

N-Nitroso-N-methylethylamine; CASRN 10595-95-6

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-Nitroso-N-methylethylamine

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/01/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — N-Nitroso-N-methylethylamine
CASRN — 10595-95-6

Not available at this time.

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

Substance Name — N-Nitroso-N-methylethylamine
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Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — N-Nitroso-N-methylethylamine
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Last Revised — 03/01/1988

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 — Increased incidence of tumors of the liver and other sites in two rat strains

II.A.2. Human Carcinogenicity Data

Inadequate. 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 are of limited use in the evaluation of carcinogenicity of individual nitrosamines.

II.A.3. Animal Carcinogenicity Data

Sufficient. As part of a survey of 65 N-nitroso compounds, Druckrey et al. (1967) administered N-nitrosomethylethylamine to 4 or 11 BD rats in drinking water at doses of 1 or 2 mg/kg/day, respectively. Treatment was continuous for life. A total of 9/15 rats developed hepatocellular carcinomas with average induction times and total doses to produce tumors in 50% of the animals of 500 days and 0.42 g/kg for the low-dose group and 360 days and 0.75 g/kg for the high-dose group.

Male and female F344 rats receiving 3.0 mg N-nitrosomethylethylamine/day in drinking water for 30 weeks showed a high incidence of hepatocellular carcinomas (19/20) as well as lung metastases and esophageal papillomas or carcinomas (Lijinsky and Reuber, 1981). Male rats receiving 600 ug or 3000 ug/week in drinking water for 30 weeks likewise developed tumors: 3/20 hepatocellular carcinomas in the low-dose group and 12/20 hepatocellular carcinomas, nasal tumors and esophageal papillomas in the high-dose group (Lijinsky and Reuber, 1980). Tumors of the liver (9/20) and nasal cavity (4/20) were also observed in male F344 rats receiving approximately 0.12 mg/rat/day in drinking water over a 30-week period (Lijinsky et al., 1982). By contrast, female rats receiving drinking water containing 6 mg N-nitrosomethylethylamine/L developed leukemias (18/20 as compared with 12/20 in controls) as the only observed treatment-related neoplastic response (Lijinsky and Reuber, 1983). Michejda et al. (1984) reported that all of a group of 20 F344 rats administered 8 mg/kg N-nitrosomethylethylamine in drinking water for 15 weeks had died of liver tumors with a median time to death of 45 weeks.

II.A.4. Supporting Data for Carcinogenicity

N-nitrosomethylethylamine is mutagenic to *Salmonella typhimurium* (Kerklaan et al., 1983; Phillipson and Ioannides, 1985) and to V79 cells (Jones and Huberman, 1980).

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 2.2E+1/mg/kg/day

Drinking Water Unit Risk — 6.3E-4/ug/L

Extrapolation Method — One-hit

Drinking Water Concentrations at Specified Risk Levels:

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

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

Tumor Type: hepatocellular carcinomas

Test animals: Rat/BD, sex not specified

Route: drinking water

Reference: Druckrey, 1967; Druckrey et al., 1967

Information in the references cited was used in quantitation of risk using the following relationship:

$$Ck/(t50)^{**} n = d$$

where: C = conversion between mmol and mg = 88.1 mg/mmol

k = empirically derived constant = 0.81E+4 mmol/kg/day

t50 = median time of tumor induction = 728

n = representative value for dialkyl nitrosamines as published by Druckrey = 2.3

d = daily dose of test compound, calculated from the above to be 0.18645 mg/kg/day

The slope factor for rats (BA) was calculated from a rearrangement of the one-hit model:

$$BA = -\ln(0.5/\text{day}) = 3.72/\text{mg/kg/day}$$

Adjusting this value by the cube root of the assumed human body weight (70 kg) to the assumed rat body weight (0.35 kg) gives the human slope factor 21.8/mg/kg/day.

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

A reported value of n=2.1 for N-nitrosomethylethylamine was not used in the calculations, since a k value for this n was not reported.

The unit risk should not be used if the water concentration exceeds 20 ug/L, since above this concentration the slope factor may differ from that stated.

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

Small numbers of rats were treated at only two doses, and there was no control group.

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

Not available.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The values in the 1986 Health and Environmental Effects Profile have received an Agency Review.

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

Agency Work Group Review — 02/11/1987

Verification Date — 02/11/1987

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-Nitroso-N-methylethylamine conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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-Nitroso-N-methylethylamine
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VI.A. Oral RfD References

None

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

Druckrey, H. 1967. Quantitative aspects in chemical carcinogens. In: Potential Carcinogenic Hazards from Drugs. UICC Monograph, Series 7. Berlin Springer-Verlag. p. 60-78.

Druckrey, H., R. Preussmann, S. Ivankovic and D. Schmael. 1967. Organotropic carcinogenic effects of 65 different N-Nitroso-compounds on BD-rats. *Z. Krebsforsch.* 69(2): 103-201.

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Kerklaan, P., S. Bouter and G. Mohn. 1983. Activation of nitrosamines and other carcinogens by mouse-liver S9, hepatocytes and in the hostmediated assay produces different mutagenic responses in salmonella. *Mutat. Res.* 110(1): 9-22.

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Lijinsky, W. and M.D. Reuber. 1981. Comparative carcinogenesis by some aliphatic nitrosamines in Fischer rats. *Cancer Lett.* 14(3): 297-302.

Lijinsky, W. and M.D. Reuber. 1983. Carcinogens in Fischer rats by nitrosodipropylamine, nitrosodibutylamine and nitrosobis(2-oxopropyl)amine given by gavage. *Cancer Lett.* 19: 207-213.

Lijinsky, W., J.E. Saavedra, M.D. Reuber, et al. 1982. Esophageal carcinogenesis in F344 rats by nitrosomethylethylamines substituted in the ethyl group. *J. Natl. Cancer Inst.* 68(4): 681-684.

Michejda, C.J., M.B. Krueger-Koepke and R.M. Kovatch. 1984. Carcinogenic effects of sequential administration of two nitrosamines to rats. *Proc. of AACR.* 25: 126.

Phillipson, C.E. and C. Ioannides. 1985. Metabolic activation of nitrosamines to mutagens by various animal species including man. *Biochem. Pharmacol.* 34(3): 441-442.

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-Nitroso-N-methylethylamine
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Date	Section	Description
03/01/1988	II.B.1.	Oral unit risk changed
10/28/2003	II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — N-Nitroso-N-methylethylamine
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Last Revised — 03/31/1987

- 10595-95-6
- Ethanamine, N-methyl-N-nitroso-
- Ethylamine, N-methyl-N-nitroso-
- Ethylmethylnitrosamine
- Methylethylnitrosamine
- Methylethylnitrosoamine
- Nitrosomethylethylamine
- Nitroso-N-methylethylamine, N-
- N-Methyl-N-nitrosoethanamine
- N-Methyl-N-nitrosoethylamine
- N-Nitrosoethylmethylamine
- N-Nitrosomethylethylamine
- N-Nitroso-N-methylethylamine