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IMMEDIATELY DANGEROUS TO LIFE OR HEALTH (IDLH) VALUE PROFILE

FOR

ACETONITRILE

[CAS[®] No.75-05-8]

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

**External Review Draft
April 2017**

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1 Foreword

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

12
13 The immediately dangerous to life or health (IDLH) air concentration values developed by the National Institute
14 for Occupational Safety and Health (NIOSH) characterize these high-risk exposure concentrations and conditions
15 [NIOSH 2013]. IDLH values are based on a 30-minute exposure duration and have traditionally served as a key
16 component of the decision logic for the selection of respiratory protection devices [NIOSH 2004].

17
18 Occupational health professionals have employed these values beyond their initial purpose as a component of the
19 *NIOSH Respirator Selection Logic* to assist in developing risk management plans for non-routine work practices
20 governing operations in high-risk environments (e.g., confined spaces) and the development of emergency
21 preparedness plans.

22
23 The approach used to derive IDLH values for high priority chemicals is outlined in the *NIOSH Current*
24 *Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health Values* [NIOSH 2013].
25 CIB 66 provides (1) an update on the scientific basis and risk assessment methodology used to derive IDLH
26 values, (2) the rationale and derivation process for IDLH values, and (3) a demonstration of the derivation of
27 scientifically credible IDLH values using available data resources.

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1 The purpose of this technical report is to present the IDLH value for acetonitrile (CAS® No. 75-05-8). The
2 scientific basis, toxicologic data, and risk assessment approach used to derive the IDLH value are summarized to
3 ensure transparency and scientific credibility.

4

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6 Director
7 National Institute for Occupational Safety and Health
8 Centers for Disease Control and Prevention

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1 Abbreviations

2		
3	ACGIH®	American Conference of Governmental Industrial Hygienists
4	AEGLs	Acute Exposure Guideline Levels
5	AIHA®	American Industrial Hygiene Association
6	BMC	benchmark concentration
7	BMD	benchmark dose
8	BMCL	benchmark concentration lower confidence limit
9	C	ceiling value
10	°C	degrees Celsius
11	CAS®	Chemical Abstracts Service, a division of the American Chemical Society
12	ERPGs™	Emergency Response Planning Guidelines
13	°F	degrees Fahrenheit
14	IDLH	immediately dangerous to life or health
15	IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance)
16		
17	LC	lethal concentration
18	LC ₅₀	median lethal concentration
19	LC _{LO}	lowest concentration that caused death in humans or animals
20	LEL	lower explosive limit
21	LOAEL	lowest observed adverse effect level
22	mg/m ³	milligram(s) per cubic meter
23	min	minutes
24	mmHg	millimeter(s) of mercury
25	NAC	National Advisory Committee
26	NAS	National Academy of Sciences
27	NIOSH	National Institute for Occupational Safety and Health
28	NLM	National Library of Medicine
29	NOAEL	no observed adverse effect level
30	NOEL	no observed effect level
31	NR	not recommended
32	OSHA	Occupational Safety and Health Administration
33	PEL	permissible exposure limit
34	ppm	parts per million
35	RD ₅₀	concentration of a chemical in the air that is estimated to cause a 50% decrease in the respiratory rate
36		
37	REL	recommended exposure limit
38	SCP	Standards Completion Program (joint effort of NIOSH and OSHA)
39	STEL	short-term exposure limit
40	TLV®	Threshold Limit Value
41	TWA	time-weighted average
42	UEL	upper explosive limit
43	WEELs®	Workplace Environmental Exposure Levels
44	µg/kg	microgram(s) per kilogram of body weight
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2 **Glossary**

3

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

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

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

20 **Acute toxicity:** Any poisonous effect produced within a short period of time following an exposure, usually 24 to
21 96 hours [U.S. EPA 2016].

