planning Guidelines
°F	degrees Fahrenheit
GD	gestation day
IDLH	immediately dangerous to life or health
LC_{50}	median lethal concentration
LC_{LO}	lowest concentration that caused death in humans or animals
LEL	lower explosive limit
LOAEL	lowest observed adverse effect level
mg/m^3	milligram(s) per cubic meter
min	minutes
mmHg	millimeter(s) of mercury
NAC	National Advisory Committee
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NR	not recommended
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
ppm	parts per million
RD_{50}	concentration of a chemical in the air that is estimated to cause a 50% decrease in the respiratory rate
RD_{50TC}	tracheally cannulated RD_{50}
REL	recommended exposure limit
STEL	short-term exposure limit
TLV®	Threshold Limit Value
TWA	time-weighted average
UEL	upper explosive limit
WEELs®	Workplace Environmental Exposure Levels
µg/kg	microgram(s) per kilogram of body weight

Glossary

Acute exposure: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

Acute Exposure Guideline Levels (AEGLs): Threshold exposure limits for the general public, applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-1, AEGL-2, and AEGL-3 are developed for five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects, ranging from transient, reversible effects to life-threatening effects [NAS 2001]. AEGLs are intended to be guideline levels used during rare events or single once-in-a-lifetime exposures to airborne concentrations of acutely toxic, high-priority chemicals [NAS 2001]. The threshold exposure limits are designed to protect the general population, including the elderly, children, and other potentially sensitive groups that are generally not considered in the development of workplace exposure recommendations (additional information available at http://www.epa.gov/oppt/aegl/).

Acute reference concentration (Acute RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hours or less) of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors (UFs) generally applied to reflect limitations of the data used. Generally used in U.S. EPA noncancer health assessments [U.S. EPA 2016].

Acute toxicity: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hours [U.S. EPA 2016].

Adverse effect: A substance-related biochemical change, functional impairment, or pathologic lesion that affects the performance of an organ or system or alters the ability to respond to additional environmental challenges.

Benchmark dose/concentration (BMD/BMC): A dose or concentration that produces a predetermined change in response rate of an effect (called the benchmark response, or BMR) compared to background [U.S. EPA 2016] (additional information available at http://www.epa.gov/ncea/bmds/).

Benchmark response (BMR): A predetermined change in response rate of an effect. Common defaults for the BMR are 10% or 5%, reflecting study design, data variability, and sensitivity limits used.

BMCL: A statistical lower confidence limit on the concentration at the BMC [U.S. EPA 2016].

Bolus exposure: A single, relatively large dose.

Ceiling value ("C"): U.S. term in occupational exposure indicating the airborne concentration of a potentially toxic substance that should never be exceeded in a worker's breathing zone.

Chronic exposure: Repeated exposure for an extended period of time. Typically exposures are more than approximately 10% of life span for humans and >90 days to 2 years for laboratory species.

Critical study: The study that contributes most significantly to the qualitative and quantitative assessment of risk [U.S. EPA 2016].

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism [U.S. EPA 2016].

ECt_{50}: A combination of the effective concentration of a substance in the air and the exposure duration that is predicted to cause an effect in 50% (one half) of the experimental test subjects.

Emergency Response Planning Guidelines (ERPGs™): Maximum airborne concentrations below which nearly all individuals can be exposed without experiencing health effects for 1-hour exposure. ERPGs are presented in a tiered fashion, with health effects ranging from mild or transient to serious, irreversible, or life threatening (depending on the tier). ERPGs are developed by the American Industrial Hygiene Association [AIHA 2006].

Endpoint: An observable or measurable biological event or sign of toxicity, ranging from biomarkers of initial response to gross manifestations of clinical toxicity.

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

Extrapolation: An estimate of the response at a point outside the range of the experimental data, generally through the use of a mathematical model, although qualitative extrapolation may also be conducted. The model may then be used to extrapolate to response levels that cannot be directly observed.

Hazard: A potential source of harm. Hazard is distinguished from risk, which is the probability of harm under specific exposure conditions.

Immediately dangerous to life or health (IDLH) condition: A condition that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment [NIOSH 2004, 2013].

