

Provisional Peer-Reviewed Toxicity Values for

2-Nitrodiphenylamine
(CASRN 119-75-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER:

Jason C. Lambert, National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY:

National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer-reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

TABLE OF CONTENTS

| | |
|---|-----|
| COMMONLY USED ABBREVIATIONS | iii |
| BACKGROUND | 1 |
| DISCLAIMERS | 1 |
| QUESTIONS REGARDING PPRTVS | 1 |
| INTRODUCTION | 2 |
| REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)..... | 3 |
| DERIVATION OF PROVISIONAL VALUES | 4 |
| CANCER WOE DESCRIPTOR..... | 4 |
| MODE-OF-ACTION DISCUSSION | 4 |
| REFERENCES | 4 |

COMMONLY USED ABBREVIATIONS

| | |
|----------------------|---|
| BMC | benchmark concentration |
| BMD | benchmark dose |
| BMCL | benchmark concentration lower bound 95% confidence interval |
| BMDL | benchmark dose lower bound 95% confidence interval |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| IUR | inhalation unit risk |
| LOAEL | lowest-observed-adverse-effect level |
| LOAEL _{ADJ} | LOAEL adjusted to continuous exposure duration |
| LOAEL _{HEC} | LOAEL adjusted for dosimetric differences across species to a human |
| NOAEL | no-observed-adverse-effect level |
| NOAEL _{ADJ} | NOAEL adjusted to continuous exposure duration |
| NOAEL _{HEC} | NOAEL adjusted for dosimetric differences across species to a human |
| NOEL | no-observed-effect level |
| OSF | oral slope factor |
| p-IUR | provisional inhalation unit risk |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional reference concentration (inhalation) |
| p-RfD | provisional reference dose (oral) |
| POD | point of departure |
| RfC | reference concentration (inhalation) |
| RfD | reference dose (oral) |
| UF | uncertainty factor |
| UF _A | animal-to-human uncertainty factor |
| UF _C | composite uncertainty factor |
| UF _D | incomplete-to-complete database uncertainty factor |
| UF _H | interhuman uncertainty factor |
| UF _L | LOAEL-to-NOAEL uncertainty factor |
| UF _S | subchronic-to-chronic uncertainty factor |
| WOE | weight of evidence |

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 2-NITRODIPEHNYLAMINE (CASRN 119-75-5)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (<http://hhpprtv.ornl.gov>) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

2-Nitrodiphenylamine, CAS No. 119-75-5, is a solid, nitroaromatic compound used in the manufacture of fuel, propellants, and explosives (ATSDR, 1995). It is also used as a solvent dye. Although the human and animal health effects are unknown, 2-nitrodiphenylamine has been shown to enter the bloodstream via oral consumption of water or food. The distribution of 2-nitrodiphenylamine following inhalation or dermal exposure has not been examined. Figure 1 shows the chemical structure of 2-nitrodiphenylamine, and Table 1 presents the physicochemical properties of 2-nitrodiphenylamine.

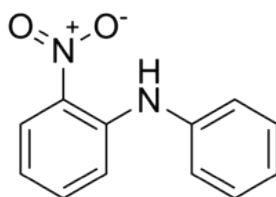


Figure 1. 2-Nitrodiphenylamine Structure (CASRN 119-75-5)

| Table 1. Physicochemical Properties for 2-Nitrodiphenylamine (CASRN 119-75-5) | |
|--|----------------------|
| Property (unit) | Value |
| Boiling point (°C at 760 mmHg) | 346 ^b |
| Melting point (°C) | 75 ^a |
| Density (g/cm ³) | 1.36 ^b |
| Vapor pressure (kPa at 20°C) | Not available |
| pH (unitless) | 5.0–7.0 ^c |
| Solubility in water (mg/L at 25°C) | 27.7 ^d |
| Relative vapor density (air = 1) | Not available |
| Molecular weight (g/mol) | 214.223 ^a |
| Flash point (°C) | Not available |
| Octanol/water partition coefficient (log K_{ow} unitless) | 3.66 ^a |

^aU.S. National Library of Medicine (2010); experimental data.

^bChemCAS (2010).

^cChemicaland21 (2010).

^dU.S. National Library of Medicine (2010); estimated data.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for 2-nitrodiphenylamine is included in the IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are

reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2010b). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for 2-nitrodiphenylamine (U.S. EPA, 1994). The toxicity of 2-nitrodiphenylamine has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2010) or the World Health Organization (WHO, 2010). The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to 2-nitrodiphenylamine. No occupational exposure limits for 2-nitrodiphenylamine have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the Occupational Safety and Health Administration (OSHA, 2010).

The HEAST (U.S. EPA, 2010b) does not report an EPA (1986) cancer weight-of-evidence (WOE) classification or an oral slope factor. The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic potential of 2-nitrodiphenylamine. 2-Nitrodiphenylamine is not included in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2008) has not prepared a quantitative estimate of carcinogenic potential for 2-nitrodiphenylamine.

