IDLH

IMMEDIATELY DANGEROUS to LIFE or HEALTH

VALUE PROFILE

Nitrogen Dioxide
CAS® No. 10102-44-0

Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

This page intentionally left blank.

Immediately Dangerous to Life or Health (IDLH) Value Profile

Nitrogen Dioxide

[CAS® No. 10102-44-0]

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

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to websites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these websites.

Ordering Information

To receive this document or information about other occupational safety and health topics, contact NIOSH:

Telephone: 1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov

or visit the NIOSH Website at: www.cdc.gov/niosh

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting www.cdc.gov/niosh/eNews.

Suggested Citation

NIOSH [2017]. Immediately dangerous to life or health (IDLH) value profile: Nitrogen dioxide. By Dotson GS, Maier A, Parker A, Haber L. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication 2017-202.

DHHS (NIOSH) Publication No. 2017-202

September 2017

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) 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 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 nitrogen dioxide (CAS® No. 10102-44-0). The scientific basis, toxicologic data, and risk assessment approach used to derive the IDLH value are summarized to ensure transparency and scientific credibility.

John Howard, M.D.
Director
National Institute for Occupational
Safety and Health
Centers for Disease Control and Prevention

This page intentionally left blank.

Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
AEGLs	Acute Exposure Guideline Levels
AIHA®	American Industrial Hygiene Association
BMCL	benchmark concentration lower confidence limit
°C	degrees Celsius
CA	California
CAS®	Chemical Abstracts Service, a division of the American Chemical Society
CIB	Current Intelligence Bulletin
ERPGs™	Emergency Response Planning Guidelines
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_{01}	lethal concentration estimated to cause death in 1% of animals
LC_{50}	median lethal concentration
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
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
REL	recommended exposure limit
STEL	short-term exposure limit
TLV®	Threshold Limit Value
TWA	time-weighted average
UEL	upper explosive limit
WEELs®	Workplace Environmental Exposure Levels

Glossary

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

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

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

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

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

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

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

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

Bolus exposure: A single, relatively large dose.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Threshold Limit Values (TLVs®): Recommended guidelines for occupational exposure to airborne contaminants, published by the American Conference of Governmental Industrial

Hygienists (ACGIH®). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse effects. TLVs may be designated as ceiling limits, STELs, or 8-hr TWA limits.

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

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

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

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

Acknowledgments

This document was developed by the Education and Information Division Paul Schulte, Ph.D., Director. G. Scott Dotson, Ph.D., was the project officer and lead NIOSH author. The basis for this document was a report contracted by NIOSH and prepared by Andrew Maier, Ph.D., Ann Parker, and Lynn Haber, Ph.D. (Toxicology Excellence for Risk Assessment [TERA]).

The following NIOSH staff are acknowledged for providing technical and editorial review of the report:

Education and Information Division

Devin Baker, M.Ed.
Charles L. Geraci, Ph.D.
Thomas J. Lentz, Ph.D.
Richard W. Niemeier, Ph.D. (retired)
R. Todd Niemeier, MS, CIH
Pranav Rane, M.P.H.
Chris Whittaker, Ph.D.

NIOSH acknowledges the following subject matter experts for their critical technical reviews:

Michael S. Bisesi, Ph.D., R.E.H.S., C.I.H., Senior Associate Dean for Academic Affairs; Director, Center for Public Health Practice; Interim Chair & Associate Professor, Division of Environmental Health Science, College of Public Health, Ohio State University, Columbus, OH

Ernest V. Falke, Ph.D., Senior Scientist, Risk Assessment Division (RAD), Office of Pollution Prevention and Toxics (OPPT), United States Environmental Protection Agency (USEPA), Washington, DC

Tala Henry, Ph.D., Director, RAD, OPPT, USEPA, Washington, DC

Randall Keller, Ph.D., C.I.H., C.S.P., D.A.B.T., Professor; Occupational Safety and Health Department, Jesse D. Jones College of Science, Engineering, and Technology, Murray State University, Murray, KY

Barry Marcel Ph.D., Environmental Health Consultant, United States Air Force, Wright-Patterson Air Force Base, OH

Richard B. Schlesinger, Ph.D., Fellow A.T.S., Senior Associate Dean for Academic Affairs and Research and Professor of Biology, Dyson College of Arts and Sciences, Pace University, New York, NY

George M. Woodall, Ph.D., Acting Coordinator, Science and Technology Policy Council Office of the Science Advisor, USEPA, Research Triangle Park, NC

This page intentionally left blank.

