# Provisional Peer-Reviewed Toxicity Values for

# *N*-Nitrosopyrrolidine
(CASRN 930-55-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

## COMMONLY USED ABBREVIATIONS

| | |
|---|---|
| BMD | Benchmark Dose |
| IRIS | Integrated Risk Information System |
| 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 |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional inhalation reference concentration |
| p-RfD | provisional oral reference dose |
| RfC | inhalation reference concentration |
| RfD | oral reference dose |
| 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 |

**PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR**
***N*-NITROSOPYRROLIDINE (CASRN 930-55-2)**

**Background**

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
    - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
    - California Environmental Protection Agency (CalEPA) values, and
    - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

**Disclaimers**

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

**Questions Regarding PPRTVs**

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) 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), or OSRTI.

## INTRODUCTION

No RfD or RfC assessment for *N*-nitrosopyrrolidine (chemical structure shown in Figure 1) is available on IRIS (U.S. EPA, 2009), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or in the HEAST (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) database (U.S. EPA, 1994, 1991a) lists an Ambient Water Quality Criteria Document (AWQCD) for nitrosamines (U.S. EPA, 1980) that includes *N*-nitrosopyrrolidine, but they did not attempt noncancer assessments. A Health Environmental Effects Profile (HEEP) for nitrosamines (U.S. EPA, 1986a) has also been located, but it does not include data for *N*-nitrosopyrrolidine. ATSDR (2009) has not published a toxicological profile for *N*-nitrosopyrrolidine. Neither CalEPA (2009a, b) nor the World Health Organization (WHO, 2009) have attempted to derive noncancer toxicity values for *N*-nitrosopyrrolidine. Occupational exposure limits for *N*-nitrosopyrrolidine have not been recommended or established by the American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2009), or the Occupational Safety and Health Administration (OSHA, 2009).

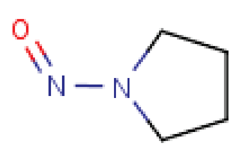


**Figure 1. Chemical Structure of *N*-Nitrosopyrrolidine**

A cancer assessment for *N*-nitrosopyrrolidine is available on IRIS (U.S. EPA, 1991b). The chemical is classified under the U.S. EPA (1986b) Guidelines for Carcinogen Assessment as "*Group B2 -- Probable Human Carcinogen*" based on oral studies in two rodent species in which tumors occurred at more than one site (Preussmann et al., 1977; Greenblatt and Lijinsky, 1972a, b). IRIS (U.S. EPA, 1991b) reports an Oral Slope Factor (OSF) of 2.1 per mg/kg-day based on hepatocellular carcinomas or adenomas in Sprague-Dawley rats administered *N*-nitrosopyrrolidine in drinking water for life (Preussmann et al., 1977). IRIS also reports an Inhalation Unit Risk (IUR) of $6.1 \times 10^{-4}$ per $\mu g/m^3$ based on the same oral data (Preussmann et al., 1977). The AWQCD (U.S. EPA, 1980) and HEEP (U.S. EPA, 1986a) for nitrosamines are cited as source documents for the IRIS assessment.

The National Toxicology Program (NTP, 2009) has not tested the toxicity or carcinogenicity of *N*-nitrosopyrrolidine. However, the 11$^{th}$ Report on Carcinogens (NTP, 2005) concludes that *N*-nitrosopyrrolidine is *"*reasonably anticipated to be a human carcinogen*"* based on sufficient evidence in experimental animals. The International Agency for Research on Cancer (IARC, 1978) classified *N*-nitrosopyrrolidine as "*Group B2 -- Probable Human Carcinogen*" based on sufficient evidence of carcinogenicity in experimental animals and inadequate evidence of carcinogenicity in humans. CalEPA (2009c) has adopted an IUR of $6.0 \times 10^{-4}$ $(\mu g/m^3)^{-1}$ and OSF of $2.1 \times 10^{0}$ $(mg/kg\text{-}day)^{-1}$ based on the IRIS values.

