IMMEDIATELY DANGEROUS TO LIFE OR HEALTH (IDLH) VALUE PROFILE

FOR

METHACRYLONITRILE

[CAS® NO. 126-98-7]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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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 non-routine 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) air 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 non-routine 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 methacrylonitrile (CAS® No.126-98-7). 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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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
IDLH	immediately dangerous to life or health
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance
LC	lethal concentration
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
NLM	National Library of Medicine
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
REL	recommended exposure limit
SCP	Standards Completion Program (joint effort of NIOSH and OSHA)
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 (29 CFR 1910.1000) or MSHA (30 CFR 57.5001) 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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1.0 Introduction

1.1 Overview of the IDLH Value for Methacrylonitrile

IDLH Value: 4.0 ppm (11 mg/m^3)

Basis for IDLH Value: Among the acute lethality studies, mice and rabbits appear to be the most sensitive species. The LC_{50} values in mice and rabbits were 36 and 37 ppm, respectively for a 4-hour exposure [Pozzani et al. 1968]. In the same study, no deaths or clinical signs were reported in mice or rabbits exposed to 19.7 ppm for 4-hours, indicating a steep concentration-response curve. The NOAEL of 19.7 ppm after duration adjustment yields a 30-minute equivalent concentration of 39 ppm. An uncertainty factor of 10 was applied to account for a steep-dose response relationship, animal to human differences, and human variability resulting in an IDLH value of 4.0 ppm.

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to methacrylonitrile and (2) the rationale behind the immediately dangerous to life or health (IDLH) value for methacrylonitrile. IDLH values are developed on the basis of the 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 methacrylonitrile, the in-depth literature search was conducted through September 2016.

1.3 General Substance Information

Chemical: Methacrylonitrile

CAS No: 126-98-7

Synonyms: Methylacrylonitrile; 2-methyl-2-Propenenitrile; 2-Cyanopropene-1; Isopropene cyanide[*]

Chemical category: Nitriles[†]

References: [*] NLM [2017], [†] IFA [2017]

Structural formula:

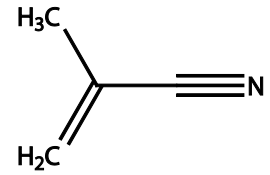

Table 1 highlights selected physiochemical properties of methacrylonitrile relevant to IDLH conditions. Table 2 provides alternative exposure guidelines for methacrylonitrile. Table 3 summarizes the Acute Exposure Guidelines Level (AEGL) values for methacrylonitrile.

Table 1: Physiochemical Properties of Methacrylonitrile

Property	Value
Molecular weight	67.09[‡]
Chemical formula	C_4H_5N
Description	Colorless liquid
Odor	Bitter almond
Odor Threshold	6.9 ppm[§]
UEL	13.2%[†]
LEL	1.7%[†]
Vapor pressure	0.4 mmHg at 25°C (77°F)[‡]
Flash point	12.78°C (55°F)[‡] - open cup
Ignition temperature	465°C (869°F)[‡]
Solubility	Sparingly soluble in water[†]

References: [‡] HSDB [2017]; [§]AIHA [2013]; [†] IFA [2017]

Table 2: Alternative Exposure Values for Methacrylonitrile

Organization	Value
NIOSH (1994) IDLH value*	None
NIOSH REL†	1 ppm (3 mg/m^3), 8-hr TWA [skin]
OSHA PEL^	Not available
ACGIH TLV®‡	1 ppm (3 mg/m^3), 8-hr TWA [skin]
AIHA ERPGs™+	Not available
AIHA WEELs®+	Not available

References: [*]NIOSH [1994]; [†]NIOSH [2017]; [^]OSHA [2017]; [‡]ACGIH [2016]; [+]AIHA [2014]

Table 3: AEGL Values for Methacrylonitrile

Classification	10-min	30-min	1-hour	4-hour	8-hour	End Point [reference]
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	1.3 ppm 3.5 mg/m^3	1.3 ppm 3.5 mg/m	1.0 ppm 2.7 mg/m^3	0.67 ppm 1.8 mg/m^3	0.33 ppm 0.89 mg/m^3	Three-fold reduction of AEGL-3
AEGL-3	3.9 ppm 11 mg/m^3	3.9 ppm 11 mg/m^3	3.1ppm 8.5 mg/m^3	2.0 ppm 5.5 mg/m^3	0.99 ppm 2.7 mg/m^3	No effect level for lethality in mice and rabbits exposed to 19.7 ppm for 4 h [Pozzani et al. 1968]

Reference: NAS [2014].