1 Introduction

1.1 Overview of the IDLH Value for Nitrogen Dioxide

IDLH value: 13 ppm (24 mg/m^3)

Basis for IDLH value: The IDLH value for nitrogen dioxide is based on a LOAEL of 30 ppm for respiratory irritation and severe cough in volunteers following a 70 minute exposure [Henschler et al. 1960]. Duration adjustment resulted in the calculation of a 30-minute equivalent LOAEL of 38 ppm. A composite uncertainty factor of 3 was applied to account for human variability yielding an IDLH value 13 ppm for nitrogen dioxide.

1.2 Purpose

This *IDLH Value Profile* presents (1) a brief summary of technical data associated with acute inhalation exposures to nitrogen dioxide and (2) the rationale behind the immediately dangerous to life or health (IDLH) value for nitrogen dioxide. IDLH values are developed on the basis of scientific rationale and logic outlined in the *NIOSH Current Intelligence Bulletin (CIB) 66: Derivation of Immediately Dangerous to Life or Health (IDLH) Values* [NIOSH 2013]. As described in CIB 66, NIOSH performs in-depth literature searches to ensure that all relevant data from human and animal studies with acute exposures to the substance are identified. Information included in CIB 66 on the literature search includes pertinent databases, key terms, and guides for evaluating data quality and relevance for the establishment of an IDLH value. The information that is identified in the in-depth literature search is evaluated with general considerations that include description of studies (i.e., species, study protocol, exposure concentration and duration), health endpoint evaluated, and critical effect levels (e.g., NOAELs, LOAELs, and LC_{50} values). For nitrogen dioxide, the in-depth literature search was conducted through July 2017.

1.3 General Substance Information

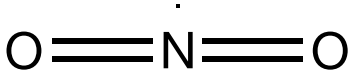
Chemical: Nitrogen dioxide

CAS No: 10102-44-0

Synonyms: Nitrogen oxide (NO_2); Nitrogen peroxide[*]

Chemical category: Nitrogen oxides; Inorganic gases[†]

Structural formula:



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

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

Table 1: Physiochemical properties of nitrogen dioxide

Property	Value
Molecular weight	46.01*
Chemical formula	NO_2*
Description	Reddish-brown gas above 21°C, pale yellow/ yellowish-brown liquid above 21°C†
Odor	Pungent, acrid‡
Odor threshold	0.058 ppm‡
UEL	Not applicable
LEL	Not applicable
Vapor pressure	720 mmHg at 20°C; 800 mmHg at 25°C*
Flash point	Not flammable
Ignition temperature	Not flammable
Solubility	Reacts with water†
Reactivity	Decomposes in water forming nitric oxide and nitric acid*

References: *NAS [2012]; †HSDB [2017]; ‡Murnane et al. [2013]

Table 2: Alternative exposure guidelines for nitrogen dioxide

Organization	Value
NIOSH (1994) IDLH value*	20 ppm
NIOSH REL†	1 ppm - STEL
OSHA PEL‡	5 ppm - Ceiling
CA OSHA PEL§	1 ppm - STEL
ACGIH® TLV¶	0.2 ppm TWA
AIHA® ERPGs™**	ERPG-1: 1 ppm; ERPG-2: 15 ppm; ERPG-3: 30 ppm
AIHA® WEELs®**	Not available

References: *NIOSH [1994]; †NIOSH [2017]; ‡OSHA [2017]; §CAL OSHA [2017]; ¶ACGIH [2016]; **AIHA [2014]

Table 3: Interim AEGL values for nitrogen dioxide

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint [reference]
AEGL-1	0.50 ppm 0.94 mg/m^3	0.50 ppm 0.94 mg/m^3	0.50 ppm 0.94 mg/m^3	0.50 ppm 0.94 mg/m^3	0.50 ppm 0.94 mg/m^3	Slight burning of the eyes, slight headache, chest tightness or labored breathing with exercise in 7/13 asthmatics [Kerr et al. 1978, 1979]
AEGL-2	20 ppm 38 mg/m^3	15 ppm 28 mg/m^3	12 ppm 23 mg/m^3	8.2 ppm 15 mg/m^3	6.7 ppm 13 mg/m^3	Burning sensation in nose and chest, cough, dyspnea, sputum production in normal volunteers [Henschler et al. 1960]
AEGL-3	34 ppm 64 mg/m^3	25 ppm 47 mg/m^3	20 ppm 38 mg/m^3	14 ppm 26 mg/m^3	11 ppm 21 mg/m^3	Marked irritation, histopathologic changes in lungs, fibrosis and edema of cardiac tissue, necrosis in liver, no deaths in monkeys [Henry et al. 1969]

Reference: NAS [2012]