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

24 **Benchmark dose/concentration (BMD/BMC):** A dose or concentration that produces a predetermined change in
25 response rate of an effect (called the benchmark response, or BMR) compared to background [U.S. EPA
26 2016] (additional information available at <http://www.epa.gov/ncea/bmds/>).

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

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

30 **Bolus exposure:** A single, relatively large dose.

31 **Ceiling value (“C”):** U.S. term in occupational exposure indicating the airborne concentration of a potentially
32 toxic substance that should never be exceeded in a worker’s breathing zone.

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

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

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- 1 **Dose:** The amount of a substance available for interactions with metabolic processes or biologically significant
2 receptors after crossing the outer boundary of an organism [U.S. EPA 2016].
- 3 **EC₅₀:** A combination of the effective concentration of a substance in the air and the exposure duration that is
4 predicted to cause an effect in 50% (one half) of the experimental test subjects.
- 5 **Emergency Response Planning Guidelines (ERPGsTM):** Maximum airborne concentrations below which nearly
6 all individuals can be exposed without experiencing health effects for 1-hour exposure. ERPGs are presented
7 in a tiered fashion, with health effects ranging from mild or transient to serious, irreversible, or life
8 threatening (depending on the tier). ERPGs are developed by the American Industrial Hygiene Association
9 [AIHA 2006].
- 10 **Endpoint:** An observable or measurable biological event or sign of toxicity, ranging from biomarkers of initial
11 response to gross manifestations of clinical toxicity.
- 12 **Exposure:** Contact made between a chemical, physical, or biological agent and the outer boundary of an
13 organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the
14 organism (e.g., skin, lungs, gut).
- 15 **Extrapolation:** An estimate of the response at a point outside the range of the experimental data, generally
16 through the use of a mathematical model, although qualitative extrapolation may also be conducted. The
17 model may then be used to extrapolate to response levels that cannot be directly observed.
- 18 **Hazard:** A potential source of harm. Hazard is distinguished from risk, which is the probability of harm under
19 specific exposure conditions.
- 20 **Immediately dangerous to life or health (IDLH) condition:** A condition that poses a threat of exposure to
21 airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse
22 health effects or prevent escape from such an environment [NIOSH 2004, 2013].
- 23 **IDLH value:** A maximum (airborne concentration) level above which only a highly reliable breathing apparatus
24 providing maximum worker protection is permitted [NIOSH 2004, 2013]. IDLH values are based on a 30-
25 minute exposure duration.
- 26 **LC₀₁:** The statistically determined concentration of a substance in the air that is estimated to cause death in 1% of
27 the test animals.
- 28 **LC₅₀:** The statistically determined concentration of a substance in the air that is estimated to cause death in 50%
29 (one half) of the test animals; median lethal concentration.
- 30 **LC_{LO}:** The lowest lethal concentration of a substance in the air reported to cause death, usually for a small
31 percentage of the test animals.
- 32
- 33 **LD₅₀:** The statistically determined lethal dose of a substance that is estimated to cause death in 50% (one half) of
34 the test animals; median lethal concentration.
- 35 **LD_{LO}:** The lowest dose of a substance that causes death, usually for a small percentage of the test animals.
- 36 **LEL:** The minimum concentration of a gas or vapor in air, below which propagation of a flame does not occur in
37 the presence of an ignition source.

