N-Nitrosodimethylamine; CASRN 62-75-9

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-Nitrosodimethylamine

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-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine

Not available at this time.

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

Substance Name — N-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — N-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine
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 rodents and nonrodent mammals 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. N-Nitrosodimethylamine produced liver tumors in BD rats when administered in drinking water (Druckrey et al., 1967) and in female Porton rats when administered in the diet (Terracini et al., 1967). Magee et al. (1976) state that dimethylnitrosamine produced many hemangiomatous tumors and some parenchymal cell tumors in the livers of rats after oral administration.

N-Nitrosodimethylamine acts as a transplacental carcinogen when administered to pregnant rats, mice, and Syrian golden hamsters by several routes (Tomatis, 1973). Increases in lung, liver, and kidney tumors were observed in both Wistar rats and Balb/C mice exposed by inhalation. Mink are very sensitive to the effects of dimethylnitrosamine, developing tumors when fed 0.05 mg/kg 2 days/week (NAS, 1978).

Peto et al. (1984) exposed groups of Colworth rats (36/sex/dose) to 15 concentrations of N-nitrosodimethylamine in drinking water (0.033-16.896 ppm). Daily water consumption was 41 mL/kg for males and 72 mL/kg for females. Tumors were generally of hepatic origin, and these tumors constituted the only cause of mortality considered treatment-related. Tumor incidences for each treatment group were not reported, but pooled data indicated possible positive trends for lung, skin, seminal vesicle, lymphatic/hematopoetic system, and liver tumors.

II.A.4. Supporting Data for Carcinogenicity

N-Nitrosodimethylamine is mutagenic for Escherichia coli, Salmonella typhimurium and Neurospora crassa, produces mitotic recombination in Sacharoyus cerevesiae, recessive lethal mutations in Drosophilla melanogaster, and chromosomal aberrations in mammalian cells. Positive responses in bacterial cells are dependent upon the addition of a mammalian metabolism system (Montesano and Bartsch, 1976). Dimethylnitrosamine 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 — 5.1E+1 per (mg/kg)/day

Drinking Water Unit Risk — 1.4E-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)	7E-2 ug/L
E-5 (1 in 100,000)	7E-3 ug/L
E-6 (1 in 1,000,000)	7E-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 = 51.45 (d + 0.1) **6 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 of 1 ug/kg/day for 3 years = 7.8E-3 or a slope factor for rats of 7.8 per (mg/kg)/day. The slope factor was thus calculated to be 51 per (mg/kg)/day by using the cube root of the ratio of the assumed human body weight (70 kg) to the reported rat body weight of (250 g).

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

The unit risk should not be used if the water concentration exceeds 7 ug/L, since above this concentration the unit risk may not be appropriate.

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

Although specific tumor incidence data was not reported, it appears that large numbers of animals were treated over a wide dose range. Both tumor incidence and latency were shown to be dose-dependent. The study was designed specifically for analysis using the Weibull model. A slope factor based on data by Druckrey et al. (1972) was determined by use of a one-hit model to be 26 per (mg/kg)/day.

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

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 1.4E-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)	7E-3 µg/cu.m
E-5 (1 in 100,000)	7E-4 ug/cu.m
E-6 (1 in 1,000,000)	7E-5 ug/cu.m

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

Calculated from data in Section II.B.2.

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

The above unit risk should not be used if the air concentration exceeds 0.7 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 — 06/26/1986, 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-Nitrosodimethylamine conducted in September 2002 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-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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

Druckrey, H., S. Ivankovic, R. Preussmann, K.J. Zulch and H.D. Mennel. 1972. Selective induction of malignant tumors of the nervous system by resorptive carcinogens. In: Experimental Biology of Brain Tumors. p. 85-112.

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

Montesano, R. and H. Bartsch. 1976. Mutagenic and carcinogenic N-nitroso compounds: Possible environmental Hazards. Mutat. Res. 32: 179-228.

NAS (National Academy of Sciences). 1978. Nitrates: An environmental assessment. A report prepared by the panel on nitrates of the Coordinating Comm. Sci. Tech. Assess. Environ. Pollut., Washington, DC.

Peto, R., R. Gray, P. Brantom and P. Grasso. 1984. Nitrosamine carcinogenesis in 5120 rodents: Chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3, 6 or 20 weeks) and of species (rats, mice, hamsters). IARC Sci. Publ. 57: 627-665.

Terracini, B., P.N. Magee and J.M. Barnes. 1967. Hepatic pathology in rats on low dietary levels of dimethylnitrosamine. Br. J. Cancer. 21: 559-565.

Tomatis, L. 1973. Transplacental carcinogenesis. In: Modern Trends in Oncology. Part I, R.W. Raven, Ed. Butterworths, London.

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.

VII. Revision History

Substance Name — N-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine

Date	Section	Description
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — N-Nitrosodimethylamine
CASRN — 62-75-9
Primary Synonym — Dimethylnitrosamine
Last Revised — 01/31/1987

- 62-75-9
- dimethylamine, N-nitroso
- dimethylnitrosamin
- Dimethylnitrosamine
- dimethylnitrosoamine
- DMNA: DMN
- methylamine, N-nitrosodi-
- NDMA
- nitrosodimethylamine
- Nitrosodimethylamine, N-
- N-methyl-N-nitrosomethanamine
- N,N-dimethylnitrosamine
- N-Nitrosodimethylamine
- RCRA waste number P082