2-Nitropropane; CASRN 79-46-9

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 2-Nitropropane

File First On-Line 03/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	03/01/1991
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 2-Nitropropane
CASRN — 79-46-9

Not available at this time.

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

Substance Name — 2-Nitropropane
CASRN — 79-46-9
Last Revised — 03/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Liver focal vacuolization and nodules **Rat Chronic Inhalation Study** **Griffin et al., 1980, 1981; Angus Chemical Co., 985a,b**	NOAEL: None LOAEL = 78 mg/cu.m (25 ppm) LOAEL(ADJ) = 16 mg/cu.m LOAEL(HEC)= 16 mg/cu.m	1000	1	2E-2 mg/cu.m

*Conversion Factors: aW = 89.09. At exposure conditions (chamber temperature and atmospheric pressure measured daily), 25 ppm = 78 mg/cu.m (author's conversion). LOAEL(ADJ) = 78 x 7 hours/day x 5 days/7 days = 16.3 mg/cu.m. The LOAEL(HEC) was

calculated for a gas:extrarespiratory effect assuming periodicity was attained. b:a lamba(a) = 183 (F344 rats), b:a lambda(h) = 154, (Gargas et al., 1989). Since b:a lambda(a) is greater than b:a lambda(h), a default value of 1.0 is used for this ratio. LOAEL(HEC) = LOAEL(ADJ) x (b:a lambda(a)/b:a lambda(h)) = 16.3 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Griffin, T.B., F. Coulston and A.A. Stein. 1980. Chronic inhalation exposure of rats to vapors of 2-nitropropane at 25 ppm. Ecotoxicol. Environ. Saf. 4(3): 267-81.

Griffin, T.B., A.A. Stein and F. Coulston. 1981. Histological study of tissues and organs from rats exposed to vapors of 2-nitropropane at 25 ppm. Ecotoxicol. Environ. Saf. 5(2): 194-201.

Angus Chemical Company. 1985a. Final report: Chronic inhalation exposure of rats to vapors of 2-nitropropane at 100 ppm. By Coulston Intl. Corp. for Angus Chem. Co. OTS No. 204292. Doc No. 8EHQ-0985-0170. Fiche No. 0200504.

Angus Chemical Company. 1985b. Chronic inhalation of 200 ppm of 2- nitropropane in rats: Six month report. By Coulston Intl. Corp. (May 1978) for Angus Chem. Co. OTS No. 204292. Doc No. 8EHQ-0985-0170. Fiche No. 0200504.

A series of inhalation exposure studies (Angus Chemical Co. 1985a,b; Griffin et al. 1980, 1981) were conducted to evaluate toxicity of 2- nitropropane in Sprague-Dawley rats. The co-critical studies report results from the different exposure concentrations evaluated in these studies. Griffin et al. (1980, 1981) reports results from the lowest concentration studied (25 ppm). Complete histopathology was conducted and results are reported for the liver in Griffin et al., 1980 and for the remaining tissues, including the lungs, in Griffin et al., 1981. The Angus Chemical Co. papers (1985a,b) report results from studies conducted by the same investigators at 100 and 200 ppm, respectively, and are included as co-critical studies to provide information about the concentration-response characteristics of the critical effect.

Sprague-Dawley rats (125/sex/group) received 0 or 25 ppm (0 or 78 mg/cu.m) 2-nitropropane 7 hours/day, 5 days/week (duration-adjusted to 0 or 16.3 mg/cu.m) for 22 months (Griffin et al., 1980; 1981). Interim sacrifices (10 animals/group) were done at 1, 3, 6, and 12 months. In addition, recovery groups were studied which were exposed for 3 and 12 months and maintained without exposure for 19 and 10 months, respectively. All surviving animals were examined at 22 months. Animals were evaluated daily for behavioral or toxic effects and weighed weekly. Hematologic parameters and brain, liver, and kidney weights were measured. Serum clinical chemistry tests to evaluate liver and thyroid function included SGPT, Ornithine cabamyl transferase, thyroxine, and triiodothyronine uptake. Complete histopathology was conducted and

results are reported for the liver in Griffin et al. (1980) and for the remaining tissues, including the lungs, in Griffin et al. (1981). Absolute and relative liver weight was significantly increased in males after 22 months exposure. Female rats showed an increase in absolute, but not relative, liver weight. Body weight, serum liver enzymes, other serum chemistry, and hematological parameters were unaffected by exposure. An increase in focal vacuolization of the cytoplasm of hepatocytes was observed in the exposed males (22/125 controls, 58/125 exposed, results pooled for all exposed animals). Slight hepatic congestion (males: 1/125 controls, 8/125 exposed; females: 0/125 controls, 7/124 exposed) and focal areas of hepatocellular nodules (males: 2/125 controls, 10/125 exposed; females: 1/125 controls, 3/124 exposed) were reported, but no statistical analysis was performed. The study suggested that male rats are more sensitive to chronic exposure to 2- nitropropane than females. No exposure-related effect on any other tissue was reported, including trachea, lung, and bronchus (Griffin et al., 1981). A LOAEL of 25 ppm (78 mg/cu.m) 2-nitropropane for mild hepatic effects was determined (HEC = 16.3 mg/cu.m).