2 Animal Toxicity Data

Nitrogen dioxide is an irritant to the mucous membranes and has been shown to cause coughing and dyspnea during exposure. Severe exposure pulmonary edema with symptoms of chest pain, cough, dyspnea, and cyanosis have been reported [NIOSH 1976; Douglas et al. 1989]. Lethality from nitrogen dioxide exposure is reported to be due to bronchospasm and pulmonary edema occurring with hypoxemia and respiratory acidosis, metabolic acidosis, decreased oxygenation of hemoglobin and low arterial blood pressure [Douglas et al. 1989]. Furthermore, after acute nitrogen dioxide intoxication and an apparent recovery, a late-onset bronchiolar injury in the form of bronchiolitis fibrosa obliterans is observed [NIOSH 1976; Hamilton 1983; Douglas et al. 1989].

Five- to 60-minute LC_{50} values for nitrogen dioxide in the rat ranged from 416 to 115 ppm, respectively in one study [Carson et al. 1962] and from 833 to 168 ppm in another study [Gray et al. 1954]. Hine et al. [1970] studied the effects of varying concentrations (50–200 ppm) and durations (5 min to 24 hours) of nitrogen dioxide exposure in several species (rat, mouse, guinea pig, rabbit and dog). During this study lethality in one guinea pig (n=6) was reported following the lowest exposure of 50 ppm for one hour (which was the shortest duration for this concentration). The highest exposure of 200 ppm for 5 minutes caused lethality in 6/12 rats, 4/6 mice and 2/2 guinea pigs. In squirrel monkeys exposed to 10–50 ppm nitrogen dioxide for 2 hours [Henry et al. 1969], exposure to 35 or 50 ppm resulted in a markedly increased respiratory rate and decreased tidal volume.

Table 4 summarizes the lethal concentration (LC) data identified in animal studies and provides 30-minute equivalent derived values for nitrogen dioxide. 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., 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 nitrogen dioxide

Reference	Species	LC_{50} (ppm)	Time (min)	Adjusted 30-min concentration* (ppm)	Composite uncertainty factor	30-min equivalent derived value (ppm)†	Final value‡ (ppm)
Carson et al. [1962]	Rabbit	315	15	258	30§	8.6	9.0
Carson et al. [1962]	Rat	162	30	162	30§	5.4	5.0
Gray et al. [1954]	Rat	174	30	174	30§	5.8	6.0

*For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment ($C^n \times t = k$); ten Berge et al. [1986] empirically estimated n = 3.5. The n = 3.5 was used during all duration adjustments for nitrogen dioxide. 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 LC_{50} values to LC_{01} values, use of lethal concentration threshold in animals, interspecies differences and human variability

Table 5: Non-lethal concentration data for nitrogen dioxide

Reference	Species	Critical adverse health effects	LOAEL (ppm)	Time (min)	Adjusted 30-min concentration* (ppm)	Composite uncertainty factor	Derived value (ppm)†	Final value‡ (ppm)
Morley and Silk [1970]	Human	Cyanosis, dyspnea and pulmonary edema	30	40	33	3§	10.9	11
Henschler et al. [1960]	Human	Burning sensation in upper respiratory tract and severe cough followed by dyspnea	30	70	38	3§	12.7	13
Norwood et al. [1966]	Human	Shortness of breath, chest discomfort, and pulmonary edema	90	40	98	3§	32.6	33
Henry et al. [1969]	Monkey	Increased respiratory rate and decreased tidal volume	35	120	52	10¶	5.2	5.0

*For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (Cn × t = k); ten Berge et al. [1986] empirically estimated n = 3.5. The n = 3.5 was used during all duration adjustments for nitrogen dioxide. 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-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.

§Composite uncertainty factor assigned to account for human variability.

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

3 Human Data

Numerous human studies are available that describe effects of nitrogen dioxide in humans. Overall, the pattern of respiratory tract effects includes initial signs of respiratory tract irritation, with latent tracheobronchial and pulmonary involvement. Douglas et al. [1989] reported that death from the inhalation of nitrogen dioxide is caused by bronchospasm and pulmonary edema. NAS [2012] stated that a characteristic of nitrogen dioxide intoxication after the acute phase is a period of apparent recovery. A second phase of symptoms may occur after several hours or several days with the development of fever with progressively more severe dyspnea, cyanosis, and cough. An estimation of the concentration causing death in humans is approximately ≥150 ppm, but no duration of exposure was given.

