IMMEDIATELY DANGEROUS TO LIFE OR HEALTH (IDLH) VALUE PROFILE

FOR

BENZONITRILE

[CAS NO. 100-47-0]

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 air concentration values (IDLH 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 benzonitrile (CAS # 100-47-0). 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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Content

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Levels
AIHA	American Industrial Hygiene Association
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
C	ceiling
CAS	chemical abstract service
ERPG	Emergency Response Planning Guidelines
IDLH	immediately dangerous to life or health
LC_{Lo}	lowest concentration of a chemical 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
NAC	National Advisory Committee
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
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	Standard Completion Program
STEL	short term exposure limit
TLV	threshold limit value
TWA	time weighted average
UEL	upper explosive limit
WEEL	workplace environmental exposure level

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 or 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 (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 USEPA noncancer health assessments [USEPA 2014].

Acute Toxicity: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hours.

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 [USEPA 2014] (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 [USEPA 2014].

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 [USEPA 2014].

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism [USEPA 2014].

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 situation 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. Mode of action is distinguished from the more detailed mechanism of action, which 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 non-governmental 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, short-term (STELs), or time-weighted average (TWA) limits.

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

Permissible Exposure Limit (PEL): 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, STEL, 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, STEL, 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, short-term (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 a TWA or ceiling limit.

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1.0 Introduction

1.1 Overview of the IDLH Value for Benzonitrile

IDLH Value 47 ppm (198 mg/m^3)

Basis for IDLH Value: The IDLH value is based on a lethality study in which all mice exposed to 700 ppm for 4 hours died [MacEwen and Vernot 1974]. The 30-minute duration adjusted concentration is 1,400 ppm. This value is supported by LOAEL values of 890 ppm and 900 ppm for potential escape impairing effects of poor coordination and labored breathing observed in mice and rats, respectively, following a 1-hour exposure [MacEwen and Vernot 1974]. The 30-minute duration adjusted concentrations are 1,121 and 1,134 ppm, respectively. An uncertainty factor of 30 to account for extrapolation from a concentration that is lethal to animals, animal to human differences, and human variability is applied to the concentration of 1,400 ppm, resulting in an IDLH value of **47 ppm**.

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to benzonitrile and (2) the rationale behind the Immediately Dangerous to Life or Health (IDLH) value for benzonitrile. IDLH values are developed based on 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, LC_{50} values). For benzonitrile, the in-depth literature search was conducted through February 2014.

1.3 General Substance Information

Chemical: Benzonitrile

CAS No: 100-47-0

Synonyms: Cyano-benzene; Phenyl cyanide; Benzoic acid nitrile*

Chemical category: Nitriles†

Structural formula:

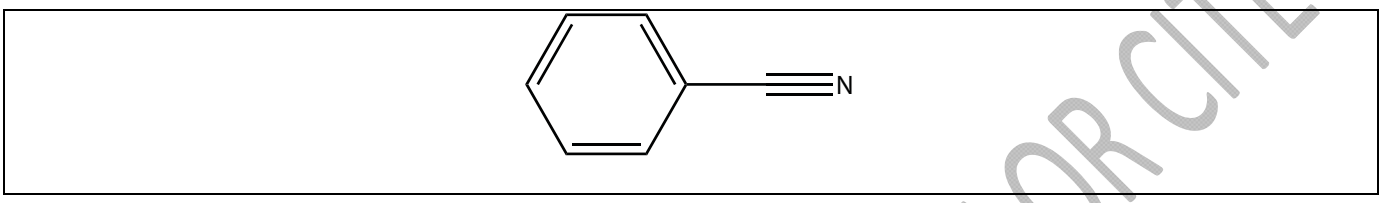

Table 1 highlights selected physiochemical properties of benzonitrile relevant to IDLH conditions. Table 2 provides alternative exposure guidelines for benzonitrile. Table 3 summarizes the Acute Exposure Guidelines Level (AEGL) values for benzonitrile.