A chronic exposure of rats to 100 ppm 2-nitropropane was performed as part of a series of studies by the authors of the principal study (Angus Chemical Co., 1985a). Sprague-Dawley rats (125 males, 125 females) were exposed to 100 ppm (312 mg/cu.m, authors conversion based on daily measurements of temperature and atmoshperic pressure) 2-nitropropane 7 hours/day, 5 days/week (duration-adjusted to 65 mg/cu.m) for 18 months. Parameters examined at the end of exposure were the same as in the principal study except that prothrombin time was measured and no histopathology was performed. Results showed an increase in the absolute and relative liver weight and a decrease in body weight (10%, not statistically significant) occurring in the males by the end of the exposure period. These effects were also evident at the 9- and 12- month interim sacrifice. Increased SGPT levels (4.6-fold increase over controls) were observed in males at 22 months of exposure. No other effects were reported with 2-nitropropane exposure and no histopathological examination of any tissue was performed. This study identifies a LOAEL for liver effects at 100 ppm (312 mg/cu.m). The study was limited because no statistical analysis was performed and histopathology was not conducted on liver or lung.

In another report by the same authors, 125 Sprague-Dawley rats of each sex inhaled 200 ppm (624 mg/cu.m, assuming the same temperature and atmospheric pressure as in the previous studies) 2-nitropropane 7 hours/day, 5 days/week (duration-adjusted to 130 mg/cu.m) for up to 6 months (Angus Chemical Co., 1985b; Griffin et al., 1978). Except for the shorter exposure duration, the study protocol and parameters examined were identical to Griffin et al. (1980, 1981). This study is included to characterize the concentration-response and time course of the critical effect and to supplement the findings at 100 ppm, which did not include histological examination. Group of 10 rats/sex were sacrificed at 10 days, 1 month and 3 months and in two recovery experiments, with the remainder killed at 6 months. At 6 months, there were no consistent exposure-related changes in body weights or hematologic parameters in the treated males or females. Increased SGPT (4.5-fold over controls) was observed after 6 months exposure

in male rats. A significant elevation (p=0.01) in the relative liver weights was reported at 3 and 6 months for both sexes and at 1 month in females compared with controls. Relative lung weights were similar for both animal groups. Morphological changes in the liver included hypertrophic areas and formation of hyperplastic nodules. Vacuolization and necrosis of hepatocytes were observed after 10 days and 1 month of exposure. At 1 month increased mitotic rates indicated cell regeneration. Diffuse cytoplasmic vacuolization, nuclear change, cell necrosis, and broken cell walls were observed to a greater extent in exposed male rats at 3 and 6 months of exposure. Hypertrophic areas and nodules were observed in males at 6 months of exposure. The hepatocellular changes in the females were milder than in males at 6 months and consisted of slight vacuolization. No histological changes were seen at any exposure duration in the CNS, kidney, or thyroid. Thickening of alveolar septa was noted in 4/10 control males and 4/10 control females and in all exposed rats after 6 months of exposure suggesting possible respiratory toxicity at this level. This study confirmed that male rats were more susceptible to hepatic effects of 2- nitropropane than females and identifies a LOAEL for liver effects and possibly for minor lung effects, although this conclusion is confounded by high incidence of the effect in the control population (LOAEL(HEC) = 130 mg/cu.m for liver and 325 mg/cu.m for respiratory effects in the thoracic region).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is used for the protection of sensitive human subpopulations. A factor of 10 is used to account for the use of a LOAEL for a mild effect and for species-to-species extrapolation. A factor of 10 is used for inadequate database due to lack of adequate developmental and reproductive studies and concern about the quality of the principal studies.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

As part of the report by the authors of the principal study, groups of 10 Long Evans rats were exposed for 2 months to 200 ppm (624 mg/cu.m, assuming the same temperature and atmospheric pressure as in the previous studies) 2- nitropropane, 7 hours/day, 5 days/week (duration-adjusted to 130 mg/cu.m) for up to 6 months (Angus Chemical Co. 1985b). Except for the shorter exposure duration, the study protocol and parameters examined were identical to Griffin et al. (1980, 1981). Long Evans rats exposed for 2 months showed cytoplasmic vacuolization of hepatocytes in males (0/10 controls vs. 10/10 exposed) with no liver effect in females. Pulmonary effects similar to those seen in the Sprague-Dawley rats were observed in both control and exposed Long Evans rats. This study confirmed that male rats were more susceptible to hepatic effects of 2-nitropropane than females and identifies a LOAEL for liver effects and possibly for minor lung effects, although this conclusion is confounded by high

incidence of the same effects in the control population (LOAEL(HEC) = 130 mg/cu.m for liver and 600 mg/cu.m for respiratory effects).