IDLH value: A maximum (airborne concentration) level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted [NIOSH 2004, 2013]. IDLH values are based on a 30-minute exposure duration.

LC_{01}: The statistically determined concentration of a substance in the air that is estimated to cause death in 1% of the test animals.

LC_{50}: The statistically determined concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; median lethal concentration.

LC_{LO}: The lowest lethal concentration of a substance in the air reported to cause death, usually for a small percentage of the test animals.

LD_{50}: The statistically determined lethal dose of a substance that is estimated to cause death in 50% (one half) of the test animals; median lethal concentration.

LD_{LO}: The lowest dose of a substance that causes death, usually for a small percentage of the test animals.

LEL: The minimum concentration of a gas or vapor in air, below which propagation of a flame does not occur in the presence of an ignition source.

Lethality: Pertaining to or causing death; fatal; referring to the deaths resulting from acute toxicity studies. May also be used in lethality threshold to describe the point of sufficient substance concentration to begin to cause death.

Lowest observed adverse effect level (LOAEL): The lowest tested dose or concentration of a substance that has been reported to cause harmful (adverse) health effects in people or animals.

Mode of action: The sequence of significant events and processes that describes how a substance causes a toxic outcome. By contrast, the term *mechanism of action* implies a more detailed understanding on a molecular level.

No observed adverse effect level (NOAEL): The highest tested dose or concentration of a substance that has been reported to cause no harmful (adverse) health effects in people or animals.

Occupational exposure limit (OEL): Workplace exposure recommendations developed by governmental agencies and nongovernmental organizations. OELs are intended to represent the maximum airborne concentrations of a chemical substance below which workplace exposures should not cause adverse health effects. OELs may apply to ceiling limits, STELs, or TWA limits.

Peak concentration: Highest concentration of a substance recorded during a certain period of observation.

Permissible exposure limits (PELs): Occupational exposure limits developed by OSHA or MSHA for allowable occupational airborne exposure concentrations. PELs are legally enforceable and may be designated as ceiling limits, STELs, or TWA limits.

Point of departure (POD): The point on the dose–response curve from which dose extrapolation is initiated. This point can be the lower bound on dose for an estimated incidence or a change in response level from a concentration-response model (BMC), or it can be a NOAEL or LOAEL for an observed effect selected from a dose evaluated in a health effects or toxicology study.

RD_{50}: The statistically determined concentration of a substance in the air that is estimated to cause a 50% (one half) decrease in the respiratory rate.

Recommended exposure limit (REL): Recommended maximum exposure limit to prevent adverse health effects, based on human and animal studies and established for occupational (up to 10-hour shift, 40-hour week) inhalation exposure by NIOSH. RELs may be designated as ceiling limits, STELs, or TWA limits.

Short-term exposure limit (STEL): A worker's 15-minute time-weighted average exposure concentration that shall not be exceeded at any time during a work day.

Target organ: Organ in which the toxic injury manifests in terms of dysfunction or overt disease.

Threshold Limit Values (TLVs®): Recommended guidelines for occupational exposure to airborne contaminants, published by the American Conference of Governmental Industrial Hygienists (ACGIH®). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse effects. TLVs may be designated as ceiling limits, STELs, or 8-hr TWA limits

Time-weighted average (TWA): A worker's 8-hour (or up to 10-hour) time-weighted average exposure concentration that shall not be exceeded during an 8-hour (or up to 10-hour) work shift of a 40-hour week. The average concentration is weighted to take into account the duration of different exposure concentrations.

Toxicity: The degree to which a substance is able to cause an adverse effect on an exposed organism.

Uncertainty factors (UFs): Mathematical adjustments applied to the POD when developing IDLH values. The UFs for IDLH value derivation are determined by considering the study and effect used for the POD, with further modification based on the overall database.

Workplace Environmental Exposure Levels (WEELs®): Exposure levels developed by the American Industrial Hygiene Association (AIHA®) that provide guidance for protecting most workers from adverse health effects related to occupational chemical exposures, expressed as TWA or ceiling limits.

