FINAL
8-15-2012

Provisional Peer-Reviewed Toxicity Values for

N,*N*-Dinitrosopentamethylenetetramine
(CASRN 101-25-7)

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

Carrie R. Fleming, PhD
National Center for Environmental Assessment, Cincinnati, OH

CONTRIBUTOR

Jason C. Lambert, PhD, DABT
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) 4
DERIVATION OF PROVISIONAL VALUES 6
CANCER WOE DESCRIPTOR 6
MODE-OF-ACTION DISCUSSION 6
REFERENCES 6

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
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 *N,N*-DINITROSOPENTAMETHYLENETETRAMINE (CASRN 101-25-7)

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

N,*N*-Dinitrosopentamethylenetetramine (systematic name 3,7-dinitroso-1,3,5,7-tetraazabicyclo-(3,3,1)-nonane), CAS No. 101-25-7, is used as a blowing agent for production of polyvinyl chloride (PVC) plastisols, polyester and silicon resins, and unicellular rubber (both natural and synthetic, which are used in carpet underlay, thermal insulation, weather stripping, cushioning, and flotation devices) (HSDB, 2003). The chemical structure of *N*,*N*-dinitrosopentamethylenetetramine is given in Figure 1. A table of available physicochemical properties of *N*,*N*-dinitrosopentamethylenetetramine is provided below (see Table 1).

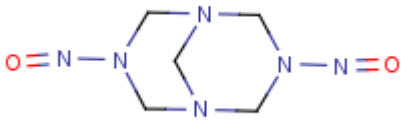

Figure 1. *N*,*N*-Dinitrosopentamethylenetetramine Structure

Table 1. Physicochemical Properties of *N*,*N*-Dinitrosopentamethylenetetramine (CASRN 101-25-7)[a]

Property (unit)	Value
Boiling point (ºC)	ND
Melting point (ºC)	203 (decomposes at 207)[b]
Density (g/cm^3)	ND
Vapor pressure (Pa at 25ºC)	ND
pH (unitless)	ND
Solubility in water (%)	1
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	186.2

[a]HSDB (2003).
[b]IARC (1976).

ND = no data.

No reference dose (RfD), reference concentration (RfC), or cancer assessment for *N*,*N*-dinitrosopentamethylenetetramine is included in the U.S. Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2011b) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2011a). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2003). The

Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for *N*,*N*-dinitrosopentamethylenetetramine (U.S. EPA, 1994). The toxicity of *N*,*N*-dinitrosopentamethylenetetramine has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011) or the World Health Organization (WHO, 2011). The California Environmental Protection Agency (Cal EPA, 2008), has not derived toxicity values for exposure to *N*,*N*-dinitrosopentamethylenetetramine. No occupational exposure limits for *N*,*N*-dinitrosopentamethylenetetramine have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute for Occupational Safety and Health (NIOSH, 2007), or the Occupational Safety and Health Administration (OSHA, 2006).

The HEAST (U.S. EPA, 2003) does not report a U.S. EPA (1986) cancer weight-of-evidence (WOE) classification or an oral slope factor. *N*,*N*-dinitrosopentamethylenetetramine is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2009) has not prepared a quantitative estimate of the carcinogenic potential of *N*,*N*-dinitrosopentamethylenetetramine. The International Agency for Research on Cancer (IARC) did review the carcinogenic potential of *N*,*N*-dinitrosopentamethylenetetramine in 1976 and re-evaluated the carcinogenicity again in 1987. The 1976 review found no observable carcinogenic effects when tested in rats by oral and intraperitoneal injection (IARC, 1976), and the 1987 subsequent evaluation determined that *N*,*N*-dinitrosopentamethylenetetramine is a Class 3 Carcinogen (*Not Classifiable as to its Carcinogenicity to Humans*) due to the lack of data in humans and inadequate evidence in animals (IARC, 1987).