2.0 Animal Toxicity Data

Several acute inhalation studies are available. Pozzani et al. [1968] reported 100% mortality in rats exposed to 85,500 ppm (essentially saturated vapor) for 3.75-14 minutes. Similarly, Younger Labs [1960] found 100% mortality in rats exposed to 85,500 ppm for 25 minutes. All rats in this latter study exhibited labored breathing, pawing at face and nose, cyanosis, and collapse prior to death. Pozzani et al. [1968] also exposed several other species in addition to rats. They determined LC_{50} values of 36, 37, and 88 ppm, respectively, for mice, rabbits and guinea pigs exposed for 4 hours. No effect was seen at 19.7 ppm for 4 hours in mice or rabbits in the same study. Based on the LC_{50} data, mice and rabbits appear to be the most sensitive species. Pozzani et al. [1968] also exposed one dog to 52.5 ppm for 7 hours and one dog each to 106 ppm for 3 and 7 hours; all of these dogs died. Dupont [1968a] exposed an unspecified number of dogs to 87.5 ppm for 7 hours, resulting in 100% mortality. Vomiting, convulsions, unconsciousness and irregular breathing were seen in the dogs prior to death. No deaths or clinical signs were seen in an unspecified number of dogs exposed to 40 ppm for 7 hours [Dupont 1968b].

Table 4 summarizes the lethal concentration (LC) data identified in animal studies and provides 30-minute equivalent derived values for methacrylonitrile. Table 5 provides non-lethal data reported in animal studies with 30-minute equivalent derived values. Information in these tables includes species of test animals, toxicological metrics (i.e., LC, BMCL, 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 Methacrylonitrile

Reference	Species	LC_{50} (ppm)	Other Lethality (ppm)	Time (min)	Adjusted 30-min Concentration* (ppm)	Composite Uncertainty Factor	30-min Equivalent Derived Value (ppm)†	Final Value (ppm) €
Pozzani et al. [1968]	Dog	--	52.5‡	420	127	30±	4.23	4.2
Pozzani et al. [1968]	Guinea Pig	88	--	240	176	30±	5.87	5.9
Pozzani et al. [1968]	Mouse	36	--	240	72	30±	2.4	2.4
Pozzani et al. [1968]	Rabbit	37	--	240	74	30±	2.46	2.5
Pozzani et al. [1968]	Rat (M)	328	--	240	656	30±	21.9	22
Pozzani et al. [1968]	Rat (F)	496	--	240	992	30±	33.1	33
DuPont [1968a]	Rat	440	--	240	880	30±	29.3	29

*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)

†The derived value is the result of the adjusted 30-min value divided by the composite uncertainty factor. The composite uncertainty factor used varies for each study on the basis of the nature and severity of the endpoint observed.

€Values rounded to the appropriate significant figure.

‡ One dog was exposed and it died.

± Composite uncertainty factor to account for adjustment of LC_{50} values to LC_{01} values, use of lethal concentration threshold in animals, interspecies differences, and human variability.

Table 5: Nonlethal Concentration Data for Methacrylonitrile

Reference	Species	Critical adverse health effects	NOAEL (ppm)	LOEL (ppm)	Time (min)	Adjusted 30-min Concentration* (ppm)	Composite Uncertainty Factor	30-min Equivalent Derived Value (mg/m^3)†	Final Value (mg/m^3) €
Pozzani et al. [1968]	Mouse	No health effected associated with this concentration	19.7	--	240	39.4	10±	3.9	4.0
Pozzani et al. [1968]	Rabbit	No health effected associated with this concentration	19.7	--	240	39.4	10±	3.9	4.0
Dupont [1968b]	Dog	No health effected associated with this concentration	40‡	--	420	96	10±	9.6	10

*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)

†The derived value is the result of the adjusted 30-min value divided by the composite uncertainty factor. The composite uncertainty factor used varies for each study on the basis of the nature and severity of the endpoint observed.

€Values rounded to the appropriate significant figure.

‡ No deaths or clinical signs reported.

±Composite uncertainty factor assigned to account for a steep-dose response relationship, interspecies differences and human variability.

3.0 Human Data

No human acute lethality studies were found. Only one human exposure study was found [Pozzani et al. 1968]. A group of 8-9 volunteers was exposed to various concentrations of methacrylonitrile, inhaling each concentration twice in the following sequence: 24, 14, 0, 7, 14, 24, 7, 2, 0, and 2 ppm. One-minute exposures to 24 ppm resulted in nose, throat, and eye irritation in 6-22% of the volunteers. A few of the volunteers experienced irritation during the course of 10-minute exposures to 2 or 14 ppm.

4.0 Summary

Among the acute lethality studies, mice and rabbits appear to be the most sensitive species. The LC_{50} values in mice and rabbits were 36 and 37 ppm, respectively for a 4-hour exposure [Pozzani et al. 1968]. In the same study, no deaths or clinical signs were reported in mice or rabbits exposed to 19.7 ppm for 4-hours, indicating a steep concentration-response curve. The NOAEL of 19.7 ppm after duration adjustment yields a 30-minute equivalent concentration of 39 ppm. An uncertainty factor of 10 was applied to account for a steep-dose response relationship, animal to human differences, and resulting in an IDLH value of 4.0 ppm.

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