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1 Introduction

1.1 Overview of the IDLH Value for Methyl Isocyanate

IDLH value: 0.12 ppm (0.28 mg/m^3)

Basis for IDLH value: The IDLH value for methyl isocyanate is based on the LOAEL for severe reproductive and developmental effects. Varma [1987] reported a LOAEL of 2 ppm for these developmental and reproductive effects in dams exposed for 3 hours on gestation day (GD) 8. This represents a one-time acute exposure at a critical developmental time of the dam and fetuses. The LOAEL was adjusted to a 30-minute equivalent duration concentration of 3.6 ppm. A composite uncertainty factor of 30 was applied to account for extrapolation from a concentration that causes severe effects in animals, animal to human differences, human variability, and uncertainty about the threshold for escape-impairing effects, yielding an IDLH value of 0.12 ppm.

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to methyl isocyanate and (2) the rationale behind the immediately dangerous to life or health (IDLH) value for methyl isocyanate. IDLH values are developed on the basis of scientific rationale and logic outlined in the *NIOSH Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health (IDLH) Values* [NIOSH 2013]. As described in CIB 66, NIOSH performs in-depth literature searches to ensure that all relevant data from human and animal studies with acute exposures to the substance are identified. Information included in CIB 66 on the literature search includes pertinent databases, key terms, and guides for evaluating data quality and relevance for the establishment of an IDLH value. The information that is identified in the in-depth literature search is evaluated with general considerations that include description of studies (i.e., species, study protocol, exposure concentration and duration), health endpoint evaluated, and critical effect levels (e.g., NOAELs, LOAELs, and LC_{50} values). For methyl isocyanate, the in-depth literature search was conducted through May 2016.

1.3 General Substance Information

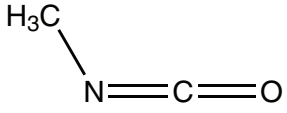
Chemical: Methyl Isocyanate

CAS No: 624-83-9

Synonyms: Methyl ester isocyanic acid; Isocyanato-methane; MIC [Isocyanate]*

Chemical category: Organic isocyanates†

Structural formula:



References: *NLM [2016]; †IFA [2016]

Table 1 highlights selected physiochemical properties of methyl isocyanate relevant to IDLH conditions. Table 2 provides alternative exposure guidelines for methyl isocyanate. Table 3 summarizes the Acute Exposure Guidelines Level (AEGL) values for methyl isocyanate.

Table 1: Physiochemical properties of methyl isocyanate

Property	Value
Molecular weight	57.06*
Chemical formula	C_2H_3NO
Description	Colorless liquid
Odor	Sharp, unpleasant
Odor threshold	2.1 ppm†
UEL	26%‡
LEL	5.3%‡
Vapor pressure	348 mmHg at 20°C (68°F)*
Flash point	-7°C (19°F)- closed cup*
Ignition temperature	534°C (994°F)*
Solubility	Hydrolysis‡

References: *HSDB [2016];†AIHA [1989]; ‡IFA [2016]

Table 2: Alternative exposure guidelines for methyl isocyanate

Organization	Value
Revised (1994) IDLH value*	3 ppm
NIOSH REL†	0.02 ppm (0.05 mg/m^3)
OSHA PEL‡	0.02 ppm (0.05 mg/m^3) [skin]
ACGIH TLV®§	TWA 0.02 ppm (0.05 mg/m^3) STEL 0.06 ppm (0.14 mg/m^3)
AIHA ERPG™¶	ERPG 1: 0.025 ppm ERPG 2: 0.5 ppm ERPG 3: 5 ppm
AIHA WEEL®¶	None

References: *NIOSH [1994]; †NIOSH [2016]; ‡OSHA [2016]; §ACGIH [2015]; ¶AIHA [2014]

Table 3: AEGL values for methyl isocyanate

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint [reference]
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	0.40 ppm 0.94 mg/m^3	0.13 ppm 0.32 mg/m^3	0.067 ppm 0.16 mg/m^3	0.017 ppm 0.034 mg/m^3	0.008 ppm 0.02 mg/m^3	Decreased fetal body weights [Varma 1987]; Cardiac arrhythmias [Tepper et al. 1987]
AEGL-3	1.2 ppm 2.8 mg/m^3	0.40 ppm 0.95 mg/m^3	0.20 ppm 0.47 mg/m^3	0.05 ppm 0.12 mg/m^3	0.025 ppm 0.06 mg/m^3	Decreased pup survival during lactation [Schwetz et al. 1987]