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- 1 **Lethality:** Pertaining to or causing death; fatal; referring to the deaths resulting from acute toxicity studies. May
2 also be used in lethality threshold to describe the point of sufficient substance concentration to begin to cause
3 death.
- 4 **Lowest observed adverse effect level (LOAEL):** The lowest tested dose or concentration of a substance that has
5 been reported to cause harmful (adverse) health effects in people or animals.
- 6 **Mode of action:** The sequence of significant events and processes that describes how a substance causes a toxic
7 outcome. By contrast, the term *mechanism of action* implies a more detailed understanding on a molecular
8 level.
- 9 **No observed adverse effect level (NOAEL):** The highest tested dose or concentration of a substance that has
10 been reported to cause no harmful (adverse) health effects in people or animals.
- 11 **Occupational exposure limit (OEL):** Workplace exposure recommendations developed by governmental
12 agencies and nongovernmental organizations. OELs are intended to represent the maximum airborne
13 concentrations of a chemical substance below which workplace exposures should not cause adverse health
14 effects. OELs may apply to ceiling limits, STELs, or TWA limits.
- 15 **Peak concentration:** Highest concentration of a substance recorded during a certain period of observation.
- 16 **Permissible exposure limits (PELs):** Occupational exposure limits developed by OSHA (29 CFR 1910.1000) or
17 MSHA (30 CFR 57.5001) for allowable occupational airborne exposure concentrations. PELs are legally
18 enforceable and may be designated as ceiling limits, STELs, or TWA limits.
- 19
- 20 **Point of departure (POD):** The point on the dose–response curve from which dose extrapolation is initiated. This
21 point can be the lower bound on dose for an estimated incidence or a change in response level from a
22 concentration-response model (BMC), or it can be a NOAEL or LOAEL for an observed effect selected from
23 a dose evaluated in a health effects or toxicology study.
- 24 **RD₅₀:** The statistically determined concentration of a substance in the air that is estimated to cause a 50% (one
25 half) decrease in the respiratory rate.
- 26 **Recommended exposure limit (REL):** Recommended maximum exposure limit to prevent adverse health
27 effects, based on human and animal studies and established for occupational (up to 10-hour shift, 40-hour
28 week) inhalation exposure by NIOSH. RELs may be designated as ceiling limits, STELs, or TWA limits.
- 29 **Short-term exposure limit (STEL):** A worker’s 15-minute time-weighted average exposure concentration that
30 shall not be exceeded at any time during a work day.
- 31 **Target organ:** Organ in which the toxic injury manifests in terms of dysfunction or overt disease.
- 32 **Threshold Limit Values (TLVs[®]):** Recommended guidelines for occupational exposure to airborne
33 contaminants, published by the American Conference of Governmental Industrial Hygienists (ACGIH[®]).
34 TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is
35 believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without
36 adverse effects. TLVs may be designated as ceiling limits, STELs, or 8-hr TWA limits.
- 37 **Time-weighted average (TWA):** A worker’s 8-hour (or up to 10-hour) time-weighted average exposure
38 concentration that shall not be exceeded during an 8-hour (or up to 10-hour) work shift of a 40-hour week.
39 The average concentration is weighted to take into account the duration of different exposure concentrations.
- 40 **Toxicity:** The degree to which a substance is able to cause an adverse effect on an exposed organism.

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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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2
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1.0 Introduction

1.1 Overview of the IDLH Value for Acetonitrile

IDLH Value: 113 ppm (190 mg/m³)

Basis for IDLH Value: The mouse LC₅₀ value of 2,693 ppm for a 60 minute exposure to acetonitrile [Willhite 1981] was selected as the basis for the IDLH value. Duration adjustment resulted in the calculation of a 30-minute equivalent LC₅₀ value of 3,393 ppm. An uncertainty factor of 30 was applied to account for extrapolation from a concentration that is lethal to animals, animal to human differences and human variability, resulting in an IDLH value for acetonitrile of 113 ppm.

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to acetonitrile and (2) the rationale behind the immediately dangerous to life or health (IDLH) value for acetonitrile. 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 LC₅₀ values). For acetonitrile, the in-depth literature search was conducted through September 2016.