Literature searches were conducted on sources published from 1900 through July 2011 for studies relevant to the derivation of provisional toxicity values for 2-nitrodiphenylamine, CAS No. 119-75-5. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUP, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMT, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

The literature search revealed no human or animal studies, at any relevant exposure duration, available for hazard or dose-response assessment. However, the ATSDR published a Toxicological Profile for Otto Fuel II (ATSDR, 1995), of which 2-nitrodiphenylamine is a minor component. In this profile, limited information on the toxicity of 2-Nitrodiphenylamine alone was included. Following an acute oral exposure to 2-nitrodiphenylamine, a LD₅₀ value of

6150 mg/kg was identified in rats (This information was obtained from a Material Safety Data Sheet on 2-nitrodiphenylamine [American Cyanamid, 1982], as cited in ATSDR, 1995). However, because the original acute study was unavailable for review, this value could not be verified by the ATSDR or the EPA. A U.S. Army review indicated that oral 2-nitrodiphenylamine exposure in rats at a dose of 3070 mg/kg resulted in an elevation of blood methemoglobin levels of 9.45% (U.S. Army, 1979; this information was obtained by the U.S. Army through personal communication with American Cyanamid). Because the actual study was unavailable for review, this information could not be verified by the ATSDR or the EPA. No other information pertaining to noncancer toxicity of 2-nitrodiphenylamine could be located.

DERIVATION OF PROVISIONAL VALUES

The lack of relevant data precludes development of both cancer and noncancer toxicity values.

CANCER WOE DESCRIPTOR

The lack of data precludes development of a WOE descriptor.

MODE-OF-ACTION DISCUSSION

The lack of data precludes development of a mode-of-action discussion.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2010) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. As cited in HSDB (Hazardous Substances Data Bank). Available online at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>. Accessed on November 09, 2010. [625688](#).

American Cyanamid. (1982) Material safety data sheet on 2-nitrodiphenylamine. American Cyanamid Company, Wayne, NJ; MSDS no. 0404-01. As cited in ATSDR, 1995.

ATSDR (Agency for Toxic Substances and Disease Registry). (1995) Toxicological profile for Otto Fuel II and its components. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available at <http://www.atsdr.cdc.gov/toxprofiles/tp77.pdf>. Accessed on November 9, 2010.

ATSDR (Agency for Toxic Substances and Disease Registry). (2010) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at <http://www.atsdr.cdc.gov/toxprofiles/index.asp>. Accessed on November 9, 2010. [595415](#).

CalEPA (California Environmental Protection Agency). (2008) All OEHHA acute, 8-hour and chronic reference exposure levels (chRELS) as on December 18, 2008. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at <http://www.oehha.ca.gov/air/allrels.html>. Accessed on November 9, 2010. [595416](#).

CalEPA (California Environmental Protection Agency). (2009) Office of Environmental Health Hazard Assessment. OEHHA Toxicity Criteria Database. Available online at <http://www.oehha.ca.gov/risk/ChemicalDB/index.asp>. Accessed on November 9, 2010. [595417](#).

ChemCAS. (2010) MSDS for 2-Nitrodiphenylamine. Available online at: <http://www.chemcas.org/drug/analytical/cas/119-75-5.asp>. Accessed on November 10, 2010.

Chemicalland21. (2010) 2-Nitrodiphenylamine. Available online at <http://chemicalland21.com/specialtychem/finechem/2-NITRODIPHENYLAMINE.htm>. Accessed on November 9, 2010.

IARC (International Agency for Research on Cancer). (2010) Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC. Available online at <http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php>. Accessed on November 9, 2010. [597416](#).

NIOSH (National Institute for Occupational Safety and Health). (2010) NIOSH Pocket Guide to Chemical Hazards. Index of chemical abstracts service registry numbers (CAS No.). Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare, Atlanta, GA. Available online at <http://www.cdc.gov/niosh/npg/npgdcas.html>. Accessed on November 9, 2010. [625692](#).

NTP (National Toxicology Program). (2005) 11th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Available online at <http://ntp.niehs.nih.gov/ntp/roc/toc11.html>. Accessed on November 9, 2010. [093207](#).

OSHA (Occupational Safety and Health Administration). (2010) Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. U.S. Department of Labor, Washington, DC; OSHA Standard 1915.1000. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286. Accessed on November 9, 2010. [625691](#).

U.S. EPA (Environmental Protection Agency). (1986) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-00/004. September 1986. Available online at http://epa.gov/raf/publications/pdfs/CA%20GUIDELINES_1986.PDF. [199530](#).

U.S. EPA (Environmental Protection Agency). (1994) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC; EPA/600/R-94/904. Available online at nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt. December. [596444](#).

U.S. EPA (Environmental Protection Agency). (2009) 2009 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA 822/R-09/011. Available online at <http://www.epa.gov/waterscience/drinking/standards/dwstandards2009.pdf>. Accessed November 9, 2010. [644141](#).

U.S. EPA (Environmental Protection Agency). (2010a) Integrated risk information system (IRIS). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at <http://www.epa.gov/iris>. Accessed November 9, 2010. [003752](#).

U.S. EPA (Environmental Protection Agency). (2010b) Health effects assessment summary tables (HEAST). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. Available online at <http://epa-heat.ornl.gov>. Accessed November 9, 2010. [595422](#).

U.S. National Library of Medicine. (2010) ChemIDplus Lite: Physical Properties, 2-nitro-*N*-phenyl-benzenamine, CAS RN: 119-75-5. Available online at <http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/PhysicalProperties.jsp?calledFrom=lite>. Accessed on November 9, 2010.

WHO (World Health Organization). (2010) Online catalogs for the Environmental Health Criteria series. Available online at <http://www.who.int/ipcs/publications/ehc/en>. Accessed November 9, 2010. [595424](#).