Literature searches were conducted on sources published from 1900 through March 21, 2012 for studies relevant to the derivation of provisional toxicity values for *N*,*N*-dinitrosopentamethylenetetramine, CAS No. 101-25-7. Searches were conducted using U.S. 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): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, 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, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

The literature search revealed no usable human or animal studies (acute-, short term-, subchronic-, or chronic-duration) for development of toxicity values for *N*,*N*-dinitrosopentamethylenetetramine. Three studies (Hadidian et al., 1968; Griswold et al., 1966; Weisburger et al., 1966) were identified that examined tumor formation in animals treated with *N*,*N*-dinitrosopentamethylenetetramine; however, none of these were suitable for development of toxicity values. They are summarized below and in Table 2. Wherever the word significant is used below, it refers to a change that the study authors reported to be statistically significant.

In a single-dose study by Griswold et al. (1966), no tumors were observed in 20 female Sprague-Dawley rats 6 months after a single gavage dose of 90 mg *N*,*N*-dinitrosopentamethylenetetramine, and mortality did not differ significantly from controls. In another study by Weisburger et al. (1966), Fisher rats (15 male and 15 female) treated with unspecified doses up to 9 mg/animal-day *N*,*N*-dinitrosopentamethylenetetramine 5 days per week for 1 year and then observed for another 6 months had no tumors. In a third study by Hadidian et al. (1968), Fisher rats were dosed by gavage 5 days per week for 52 weeks with 0, 0.03, 0.1, 0.3, 1, 3, or 9 mg/animal-day *N*,*N*-dinitrosopentamethylenetetramine and observed for another 6 months afterward. This study shares authors with the study by Weisburger et al. (1966) and may be a more detailed report of the same experiments. Hadidian et al. (1968) utilized 3 animals/sex/dose group for all doses except there were 15 animals/sex in the 3 mg/animal-day group. The study authors reported no significant changes in survival, body weight, or liver weight and no significant increase in tumor incidence. Due to low group sizes and/or short dosing duration, the negative results from these studies are inconclusive and do not support development of toxicity values for *N*,*N*-dinitrosopentamethylenetetramine. In all three of these studies, the authors performed preliminary range-finding studies aimed at identifying the maximally tolerated dose (MTD); these experiments were aimed at identifying doses at which mortality occurred, and, therefore, also do not support development of provisional reference values for *N*,*N*-dinitrosopentamethylenetetramine.

Table 2. Summary of Potentially Relevant Data for *N,N*-Dinitrosopentamethylenetetramine (CASRN 101-25-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference	Comments
Carcinogenic	0/20, Sprague-Dawley rat, gavage, once, 6 mo follow-up	90 mg	No tumors observed	NR	NC	NR	(Griswold et al., 1966)	Animals were dosed once orally (presumably via gavage) and observed for tumors after 6 mo.
	15/15, Fischer rat, gavage, 5 d/wk, 1 yr, 6 mo follow-up	9 mg/animal-d	No tumors observed	NR	NC	NR	(Weisburger et al., 1966)	Animals were treated for 1 yr, then maintained for an additional 6 mo before examining for tumors.
	3–15/3–15, Fischer rat, gavage, 5 d/wk, 1 yr, 6 mo follow-up	0, 0.03, 0.1, 0.3, 1, 3, 9 mg/animal-d	No significant increase in tumors observed; one squamous cell carcinoma on the tongue of a female administered 1 mg/d	NR	NC	NR	(Hadidian et al., 1968)	Animals were treated for 52 wk, then observed for an additional 6 mo after end of treatment. There were controls (negative, untreated, or vehicle; stated to be 30/sex) for each chemical tested, but it appears that the results were combined into one table. There were only 3 animals/sex/treatment in all groups except the 3 mg/d/animal group, which had 15 animals/sex.

[a]For this document, these values have not been converted to adjusted daily dose (ADD in mg/kg-d), human equivalent dose (HED in mg/kg-d), or human equivalent concentration (HEC in mg/m^3) units.
[b]NR = Not relevant; NC = Not calculated.