Due to the presence of a quantitative cancer assessment for *N*-nitrosopyrrolidine on IRIS (U.S. EPA, 2009), no provisional cancer assessment is necessary or performed in this document.

Literature searches were conducted from the 1960s through January 2009 for studies relevant to provisional noncancer toxicity values for *N*-nitrosopyrrolidine. The databases searched include RTECS, HSDB, TSCATS, MEDLINE, TOXLINE, DART, CCRIS, GENETOX, CHEMABS, BIOSIS, and Current Contents (last 6 months).

## REVIEW OF PERTINENT DATA

### Human Studies

No pertinent data have been located regarding health effects of *N*-nitrosopyrrolidine in humans following oral or inhalation exposure

### Animal Studies

#### *Oral Exposure*

Numerous animal studies have been conducted in which *N*-nitrosopyrrolidine was administered in drinking water. However, all of these studies (Anderson et al., 1993 [lung tumors in mice]; Gray et al., 1991[liver tumors in rats]; Berger and Schmaehl, 1988 [liver tumors in rats]; Berger et al., 1987 [dose-dependent incidence of liver tumors in rats]; Chung et al., 1986 [hepatocellular carcinomas, liver neoplastic nodules, altered liver cell foci in rats]; Hoos et al., 1985 [liver tumors in rats]; Peto and Gray, 1984 [dose-dependent incidence of liver tumors in rats]; Ketkar et al., 1982 [liver tumors in hamsters]; Crampton, 1980 [unspecified tumor incidence]; Habs et al., 1980 [liver and other tumors in rats]; Preussmann et al., 1976 [liver tumors in rats], 1977 [liver and other tumors in rats]; Takatori et al., 1977 [carcinogenicity by *N*-nitrosopyrrolidine derivatives]; Lijinsky and Taylor, 1976 [hepatocellular and olfactory carcinoma in rats]; Greenblatt and Lijinsky, 1972a [hepatocellular carcinoma in rats; genital tumors in some male rats]; and Druckrey et al., 1969 [review for organtropic and transplacental carcinogenesis by *N*-nitroso compounds]) were either designed as cancer bioassays with limited or no evaluation and reporting of noncancer endpoints, or they did not note or observe independent noncancer effects (not as part of tumor progression). Only a subset of these studies (Gray et al., 1991; Berger and Schmaehl, 1988; Berger et al., 1987; and Chung et al., 1986) did report potential noncancer endpoints, such as the incidence of altered liver foci. However, these foci formations did not occur at any dose in the absence of hepatocellular cancer. Since altered liver hepatocytes are widely considered to be progenitors to hepatocellular neoplasias, and there was no further information to verify them as independent noncancer events, these studies have not been considered further for assessment of noncancer endpoints.

A noteworthy study was conducted by Zerban and Bannasch (1983). Sprague-Dawley rats (137 males/dose) were administered 0.5 mg/kg-day *N*-nitrosopyrrolidine (purity not specified) via drinking water for 460 days and followed for 100 days after treatment. An additional 133 male Sprague-Dawley rats served as controls. Three control animals and three treated animals were killed at 8-week intervals for up to 560 days. Liver tissues were fixed, stained for cytochemical analysis, and examined microscopically for spongiosis hepatis (a degenerative lesion of hepatic perisinusoidal cells generally considered to be related to tumor formation). No other toxicological evaluations were performed. No information on mortality was reported. Spongiosis hepatis was not observed in any control or treated animals sacrificed during the treatment period, but was found in 1/73 (1%) control animals and 4/79 (5%) treated animals examined during the observation period following treatment, a difference that was not statistically significant ($p = 0.209$; Fisher’s exact test performed for this review). Some spongiotic lesions were associated with morphologically normal tissue, while others were associated with hepatic foci (clear, acidophilic, basophilic, or mixed), neoplastic hepatic nodules, or hepatocellular carcinomas (incidences were not reported, although it was reported that the “majority” of spongiotic lesions occurred outside of neoplastic nodules and carcinomas for *N*-nitrosopyrrolidine). This study evaluated insufficient endpoints to establish effect levels for noncancer effects of *N*-nitrosopyrrolidine.