1.3 General Substance Information

Chemical: Acetonitrile

CAS No: 75-05-8

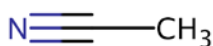
Synonyms: Cyanomethane; ethanenitrile; nitrile of acetic acid; methyl cyanide; ethyl nitrile; methanecarbonitrile*

Chemical category: Nitriles

References: * NAS [2014], † IFA [2017]

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1 **Structural formula:**



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

11 **Table 1: Physiochemical Properties of Acetonitrile**

12
13

Property	Value
Molecular weight	41.05 [‡]
Chemical formula	CH ₃ CN*
Description	Colorless liquid [†]
Odor	Pungent
Odor Threshold	Not available
UEL	Not available
LEL	Not available
Vapor pressure	88.8 mmHg at 25°C (77°F) [†]
Flash point	5.6°C (42.1°F) open cup [†]
Ignition temperature	Not available
Solubility	Infinitely soluble in water; readily miscible with ethanol, ether, acetone, chloroform, carbon tetrachloride, and ethylene chloride; immiscible with saturated hydrocarbons (petroleum fractions) [†]

14 **References:** [‡] HSDB [2017]; ^{*} NLM [2017]; [†] IFA [2017]

15
16
17 **Table 2: Alternative Exposure Values for Acetonitrile**

18

Organization	Value
NIOSH (1994) IDLH value*	None
NIOSH REL [†]	20 ppm (33 mg/m ³), 8-hr TWA
OSHA PEL [^]	40 ppm (66 mg/m ³), 8-hr TWA
ACGIH TLV [‡]	20 ppm (33 mg/m ³), 8-hr TWA
AIHA ERPGs ^{TM+}	None
AIHA WEELS ^{@+}	None

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

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Table 3: AEGL Values for Acetonitrile

Classification	10-min	30-min	1-hour	4-hour	8-hour	End Point [reference]
AEGL-1	13 ppm 22 mg/m ³	13 ppm 22 mg/m ³	13 ppm 22 mg/m ³	13 ppm 22 mg/m ³	NR	Slight chest tightness and cooling sensation in lung [Pozzani et al. 1959]
AEGL-2	80 ppm 130 mg/m ³	80 ppm 130 mg/m ³	50 ppm 84mg/m ³	21 ppm 35mg/m ³	14 ppm 24 mg/m ³	One-third of AEGL-3 values
AEGL-3	240 ppm 74 mg/m ³	240 ppm 400 mg/m ³	150 ppm 250 mg/m ³	64 ppm 110 mg/m ³	42 ppm 71 mg/m ³	No-effect level for maternal and fetal lethality in rats [Sailienfait et al. 1993]

Reference: NAS [2014].

2.0 Animal Toxicity Data

LC₅₀ data and information on nonlethal effects of acetonitrile are available in multiple species, with pulmonary effects increasing with progression to lethality as the exposure concentration increased [Monsanto 1986; Pozzani et al. 1959; Willhite 1981]. A study performed in rats reported a LOAEL of 10,100 ppm and a LC₅₀ value of 19,950 ppm for a 4-hour exposure, suggesting a potentially steep dose-response curve following inhalation of acetonitrile [Monsanto 1986]. Pozzani et al. [1959] investigated the effects of inhalation exposures to acetonitrile in multiple species, including rats, dogs, and guinea pigs. Male and female rats were exposed to concentrations ranging from 1,000 to 32,000 ppm for either 1 or 2 hours. The 4-hour LC₅₀ value for both sexes was calculated at 16,000 ppm [NAS 2014]. The 8-hour LC₅₀ values for male and female rats were 7,551 and 12,435 ppm, respectively [NAS 2014]. In another experiment, dogs were treated for 4 hours at concentrations ranging from 2,000-32,000 ppm. No LC₅₀ value was calculated, but Pozzani et al. [1959] reported that all animals treated at 16,000 and 32,000 ppm died. Pozzani et al. [1959] exposed guinea pigs to acetonitrile at concentrations ranging from 4,000-16,000 ppm for 4 hours. The 4-hour LC₅₀ value was calculated at 5,655 ppm [NAS 2014].