Henschler et al. [1960] investigated the adverse effects of acute inhalation exposures to nitrogen dioxide. Using a controlled exposure design, healthy male volunteers were exposed to various concentrations of nitrogen dioxide and durations. The authors reported that a 2-hour exposure to 20 ppm did not cause irritation, but exposures at 30 ppm for 2 hours cause definite discomfort. Effects observed after 30 to 40 minutes of exposure were limited to minimal signs of irritation in the nose and throat. After 70 minutes of exposure, volunteers reported a burning sensation with increasingly severe cough. With continued exposure, coughing decreased, but the burning sensation moved to deeper portions of the lung, accompanied by sputum secretion and dyspnea. The authors reported that the condition was described as bothersome and barely tolerable by the subjects. In addition, a sensation of pressure and increased sputum secretion continued for several hours after cessation of exposure. This study design cannot provide information on the degree to which latent respiratory tract effects would have occurred following exposure for only 30 minutes in the subjects. In another study, Morley and Silk [1970] described occupational exposures to nitrous fumes, which may include nitrogen dioxide, dinitrogen trioxide, dinitrogen tetroxide, and dinitrogen pentoxide, in eleven welders. Health effects associated with exposures to the nitrous fumes included a variety of symptoms such as cough, headache, tightness/pain in chest, and nausea. Two of seven workers were hospitalized with cyanosis, dyspnea and pulmonary edema following exposure to 30 ppm of nitrogen dioxide for 40 minutes [Morley and Silk 1970]. Another welder developed shortness of breath, chest discomfort, and pulmonary edema while using an acetylene torch for metal-cutting in a poorly ventilated enclosed space for 30 minutes. The authors noted that seven other workers were exposed during this incident, but were unaffected. This indicates the potential for human variability in response to nitrogen dioxide. Simulation of the accident produced a nitrogen dioxide concentration of 90 ppm [Norwood et al. 1966]. The reports of effects in welders as the basis for IDLH value derivation are limited since the effects of the complex mix of materials released during welding need to be considered. Table 5 provides non-lethal data reported in human studies with 30-minute equivalent derived values.

4 Summary

Nitrogen dioxide is an irritant to the mucous membranes and has been shown to cause coughing and dyspnea during exposure. Severe exposure pulmonary edema with symptoms of chest pain, cough, dyspnea, and cyanosis have been reported [NIOSH 1976; Douglas et al. 1989]. Human data indicate that acute inhalation exposures may induce potential escape-impairing effects of dyspnea, cyanosis, and pulmonary edema [Henschler et al. 1960; Norwood et al. 1969; Morley and Silk 1970]. Exposure to nitrogen dioxide at 30 ppm for 70 minutes resulted in a severe cough and an increased burning sensation of the upper respiratory tract that progressed with continued exposures to include the lower section of the airways and in the chest [Henschler et al. 1960]. These effects can be considered a LOAEL and serve as the basis of the IDLH value for nitrogen dioxide. Duration adjustment (see Table 5) resulted in the calculation of a 30-minute equivalent concentration of 38 ppm. Application of a composite uncertainty factor of 3 to account for human variability yielding an IDLH value 13 ppm for nitrogen dioxide.

5 References

ACGIH [2016]. Annual TLVs® (Threshold Limit Values) and BEIs® (Biological Exposure Indices) booklet. Cincinnati, OH: ACGIH Signature Publications.

AIHA [2006]. AIHA Emergency Response Planning (ERP) Committee procedures and responsibilities. Fairfax, VA: American Industrial Hygiene Association, https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/ERP-SOPs2006.pdf.

AIHA [2014]. Emergency response planning guidelines (ERPG) and workplace environmental exposure levels (WEEL) handbook. Fairfax, VA: American Industrial Hygiene Association Press, https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2014%20ERPG%20Values.pdf.

CA OSHA [2017]. Permissible exposure limits for chemical contaminants. https://www.dir.ca.gov/title8/5155table_ac1.html.

Carson TR, Rosenholtz MS, Wilinski FT, Weeks MH [1962]. The responses of animals inhaling nitrogen dioxide for single, short-term exposures. Am Ind Hyg Assoc J *23*:457–462.

Douglas WW, Hepper NGG, Colby TV [1989]. Silo-filler's disease. Mayo Clin Proc *64*:291–304.

Gray E, Le B, Patton FM, Goldberg SB, Kaplan E [1954]. Toxicity of the oxides of nitrogen. II. Acute inhalation toxicity of nitrogen dioxide, red fuming nitric acid, and white fuming nitric acid. Arch Ind Hyg Occup Med *10*:418–422.

Hamilton A [1983]. Nitrogen compounds. In: Hamilton and Hardy's Industrial Toxicology. 4th ed. Boston: John Wright-PSG, Inc., pp.184–186.