Table 1: Physiochemical Properties of Benzonitrile

Property	Value
Molecular weight	103.12‡
Chemical formula	C_7H_5N
Description	Colorless liquid
Odor	Volatile oil of almond scent
Odor Threshold	2.90×10^{-5} mg/L (0.007 ppm).‡
UEL	12%†
LEL	9%†
Vapor pressure	2×10^{-13} mmHg at 20°C (68°F)‡
Flash point	67°C (152.6°F)†
Ignition temperature	550°C (1022°F)†
Solubility	Sparingly soluble in water†

Abbreviation: °C – Celsius; °F – Fahrenheit; mmHg – millimeter mercury; LEL – lower explosive limit; UEL – upper explosive limit
* NLM [2012]
† IFA [2012]
‡ HSDB [2012]

Table 2: Alternative Exposure Guidelines for Benzonitrile

Organization	Value
Original SCP IDLH value	None
NIOSH REL	Not available
OSHA PEL	Not available
ACGIH TLV [2014]	Not available
AIHA ERPG [2010]	Not available
AIHA WEEL [2010]	Not available

Abbreviation: ACGIH – American Conference of Governmental Industrial Hygienists; AIHA – American Industrial Hygiene Association; ERPG – Emergency Response Preparedness Guidelines; IDLH – immediately dangerous to life or health; NIOSH – National

Institute for Occupational Safety and Health; OSHA – Occupational Safety and Health Administration; PEL – permissible exposure limit; REL – recommended exposure limit; SCP – Standards Completion Program; WEEL – workplace environmental exposure level

Table 3: AEGL Values for Benzonitrile

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	11 ppm (48 mg/m^3)	7.8 ppm (33 mg/m^3)	6.2 ppm (26 mg/m^3)	2.5 ppm (10 mg/m^3)	1.2 ppm (5.2 mg/m^3)	One-third of AEGL-3 values
AEGL-3	34 ppm (140 mg/m^3)	24 ppm (99 mg/m^3)	19 ppm (79 mg/m^3)	7.4 ppm (31 mg/m^3)	3.7 ppm (16 mg/m^3)	Estimated lethal threshold in mice [MacEwen and Vernot 1974]

Abbreviation: AEGL – acute exposure guideline levels; mg/m^3 – milligrams per cubic meter; min – minute; NR – not recommended due to insufficient data; ppm – parts per million

* **References**: NAS [2014]

2.0 Animal Toxicity Data

Some of the lethality studies reported non-lethal effects. The MacEwen and Vernot [1974] lethality study reported non-lethal effects in mice exposed to 890 ppm of benzonitrile for durations ranging from 60 to 120 minutes and rats exposed to 900 ppm for 60 to 240 minutes. Mice showed signs of irritation of the extremities during the first hour of exposure, followed by poor coordination and labored breathing after 60 to 90 minutes; these effects could be identified as escape-impairing. The rats showed signs of irritation of extremities, labored breathing, poor coordination, and decreased weight gain; these effects could also be escape-impairing. Mice exposed for 4 hours in the same study also had hepatic congestion and sinusoidal dilatation. Industrial Bio-Test [1970] exposed groups of male (n = 5) and female (n =5) rats to benzonitrile at concentrations of 190 and 1,900 ppm for 4 hours and observed for 14 days. No effects or deaths were reported in animals exposed to 190 ppm. In the higher treatment group, 3 female rats died after exposure to 1,900 ppm. Two of the animals died 2 hours post exposure, while the third died 6 days after exposure. NAS [2014] noted that the clinical signs of acute toxicity of benzonitrile included labored breathing, poor coordination, hypoactivity, salivation, lacrimation, muscular weakness and dyspnea.