DERIVATION OF PROVISIONAL VALUES

Limitations in the available data preclude development of both cancer and noncancer toxicity values for *N*,*N*-dinitrosopentamethylenetetramine.

CANCER WOE DESCRIPTOR

Limitations in the available data preclude development of a WOE descriptor.

MODE-OF-ACTION DISCUSSION

Limitations in the available data preclude a mode-of-action discussion.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2011). 2011 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. http://www.acgih.org/store/ProductDetail.cfm?id=2147.

ATSDR (Agency for Toxic Substances and Disease Registry). (2011). Toxicological profiles: Information about contaminants found at hazardous waste sites, from http://www.atsdr.cdc.gov/toxprofiles/index.asp

Cal EPA (California Environmental Protection Agency). (2008). OEHHA acute, 8-hour and chronic Reference Exposure Levels (chRELs) [Database]. Retrieved from http://www.oehha.ca.gov/air/allrels.html

Cal EPA (California Environmental Protection Agency). (2009). Appendix A: Hot spots unit risk and cancer potency values. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://www.oehha.ca.gov/air/hot_spots/2009/AppendixA.pdf.

Griswold, DP, Jr; Casey, AE; Weisburger, EK; Schabel, FM, Jr. (1966). On the carcinogenicity of a single intragastric dose of hydrocarbons, nitrosamines, aromatic amines, dyes, coumarins, and miscellaneous chemicals in female Sprague-Dawley rats. Cancer Res 26: 619-625.

Hadidian, Z; Fredrickson, TN; Weisburger, EK; Weisburger, JH; Glass, RM; Mantel, N. (1968). Tests for chemical carcinogens: Report on the activity of derivatives of aromatic amines, nitrosamines, quinolines, nitroalkanes, amides, epoxides, aziridines, and purine antimetabolites. J Natl Cancer Inst 41: 985-1036.

HSDB (Hazardous Substances Data Bank). (2003). Dinitrosopentamethylenetetramine - CASRN: 101 25 7. Washington, DC: National Library of Medicine.

IARC (International Agency for Research on Cancer). (1976). Dinitrosopentamethylenetetramine. In Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics (Vol. 11). Lyon, France.

IARC (International Agency for Research on Cancer). (1987). Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1 to 42 (Vol. Suppl. 7). Lyon, France.

NIOSH (National Institute for Occupational Safety and Health). (2007). NIOSH pocket guide to chemical hazards. (2005-149). Cincinnati, OH.

NTP (National Toxicology Program). (2011). Report on carcinogens: Twelfth edition. Washington, DC: U.S. Department of Health and Human Services. http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf.

OSHA (Occupational Safety & Health Administration). (2006). Table Z-1 limits for air contaminants. Occupational Safety and Health Administration. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

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

U.S. EPA (U.S. Environmental Protection Agency). (1994). Chemical assessments and related activities (CARA). (600R94904; OHEA-I-127). Washington, DC: Office of Health and Environmental Assessment, Office of Research and Development. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt.

U.S. EPA (U.S. Environmental Protection Agency). (2003). Health Effects Assessment Summary Tables (HEAST), from http://epa-heast.ornl.gov/

U.S. EPA (U.S. Environmental Protection Agency). (2011a). 2011 Edition of the drinking water standards and health advisories. (EPA 820-R-11-002). Washington, DC. http://water.epa.gov/action/advisories/drinking/drinking_index.cfm.

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Integrated risk information system (IRIS), from http://www.epa.gov/iris/index.html

Weisburger, JH; Weisburger, EK; Mantel, N. (1966). New carciogenic nitrosamines in rats. Naturwissenschaften 53: 508.

WHO (World Health Organization). (2011). Online catalog for the Environmental Health Criteria Series, from http://www.who.int/ipcs/publications/ehc/en/