Pathological investigations revealed that exposed animals experienced prostration, convulsive seizures, and death with pathological examination revealing pulmonary effects including congestion and hemorrhaging. Willhite [1981] investigated the relative toxicity of the following aliphatic nitrile compounds: acetonitrile, propionitrile, and n-butyronitrile. Mice were exposed via the inhalation route to 1 of 5 or 6 concentrations of the test compound for 60 minutes. All deaths occurred within 3 days of the cessation of exposure. Animals that survived past 3 days were observed for 14 days with gross pathology conducted following termination. Willhite [1981] stated that all animals experienced similar signs regardless of the aliphatic nitrile compound to which they were exposed. These signs included dyspnea, tachypnea, gasping, tremors, and convulsions. For acetonitrile, the concentration ranged

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1 from 500-5000 ppm. Willhite [1981] reported a 60-minute LC₅₀ value of 2,693 ppm (95% CI 1,955-4,272) for
2 acetonitrile.

3

4 Table 4 summarizes the lethal concentration (LC) data identified in animal studies and provides 30-minute
5 equivalent derived values for acetonitrile. Information in this table includes species of test animals, toxicological
6 metrics (i.e., LC, BMCL, NOAEL, LOAEL), adjusted 30-minute concentration, and the justification for the
7 composite uncertainty factors applied to calculate the derived values.

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Table 4: Lethal Concentration Data for Acetonitrile

Reference	Species	LC ₅₀ (ppm)	LC _{Lo} (ppm)	Time (min)	Adjusted 30-min Concentration* (ppm)	Composite Uncertainty Factor	30-min Equivalent Derived Value (ppm) [†]	Final Value (ppm) [€]
Pozzani et al. [1959]	Guinea Pig	5,655	--	240	11,310	30 [‡]	377	377
Pozzani et al. [1959]	Monkey	2,510	--	420	6,049	30 [‡]	201.6	202
Pozzani et al. [1959]	Rats	7,551	--	480	19,027	30 [‡]	634.2	634
Pozzani et al. [1959]	Rabbit	2,828	--	240	5,656	30 [‡]	188.5	189
Willhite [1981]	Mouse	2,693	--	60	3,393	30 [‡]	113.1	113

* 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].

[†] The derived value is the result of the adjusted 30-minute LC 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.

[‡] Composite uncertainty factor to account for adjustment of LC₅₀ values to LC₀₁ values, use of lethal concentration threshold in animals, interspecies differences and human variability.

1 **3.0 Human Data**

2
3 Three study participants were exposed to 40-160 ppm acetonitrile for 4 hours [Pozzani et al. 1959]. One study
4 participant reported slight chest tightness and cooling sensation in the lung following the 40 ppm exposure, other
5 participants did not report symptoms at this concentration. At the 160 ppm exposure, one of the previously
6 unaffected subjects reported slight transitory flushing of face after 2 hours and slight bronchial tightness 5 hours
7 later that resolved overnight.

8 **4.0 Summary**

9
10 Limited human data on acetonitrile were identified. Pozzani et al. [1959] reported that effects of acetonitrile in
11 human volunteers exposed for 4 hours to airborne concentrations ranging from 40-160 ppm. Although this data
12 provided some insight into the effects of acetonitrile on humans, it is insufficient to serve as the basis of an IDLH
13 value. In comparison, animal data from studies that investigated the effects of acute exposures to acetonitrile in
14 rats, rabbits, guinea pigs, dogs, and monkeys [Monsanto 1986; Pozzani et al. 1959; Willhite 1981] were
15 evaluated. Among these species, mice appear to be the most sensitive species. The mouse LC₅₀ value of 2693
16 ppm for a 60 minute exposure to acetonitrile was selected as the basis for the IDLH value. Duration adjustment
17 resulted in the calculation of a 30-minute equivalent LC₅₀ value of 3393 ppm. An uncertainty factor of 30 was
18 applied to account for extrapolation from a concentration that is lethal to animals, animal to human differences
19 and human variability. This results in an IDLH value of 113 ppm.

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