Reference: NAS [2003]

2 Animal Toxicity Data

Methyl isocyanate is one of the most reactive isocyanates and rapidly degrades in water [Varma and Guest 1993; NAS 2003]. The reactive nature of methyl isocyanate contributes to its toxicological potential and ability to cause irritation and cytotoxicity in the respiratory tract. The database for acute lethality in animals consists of multiple studies in rabbits [Pant et al. 1987; Dow Chemical 1990], guinea pigs [Mellon Institute 1966, 1970; Dodd et al. 1985, 1986, 1987; Kolb et al. 1987; Troup et al. 1987; Ferguson and Alarie 1991], rats [Mellon Institute 1963a, 1970; IRDC 1964; Kimmerle and Eben 1964; Eastman Kodak 1966; Fait and Dodd 1981; Dodd et al. 1985, 1986, 1987; Nemery et al. 1985a; Salmon et al. 1985; Bucher et al. 1987a,b; Dinsdale et al. 1987; Pant et al. 1987; Vijayaraghavan and Kaushik 1987; Dutta et al. 1988; Sethi et al. 1989; Dow Chemical 1990; Jeevaratnam et al. 1990; Man Tech Environmental 1992; Jeevaratnam and Sriramachari 1994; Sriramachari and Jeevaratnam 1994], and mice [Dodd et al. 1985, 1986; Boorman et al. 1987a,b; Bucher et al. 1987a; Vijayaraghavan and Kaushik 1987; Varma et al. 1988]. Based on histopathology and necropsy reports, lethality appears to be primarily caused by damage to the respiratory system.

Multiple studies have reported varied non-lethal effects following acute exposure to methyl isocyanate. Studies in guinea pigs indicate that exposure to methyl isocyanate for 15 minutes causes hypoxia and metabolic acidosis at concentrations as low as 240 ppm [Fedde et al. 1987; Maginniss et al. 1987]. Rats acutely exposed to methyl isocyanate developed severe inflammation and erosion of the respiratory tract [Mitsumori et al. 1987] and hypoxia [Troup et al. 1987]. Studies that observed acutely exposed rats for extended periods of time reported evidence of pulmonary obstruction [Stevens et al. 1987; Bucher and Uriah 1989]. Tepper et al. [1987] reported an increase in cardiac arrhythmia in rats at 4-6 months post-exposure to a 2 hour exposure to 3 ppm methyl isocyanate. In mice, a RD_{50} value of 1.3 – 2.9 ppm and a RD_{50TC} of 1.9 ppm have been estimated [Ferguson et al. 1986; James et al. 1987].

Developmental and reproductive studies have determined that acute exposure to methyl isocyanate significantly decreases maternal body, fetal, and placental weight and significantly increases the total number of resorptions and skeletal malformations in both rats and mice [Varma 1987; Varma et al. 1990; Singh et al. 1994]. Varma. [1987] reported a LOAEL of 2 ppm for developmental and reproductive effects, including decreased fetal and placental weights, in dams exposed for 3 hours on GD 8. At higher concentrations including 6 and 9 ppm, increased incidents of skeletal malformations were observed. This represents a one-time acute exposure at a critical developmental time of the dam and fetuses.

A subset of the studies highlighted in Sections 2.0 and 3.0 provides sufficient information, such as experimental protocol, exposure concentration and duration, test species description and critical effect levels [NIOSH 2013], to derive potential IDLH values for methyl isocyanates. Table 4 summarizes the LC data identified in animal studies and provides 30-minute equivalent derived values for methyl isocyanate. Table 5 provides non-lethal data reported in human and animal studies with 30-minute equivalent derived values. Information in these tables includes species of test animals, toxicological metrics (i.e., LC, NOAEL, LOAEL), adjusted 30-minute concentration, and the justification for the composite uncertainty factors applied to calculate the derived values.

