

# IDLH

## IMMEDIATELY DANGEROUS to LIFE or HEALTH VALUE PROFILE

Benzonitrile  
CAS<sup>®</sup> No. 100-47-0

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

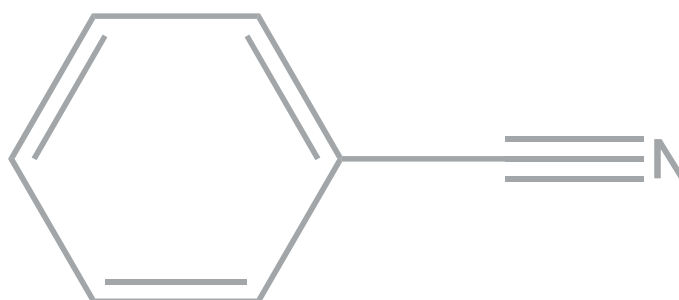


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## Foreword

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 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 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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Prevention

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## Abbreviations

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

**EC<sub>50</sub>:** 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<sub>01</sub>:** The statistically determined concentration of a substance in the air that is estimated to cause death in 1% of the test animals.

**LC<sub>50</sub>:** 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<sub>10</sub>:** The lowest lethal concentration of a substance in the air reported to cause death, usually for a small percentage of the test animals.

**LD<sub>50</sub>:** 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<sub>10</sub>**: 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<sub>50</sub>**: 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.

## Acknowledgments

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# 1 Introduction

## 1.1 Overview of the IDLH Value for Benzonitrile

**IDLH value:** 14 ppm (66 mg/m<sup>3</sup>)

**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 100 to account for extrapolation from a concentration that is 100% 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 14 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<sub>50</sub> values). For benzonitrile, the in-depth literature search was conducted through May 2016.

## 1.3 General Substance Information

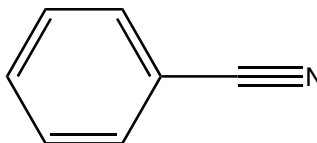
**Chemical:** Benzonitrile

**CAS No:** 100-47-0

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

**Chemical category:** Nitriles<sup>†</sup>

**Structural formula:**



References: \*NLM [2016]; †IFA [2016]

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 (AEG) values for benzonitrile.

**Table 1: Physiochemical properties of benzonitrile**

Property	Value
Molecular weight	103.12*
Chemical formula	C <sub>7</sub> H <sub>5</sub> N
Description	Colorless liquid
Odor	Volatile oil of almond scent
Odor threshold	2.90 × 10 <sup>-5</sup> mg/L (0.007 ppm)*
UEL	12%†
LEL	9%†
Vapor pressure	2 × 10 <sup>-13</sup> mmHg at 20°C (68°F)*
Flash point	67°C (152.6°F)†
Ignition temperature	550°C (1022°F)†
Solubility	Sparingly soluble in water†

References: \*HSDB [2016]; †IFA [2016]

**Table 2: Alternative exposure guidelines for benzonitrile**

Organization	Value
Revised (1994) IDLH value*	None
NIOSH REL†	None
OSHA PEL‡	None
ACGIH TLV®§	None
AIHA ERPG™¶	None
AIHA WEEL®¶	None

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



**Table 3: AEGL values for benzonitrile**

<b>Classification</b>	<b>10-min</b>	<b>30-min</b>	<b>1-hour</b>	<b>4-hour</b>	<b>8-hour</b>	<b>Endpoint [reference]</b>
AEGL-1	NR	NR	NR	NR	NR	NR
AEGL-2	11 ppm (48 mg/m <sup>3</sup> )	7.8 ppm (33 mg/m <sup>3</sup> )	6.2 ppm (26 mg/m <sup>3</sup> )	2.5 ppm (10 mg/m <sup>3</sup> )	1.2 ppm (5.2 mg/m <sup>3</sup> )	One-third of AEGL-3 values
AEGL-3	34 ppm (140 mg/m <sup>3</sup> )	24 ppm (99 mg/m <sup>3</sup> )	24 ppm (99 mg/m <sup>3</sup> )	7.4 ppm (31 mg/m <sup>3</sup> )	3.7 ppm (16 mg/m <sup>3</sup> )	Estimated lethal threshold in mice [MacEwen and Vernot 1974]

Reference: NAS [2014]

## 2 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. Labored breathing and poor coordination may be considered escape-impairing effects. 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	LC <sub>Lo</sub> (ppm)	Time (min)	Adjusted 30-minute concentration* (ppm)	Composite uncertainty factor	30-min Equivalent derived value (ppm) <sup>†</sup>	Final value (ppm) <sup>‡</sup>
MacEwen and Vernot [1974] <sup>§</sup>	Mouse	700 <sup>†</sup>	—	240	1,400	100 <sup>**</sup>	14	14
Industrial Bio-Test [1970]	Rat	1,900 <sup>††</sup>	—	240	3,800	30 <sup>##</sup>	126.7	127

\*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. Additional information on the calculation of duration-adjusted concentrations can be found in NIOSH [2013].

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

<sup>‡</sup>Values rounded to the appropriate significant figure.

<sup>§</sup>Identified study is the primary basis of the IDLH value for benzonitrile.

<sup>†</sup>700 ppm reported by MacEwen and Vernot [1974] resulted in 100% mortality.

<sup>\*\*</sup>Composite uncertainty factor to account for adjustment of LC100 values to LC01 values, interspecies differences and human variability.

<sup>††</sup>1900 ppm reported by Industrial Bio-Test [1970] resulted in 30% mortality.

<sup>##</sup>Composite uncertainty factor to account for the use of lethal concentration threshold in animals, interspecies differences, and human variability.

**Table 5: Non-lethal concentration data for benzonitrile**

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) <sup>†</sup>	Final value (ppm) <sup>‡</sup>
MacEwen and Vernot [1974]	Mouse	Extremities irritation; labored breathing	—	890	60	1,121	10 <sup>§</sup>	112.1	112
MacEwen and Vernot [1974]	Rat	Extremities irritation	—	900	60	1,134	10 <sup>§</sup>	113.4	113
MacEwen and Vernot [1974]	Rat	Labored breathing	—	900	180	1,635	10 <sup>§</sup>	163.5	164

\*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. Additional information on the calculation of duration-adjusted concentrations can be found in NIOSH [2013].

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

<sup>‡</sup>Values rounded to the appropriate significant figure.

<sup>§</sup>Composite uncertainty factor assigned to account for adjusting from a LOAEL to NOAEL, interspecies differences and human variability.

## 3 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 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 [MacEwan 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 [MacEwan and Vernot 1974]. Application of an uncertainty factor of 100 to the adjusted 30-minute concentration of 1,400 ppm to account for extrapolation from a concentration that is 100% lethal to animals, animal to human differences, and human variability, yields an IDLH value for benzonitrile of 14 ppm.

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