In a 6-month (24-week) inhalation study, male Sprague-Dawley rats (50 animals/group) and 15 male New Zealand rabbits were exposed to 0, 27, or 207 ppm (0, 98.4, or 754 mg/cu.m) 2-nitropropane (94.45% purity) 7 hours/day, 5 days/week (duration-adjusted to 0, 20.5, or 157 mg/cu.m) (Lewis et al., 1979). Groups of 10 rats were sacrificed at 2 and 10 days, and at 1, 3, and 6 months. Groups of 5 rabbits were sacrificed at 1, 3, and 6 months. Hematology, serum biochemistry, and tissue edema tests (wet/dry weight ratios) were conducted as well as necropsy and histopathologic examination in all organs including the lungs. There were no treatment-related effects observed at the low concentration in rats or rabbits or in rabbits at the high concentration. At 207 ppm, there was a significant ($p=0.005$) increase in the lung and liver weights in the rats within 3 months compared with the controls. There was a higher incidence of focal necrosis, hypertrophic nodules with large vesiculated nuclei, and pale appearance of the liver. Elevated SGPT levels were reported (values not given) at 1 and 6 month sacrifices. In the lungs, hemorrhagic foci on the lobes and a mild incidence of pulmonary edema were observed in the high-concentration rats compared with the controls within 1 month after exposure. Multiple hepatocellular carcinomas were also present in the livers of all rats in the high-concentration group sacrificed at 6 months postexposure. Mild pulmonary effects (congestion and alveolar septal edema) were observed in 3/5 exposed rabbits at 1 month of exposure, but not at 3 or 6 months. A NOAEL of 27 ppm and a LOAEL of 207 ppm 2-nitropropane for hepatic and pulmonary effects in rats were determined for this study (NOAEL(HEC) = 20.5 mg/cu.m for liver effects and 51.2 mg/cu.m for respiratory effects in the thoracic region).

There were no reproductive or developmental studies available for inhalation or oral exposure to 2-nitropropane in animals. The single available study (Hardin et al., 1981) reported fetal toxicity (delayed fetal heart development) following i.p. injection of 170 mg/kg in Sprague-Dawley rats (number not specified) on days 1-15 of gestation. No maternal toxicity was reported. No other details were reported.

No occupational epidemiological studies are available. Human case reports of a total of 7 acutely exposed workers, 6 of whom were fatalities, have been described (Rondia, 1979; Hine et al., 1978: Harrison et al., 1985). All of these cases showed evidence of liver damage.

I.B.5. Confidence in the Inhalation RfC

Study — Low
Database — Low
RfC -- Low

Confidence in the critical studies is rated low because only a single exposure concentration was studied and it identified only a LOAEL. The critical effect is hepatotoxicity which is supported by other subchronic inhalation studies. Low confidence in the database results from a lack of reproductive or developmental studies. Low confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1985

Agency Work Group Review — 11/15/1990

Verification Date — 11/15/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for 2-Nitropropane conducted in November 2001 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.

I.B.7. EPA Contacts (Inhalation RfC)

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).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2-Nitropropane
CASRN — 79-46-9

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. Bibliography

Substance Name — 2-Nitropropane
CASRN — 79-46-9

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

Angus Chemical Company. 1985a. Final report: Chronic inhalation exposure of rats to vapors of 2-nitropropane at 100 ppm. By Coulston Intl. Corp. for Angus Chem. Co. OTS No. 204292. Doc No. 8EHQ-0985-0170. Fiche No. 0200504.

Angus Chemical Company. 1985b. Chronic inhalation of 200 ppm of 2- nitropropane in rats: Six month report. By Coulston Intl. Corp. (May 1978) for Angus Chem. Co. OTS No. 204292. Doc No. 8EHQ-0985-0170. Fiche No. 0200504.

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Lewis T.R., C.E. Ulrich, W.M. Busey. 1979. Subchronic inhalation toxicity of nitromethane and 2-nitropropane. J. Environ. Pathol. Toxicol. 2(5): 233-249.

Rondia, D. 1979. 2-Nitropropane: One more death. Vet. Hum. Toxicol. 21(Suppl): 183-185.

U.S. EPA. 1985. Health and Environmental Effects Profile for 2-Nitropropane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC. EPA/600/X-85/112.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 2-Nitropropane
CASRN — 79-46-9

Date	Section	Description
03/01/1991	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2-Nitropropane
CASRN — 79-46-9
Last Revised — 03/01/1991

- 79-46-9
- Propane, 2-nitro-
- Dimethylnitromethane
- HSDB 1134
- Isonitropropane
- Nitroisopropane
- NSC 5369
- PROPANE, 2-NITRO-
- RCRA WASTE NUMBER U171
- 2-nitropropane