Table 4: Lethal concentration data for methyl isocyanate

Reference	Species	LC_{50} (ppm)	LC_{Lo} (ppm)	Time (min)	Adjusted 30-minute concentration* (ppm)	Composite uncertainty factor	30-min Equivalent derived value (ppm)†	Final value (ppm)‡
Dodd et al. [1985, 1986]	Guinea Pig	5.4	—	360	12.4	100§	0.124	0.12
Ferguson and Alarie [1991]	Guinea Pig	26.5	—	180	48.2	100§	0.482	0.48
Vijayaraghavan and Kaushik [1987]	Mouse	112.4	—	30	112.4	100§	1.12	1.1
Kimmerle and Eben [1964]	Rat	5.0	—	240	10.0	100§	0.1	0.10
ManTech Environmental [1992]	Rat	45.0	—	60	56.7	100§	0.567	0.57

* For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment ($C^n \times t = k$); no empirically estimated n values were available, therefore the default values were used, n = 3 for exposures greater than 30 minutes and n = 1 for exposures less than 30 minutes. For additional information, see NIOSH [2013].

†The derived value is the result of the adjusted 30-minute concentration divided by the composite uncertainty factor.

‡Values rounded to the appropriate significant figure.

§Composite uncertainty factor to account for adjustment of LC_{50} values to LC_{01} values in animals, interspecies differences and human variability.

Table 5: Non-lethal concentration data for methyl isocyanate

Reference	Species	Critical nonlethal effect	NOAEL (ppm)	LOAEL (ppm)	Time (min)	Adjusted 30-minute concentration* (ppm)	Composite uncertainty factor	30-min equivalent derived value (ppm)†	Final value (ppm)‡
Mellon Institute [1970]	Human	Ocular and respiratory irritation	0.5	—	10	0.2	3§	0.067	0.07
Mellon Institute [1963b]	Human	Ocular irritation	—	1	10	0.3	10¶	0.03	0.03
Kimmerle and Eben [1964]	Human	Ocular and mucous membranes irritation	—	4	5	0.7	10¶	0.07	0.07
Fedde et al. [1987]	Rats	Cardiac effects	—	3	120	4.8	30**	0.16	0.16
Tepper et al. [1987]	Guinea Pig	Hypoxia and metabolic acidosis	—	240	15	120	30**	4.00	4.0
Varma [1987]††	Mouse	Developmental and reproductive effects	—	2	180	3.6	30**	0.12	0.12
Varma et al. [1990]	Rat	Developmental and reproductive effects	—	9	180	16.4	30**	0.546	0.55

*For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (C^n x t = k), with n=3 for exposures greater than 30 minutes and n = 1 for exposures less than 30 minutes. For additional information, see NIOSH [2013].
†The derived value is the result of the adjusted 30-minute concentration divided by the composite uncertainty factor.
‡Values rounded to the appropriate significant figure.
§Composite uncertainty factor assigned to account for human variability.
¶Composite uncertainty factor assigned to account for adjusting from a LOAEL to NOAEL and human variability.
**Composite uncertainty factor assigned to account for adjusting from a LOAEL to NOAEL, severe effects, interspecies differences, human variability, and uncertainty about the threshold for escape-impairing effects
††Identified study is the primary basis of the IDLH value for methyl isocyanate.

3 Human Data

An accidental release in Bhopal, India is the source of most information on human exposures to methyl isocyanate. Although actual exposure concentrations are unknown, Karlsson et al. [1985] estimated a concentration range of 10 to 3,000 ppm, with higher concentrations occurring closer to the site of release, based on dispersion calculations. Although multiple deaths were reported, most occurred 8-72 hours post-release [Varma 1989; Varma and Guest 1993]. Symptoms reported with the most frequency were ocular irritation, coughing, respiratory distress, pulmonary congestion, nausea, vomiting, muscle weakness, and hypoxia resulting in CNS involvement [Kamat et al. 1985; Misra et al. 1987; Lorin and Kulling 1986; Andersson et al. 1988; Kamat et al. 1992]. Most of these symptoms resolved within 2 weeks post-release, but many of those exposed, including adults and children, reported continued restrictive respiratory, ophthalmological, neuromuscular, and gastrointestinal symptoms for years after the accident [Andersson et al. 1984, 1985; Kamat et al. 1985; Irani and Mahashur 1986; Maskati 1986; Naik et al. 1986; Khurrum and Ahmad 1987; Andersson et al. 1990; Kamat et al. 1992; Cullinan et al. 1997; Misra and Kalita 1997]. Varma [1987] conducted a preliminary survey 9 months after the Bhopal incident. A total of 3270 families surveyed and 865 women reported that they were pregnant at the time of the release of methyl isocyanate. Varma [1987] stated that 43.8% of these pregnancies did not lead to live births. In addition, 14.2% (n = 69) of the 486 live births died within 30 days compared to infant death rates of ~3% within 30 days after birth in the 2 years period after the incident. Varma [1987] concluded that exposure to methyl isocyanate adversely impacts the course of pregnancy.

