N-Nitrosodiethylamine; CASRN 55-18-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR N-Nitrosodiethylamine

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	01/31/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine
Last Revised — 01/31/1987

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Induction of tumors at multiple sites in both rodent and nonrodent species exposed by various routes

II.A.2. Human Carcinogenicity Data

Human exposure to nitrosamines results from contact with mixtures containing these compounds (e.g., cutting oils, tobacco products). Because of potential confounding by the other substances in these mixtures, data from human exposure is of limited use in the evaluation of carcinogenicity of individual nitrosamines.

II.A.3. Animal Carcinogenicity Data

There is a large database on the carcinogenicity of nitrosamines, most of which pertains to structure-activity relationships rather than to dose- response. Diethylnitrosamine administered by gavage, in drinking water, or by feeding produces liver tumors in the following species: rats, mice, hamsters, guinea pigs, rabbits, dogs, and monkeys (Yamamoto et al., 1972; Druckrey et al., 1967, 1963; Magee et al., 1976; Rajewsky et al., 1966; Tomatis, 1973).

Tracheal and lung tumors have been observed in Syrian golden hamsters upon administration of diethylnitrosamine by gavage or inhalation (Magee et al., 1976). Diethylnitrosamine administered to pregnant mice, rats, and hamsters has been shown to act transplacentally, inducing tumors in the progeny (Tomatis, 1973; Mohr, 1966; Druckrey, 1973a,b).

Peto et al. (1984) exposed groups of 48 Colworth rats/sex to diethylnitrosamine in drinking water at 15 concentrations between 0.033 and 16.896 ppm. Six animals/group were sacrificed at 6 and at 12 months and the remainder kept on treatment until natural death. Water consumption was 41 and 72 mL/kg for adult males and females. Data on tumor incidence was not reported for each group, but data pooled by sex indicated positive trends for tumors of the nasopharynx, lower jaw, stomach, kidney, ovaries, seminal vesicles, liver, and esophagus. Dose-related increases in incidence of upper GI tumors and liver cell tumors were observed in C57-BO mice, and tracheal and liver cell tumors were observed in Syrian hamsters (Peto et al., 1984).

II.A.4. Supporting Data for Carcinogenicity

Diethylnitrosamine is mutagenic for S. typhimurium, E. coli, and Neurospora crassa, and produced mitotic recombination in S. cerevisiae, recessive lethal mutations in D. melanogaster, and chromosomal aberrations in mammalian cells. Positive responses in bacterial cells are dependent upon the addition of a mammalian metabolic system (Montesano and Bartsch, 1976). Diethylnitrosamine is structurally related to known carcinogens.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 1.5E+2 per (mg/kg)/day

Drinking Water Unit Risk — 4.3E-3 per (µg/L)

Extrapolation Method — Weibull, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-2 ug/L
E-5 (1 in 100,000)	2E-3 ug/L
E-6 (1 in 1,000,000)	2E-4 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — liver
Test animals — rat/Colworth, female
Route — drinking water
Reference — Peto et al., 1984

Specific tumor incidences were not published. Data from Peto et al. (1984) on incidence of liver tumors of all types in female rats were shown to follow this relationship:

	CI = 32.09 (d + 0.04) **4 x t**7
where:	CI = cumulative incidence
	d = dose (mg/kg/day)
	t = time in years

Using procedures described in U.S. EPA (1980) to correct for background response, the increased risk associated with exposure to 1 ug/kg/day for 3 years = 2.27E-2, corresponding to a slope factor in rats of 22.7 per (mg/kg)/day. The slope factor was calculated using the cube root of the ratio of the assumed adult human weight of 70 kg and the reported rat weight of 250 g.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Peto et al. (1984) reported liver and esophageal tumors to be the only treatment-related cause of death. The unit risk should not be used if the water concentration exceeds 2 ug/L, since above this concentration the unit risk may not be appropriate.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Although specific incidences were not reported, it appears that large numbers of animals were observed for their lifetime. Tumor induction was dose-related as regards both numbers of animals with tumors and latency. The study was designed specifically for analysis using the Weibull model. A slope factor calculated in the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1980) based on data of Druckrey et al. (1963) was 43 per (mg/kg)/day, within a factor of 4 of the above risk estimate.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.3E-2 per (µg/cu.m)

Extrapolation Method — Weibull, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-3 ug/cu.m
E-5 (1 in 100,000)	2E-4 ug/cu.m

Risk Level	Concentration
E-6 (1 in 1,000,000)	2E-5 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

The inhalation risk estimates were calculated from the oral exposure data in II.B.2.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk should not be used if the air concentration exceeds 2E-1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

See II.B.4.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1980, 1986

The values in the Health and Environmental Effects Profile for Nitrosamines (U.S. EPA, 1986) received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 07/23/1986, 08/13/1986, 10/29/1986

Verification Date — 10/29/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for N-Nitrosodiethylamine conducted in August 2003 identified one or more significant new studies.

IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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Druckrey, H., R. Preussmann, S. Ivankovic and D. Schmaehl. 1967. Organotropism and carcinogenic effects of 65 different N-nitroso compounds in BD-rats. Z. Kerbsforsch. 69(2): 103-201.

Druckrey, H. 1973a. Chemical structure and action in transplacental carcinogenesis and teratogenesis. IARC Sci. Publ., Lyon, France. No. 4. p. 45-58.

Druckrey, H. 1973b. Specific carcinogenic and teratogenic effects of "indirect" alkylating methyl and ethyl compounds, and their dependency on stages of oncogenic development. Xenobiotica. 3: 271.

Magee, P.N., R. Montesano and R. Preussman. 1976. N-Nitroso compounds and related carcinogens. ACS Monograph. 173: 491-625.

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U.S. EPA 1980. Ambient Water Quality Criteria for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-064. NTIS PB 81-117756.

U.S. EPA. 1986. Health and Environmental Effects Profile for Nitrosamines. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

Yamamoto, R.S., R. Kroes and J.H. Weisburger. 1972. Carcinogenicity of diethylnitrosamine in Mystromys albicaudatus (African white-tailed rat). (36573). Proc. Soc. Exp. Biol. Med. 140: 890.

VII. Revision History

Substance Name — N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine

Date	Section	Description
10/28/2003	II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — N-Nitrosodiethylamine
CASRN — 55-18-5
Primary Synonym — Diethylnitrosamine
Last Revised — 01/31/1987

- 55-18-5
- DANA: DEN
- DENA
- diaethylnitrosamin
- diethylamine, N-nitroso
- Diethylnitrosamine
- diethylnitrosoamine
- ethylamine, N-nitrosodi-
- NDEA
- N-ethyl-N-nitroso-ethanamine
- nitrosodiethylamine
- Nitrosodiethylamine, N-
- N,N-diethylnitrosamine
- N-Nitrosodiethylamine
- RCRA waste number U174