Table 4 summarizes the LC data identified in animal studies and provides 30-minute equivalent derived values for benzonitrile. 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, 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 Benzonitrile

Reference	Species	Other lethality (ppm)	LC_{Lo} (ppm)	Time (min)	Adjusted 30-min Concentration*	Composite Uncertainty Factor	Derived Value† (ppm)
MacEwen and Vernot [1974]	**Mouse**	**700‡**	**--**	**240**	**1,400**	**30±**	**47**
Industrial Bio-Test [1970]	Rat	1,900§	--	240	3,800	30±	127

Abbreviation: LC – lethal concentration; LC_{Lo} – lowest concentration of a chemical that caused death in humans or animals; min – minute; ppm – parts per million

* For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (C^n x 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-minute concentration divided by the composite uncertainty factor.

‡ 700 ppm reported by MacEwen and Vernot [1974] resulted in 100% mortality.

±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.

§1900 ppm reported by Industrial BioTest [1970] resulted in 30% mortality.

Table 5: Non-lethal Concentration Data for Benzonitrile

Reference	Species	NOAEL (ppm)	LOAEL (ppm)	Time (min)	Adjusted 30-min Concentration*	Composite Uncertainty Factor	Derived Value† (ppm)
MacEwen and Vernot [1974]	Mouse	--	890	60	1,121	10±	112
MacEwen and Vernot [1974]	Rat	--	900	60	1,134	10±	113
MacEwen and Vernot [1974]	Rat	--	900	180	1,635	10±	164
Industrial Bio-Test [1970]	Rat	190	--	240	380	3‡	127

Abbreviation: NOAEL – no observed adverse effect level; min – minute; LOAEL – lowest observed adverse effect level; ppm – parts per million

* For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (C^n x 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-minute concentration divided by the composite uncertainty factor.

±Composite uncertainty factor assigned to account for adjusting from a LOAEL to NOAEL, interspecies differences and human variability.

‡Composite uncertainty factor assigned to account for interspecies differences and human variability

3.0 Human Data

No relevant human studies were located. Snyder [1990] included a report of an occupational accident where a worker was drenched in benzonitrile. The worker experienced severe respiratory distress, convulsions and periods of unconsciousness. No additional information about the exposure scenario or magnitude was provided.

4.0 Summary

No human data were available to serve as the basis of the IDLH value for benzonitrile. Animal data are available that include description of lethality and non-lethal effects in rodents. MacEwan and Vernot [1974] reported 100% lethality in mice exposed to 700 ppm for 4 hours; this serves as the basis of the IDLH value for benzonitrile. A 30-minute duration equivalent concentration was calculated at 1,400 ppm. Rats and mice experience poor coordination and labored breathing after a 1-hour exposure period to 890 and 900 ppm, respectively [MacEwen and Vernot 1974]. The LOAEL value of 890 ppm was duration adjusted to a 30-minute exposure concentration, resulting in a value of 1,121 ppm. The similarity of the duration-adjusted values for lethality at 1,400 ppm and non-lethal effects at 1,121 ppm reflects either a steep concentration–response curve or uncertainties with the duration extrapolation. The IDLH value is based on 100% lethality in mice exposed to 700 ppm for 4 hours [MacEwen and Vernot 1974]. Application of an uncertainty factor of 30 to the adjusted 30-minute concentration of 1,400 ppm to account for extrapolation from a concentration that is lethal to animals, animal to human differences, and human variability, yields an IDLH value for benzonitrile of 47 ppm.

It should be noted that the IDLH value for benzonitrile differs by more than an order of magnitude from the AEGL-2 30-minute value, which is intended to represent an airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape [NAS 2001]. Data to calculate an AEGL-2 value for benzonitrile were deemed insufficient resulting in the establishment of an AEGL-2 equal to 1/3 of the calculated AEGL-3 value, which is intended to represent an airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death [NAS 2001, 2014]. The AEGL-3 value for 30-minutes was set at 24 ppm and was based on lethal threshold estimates in mice reported in MacEwan and Vernot [1974]. NIOSH used the same

study as the basis of the IDLH value of 47 ppm for benzonitrile. The differences between the AEGL-3 value and IDLH value can be attributed to the alternative critical endpoint and duration adjustments.

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