In addition to information from the Bhopal release, a case report and multiple experimental studies on human volunteers exist. Skin irritation and respiratory irritation were reported in workers exposed to unknown concentrations of methyl isocyanate for unknown durations [Union Carbide 1973]. In one experimental study, four volunteers were exposed to 0.4 to 21 ppm methyl isocyanate for 1-5 minutes [Kimmerle and Eben 1964]; minor irritation of the mucous membranes was reported at 2 ppm with more pronounced ocular irritation at 4 ppm. Volunteers reported that exposure to 21 ppm was instantaneously intolerable. Another experimental study exposed 8 volunteers to 1.75 ppm for 1 minute and then re-exposed 6 of the 8 to 0.5 ppm for 10 minutes [Mellon Institute 1970]. All volunteers reported ocular irritation and multiple volunteers reported nose and throat irritation in both exposures. A third study exposed 7 male volunteers to 0.3 to 5.0 ppm for 1 minute or to 1 ppm for 10 minutes [Mellon Institute 1963b]. Exposure to 2.5 and 5.0 ppm for 1 minute resulted in eye and nose irritation. One volunteer exposed to 5.0 ppm also reported throat irritation. Volunteers exposed to 1 ppm for 10 minutes reported eye, nose, and throat irritation.

4 Summary

Methyl isocyanate is one of the most reactive isocyanates and rapidly degrades in water [Varma and Guest 1993; NAS 2003]. The reactive nature of methyl isocyanate contributes to its toxicological potential and ability to cause irritation and cytotoxicity in the respiratory tract. Numerous studies in animals and humans reported irritation of the eyes, nose and throat following exposures to methyl isocyanate. These effects varied based on exposure duration and concentration. Mild irritation in humans was reported at 2 ppm, while intolerable irritation occurred at 21 ppm [Kimmerle and Eben 1964]. Tepper et al. [1987] reported cardiac arrhythmia in rats at 4-6 months post-exposure to a 2-hour exposure to 3 ppm methyl isocyanate. Despite the absence of exposure data, Varma [1987] concluded that exposures to methyl isocyanate associated with the Bhopal incident adversely impacted pregnancies. More specifically, 43.8% of reported pregnancies (n = 865) did not result in a live birth. The infant death rates were substantially higher with 14.2% (n = 69) of the 486 live births died within 30 days compared to infant death rates of ~3% within 30 days after birth in the 2 years period after the incident. Varma [1987] also reported increased fetal resorptions and increased skeletal malformations in mice exposed for 3 hours on GD 8 to methyl isocyanate at concentrations as low as 6 ppm. This study reported a LOAEL of 2 ppm for developmental and reproductive effects, including, in mice dams exposed for 3 hours on GD 8. This represents a one-time acute exposure at a critical developmental time of the dam and fetuses. The reproductive and developmental effects occurred at lower concentrations than the cardiac effects and at concentration similar to mild irritation in exposed humans. Reproductive and development effects are identified as the most sensitive health endpoint and serve as the basis of the IDLH value for methyl isocyanate. The LOAEL of 2 ppm when adjusted to a 30-minute equivalent duration concentration is 3.6 ppm. A composite uncertainty factor of 30 was applied to account for extrapolation from a concentration that causes severe effects in animals, animal to human differences, human variability, and uncertainty about the threshold for escape-impairing effects, yielding an IDLH value of 0.12 ppm for methyl isocyanate. This IDLH value should be protective against the reproductive, developmental and cardiac effects associated with methyl isocyanate exposure. Additionally, it is supported by duration-adjusted estimates of the irritation threshold in humans [Mellon Institute 1963b; Kimmerle and Eben 1964].

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