Henry MC, Ehrlich R, Blair WH [1969]. Effect of nitrogen dioxide on resistance of squirrel monkeys to Klebsiella pneumoniae infection. Arch Environ Health *18*:580–587.

Henschler D, Stier A, Beck H, Neuman W [1960]. [Odor threshold of a few important irritant gasses (sulfur dioxide, ozone, nitrogen dioxide) and observations in humans exposed to low concentrations.] Archiv für Gewerbepathologie und Gewerbehygiene *17*:547–570. (translated from German).

Hine CH, Meyers FH, Wright RW [1970]. Pulmonary changes in animals exposed to nitrogen dioxide, effects of acute exposures. Toxicol Appl Pharmacol *16*:201–213.

HSDB [2017]. Hazardous Substances Data Bank. Bethesda, MD: National Library of Medicine, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) [2017]. GESTIS: database on hazardous substances, http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp.

Kerr HD, Kulle TJ, McIlhany ML, Swidersky P [1978]. Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. EPA/600/1-78/025. Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Kerr HD, Kulle TJ, McIlhany ML, Swidersky P [1979]. Effects of nitrogen dioxide on pulmonary function in human subjects: An environmental chamber study. Environ. Res. *19*(2):392–404.

Morley R, Silk SJ [1970]. The industrial hazard from nitrous fumes. Ann Occup Hyg *13*:101–107.

Murnane SS, Lehocky AH, Owens PD. [2013]. Odor thresholds for chemicals with established occupational health standards, 2nd Edition. Falls Church, VA: American Industrial Hygiene Association, p. 39, 111.

NAS [2001]. Standing operating procedures for developing Acute Exposure Guidelines Levels for hazardous chemicals. National Academy of Sciences, National Research Council (NRC), Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels. Washington, DC: National Academy Press, IBSN: 0-309-07553-X, http://www.epa.gov/sites/production/files/2015-09/documents/sop_final_standing_operating_procedures_2001.pdf.

NAS [2012]. Acute Exposure Guideline Levels (AEGLs) for selected airborne chemicals. Vol. 11. Nitrogen Dioxide (CAS Reg. No. 10102-44-0). National Academy of Sciences, National Research Council, Committee on Toxicology, Subcommittee on Acute Exposure Guideline Levels. Washington, DC: National Academy Press, https://www.epa.gov/sites/production/files/2015-09/documents/nitrogen_oxides_volume_11_1.pdf

NIOSH [1976]. Criteria for a recommended standard: occupational exposure to oxides of nitrogen (nitrogen dioxide and nitric oxide). Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 76-149.

NIOSH [1994]. Documentation for immediately dangerous to life or health concentrations (IDLHs). Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, http://www.cdc.gov/niosh/idlh/intridl4.html.

NIOSH [2004]. NIOSH respirator selection logic. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-100, http://www.cdc.gov/niosh/docs/2005-100/pdfs/2005-100.pdf.

NIOSH [2013]. NIOSH current intelligence bulletin 66: derivation of immediately

dangerous to life or health (IDLH) values. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2014-100, http://www.cdc.gov/niosh/docs/2014-100/pdfs/2014-100.pdf.

NIOSH [2017]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-149, http://www.cdc.gov/niosh/npg/.

NLM [2017]. ChemIDplus lite. Washington, DC: National Library of Medicine, http://chem.sis.nlm.nih.gov/chemidplus/.

Norwood WD, Wisehart DE, Earl CA, Adley FE, Anderson DE [1966]. Nitrogen dioxide poisoning due to metal-cutting with oxyacetylene torch. J Occup Med *8*:301–306.

OSHA [2017]. Chemical sampling information, https://www.osha.gov/dts/chemicalsampling/toc/toc_chemsamp.html.

ten Berge WF, Zwart A, Appelman LM [1986]. Concentration-time mortality response relationship of irritant and systematically acting vapors and gases. J Haz Mat *13*:301–309.

U.S. EPA [2016]. Integrated Risk Information System (IRIS). Washington, DC: U.S. Environmental Protection Agency, http://www.epa.gov/iris/.

This page intentionally left blank.

Delivering on the Nation's promise:
safety and health at work for all people
through research and prevention

To receive NIOSH documents or more information about occupational safety and health topics, contact NIOSH at

1–800–CDC–INFO (1–800–232–4636)
TTY: 1–888–232–6348
E-mail: cdcinfo@cdc.gov

or visit the NIOSH Website at www.cdc.gov/niosh.

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting www.cdc.gov/niosh/eNews.

DHHS (NIOSH) Publication No. 2017–202