Male albino rats (six of unspecified strain and age) were administered a hypercholesterolemic diet containing *N*-nitrosopyrrolidine at 100 ppm and sacrificed after 4 weeks (Mittal et al., 2007). Another treatment group of six rats received the same diet plus 5% chickpea seed coat fiber (intended to reduce absorption of *N*-nitrosopyrrolidine). Six rats that received the hypercholesterolemic diet alone served as controls. Due to effects of *N*-nitrosopyrrolidine treatment on feed intake and body weight, and incomplete reporting of these data in the study, the ingested dose of *N*-nitrosopyrrolidine in the treated group could not be reliably estimated. Blood samples collected at 4 weeks were analyzed for hematology (hemoglobin [Hgb] and osmotic fragility of erythrocytes) and serum chemistry (creatinine, urea, aspartate aminotransferase [AST], and alanine aminotransferase [ALT]). Organ weights of the heart, liver, lungs, spleen, and kidneys were noted, and these tissues were subject to histopathological examination. Oxidation status in these tissues and in erythrocytes was assessed by measuring lipid peroxidation (LPO) and the activity levels of the antioxidant enzymes catalase (CAT), peroxidase (Px), and superoxide dismutase (SOD).

It was not reported whether any mortality was observed in this study (Mittal et al., 2007). Food intake of rats administered *N*-nitrosopyrrolidine was considerably reduced to less than half that of control animals (see Table 1). While control animals experienced no change in body weight over the course of the study, the treated animals lost an average of 10 g. The researchers characterized the change in food intake as "substantial" and the change in body weight as "marginal." However, the actual body weights were not reported. Serum creatinine, urea, ALT, and AST were all significantly increased ($p < 0.01$) in treated animals (see Table 1). Hgb levels were unchanged, but the osmotic fragility of erythrocytes (hemolysis) was increased. Relative liver weight was significantly decreased ($p < 0.05$) in the treated group, while relative weights of the other organs were all increased (statistically significant for heart ($p < 0.01$) and spleen $p < 0.05$); however, the absolute organ weights were not reported. The authors reported histopathological lesions in the heart (lipid droplets and degenerative changes in myocardial fibers), coronary vessel (accumulation of fat droplets in walls, periarterial edema, degenerative changes in muscle fibers), lungs (chronic interstitial pneumonia together with infiltration of leukocytes), spleen (congestion, hemorrhage, severe depletion of lymphoid cells), liver (accumulation of lipid droplets in hepatocytes, severe granular degeneration with infiltration of fibroblasts), and kidneys (severe granular degeneration). However, no incidence data were provided. LPO was significantly increased ($p < 0.05$) compared with the control in erythrocytes and in the heart, lung, liver, spleen, and kidney. SOD activity was significantly decreased ($p < 0.05$) in erythrocytes and increased in the heart. Px activity was significantly increased ($p < 0.05$) in erythrocytes, heart, lung, and liver, but decreased in spleen. CAT activity was significantly decreased ($p < 0.05$) in erythrocytes, lung, and liver, but increased in spleen. Differences from control were reduced (to varying degrees for the different endpoints) in rats fed the diet supplemented with 5% chickpea seed coat fiber.

**Table 1. Selected Changes in Albino Rats Treated with *N*-Nitrosopyrrolidinein the Diet for 4 Weeks**[a]

| Parameter | Control | 100 ppm |
|---|---|---|
| **Males** | | |
| Number of animals examined | 6 | 6 |
| Food intake/day (g) | 11.5 ± 0.99[b] | 5.5 ± 0.40[c] |
| Change in body weight (g) | Nil | - (10.0 ± 1.69) |
| Serum chemistry | | |
| ALT (U/L) | 8.96 ± 0.64 | 14.50 ± 0.35[c] |
| AST (U/L) | 5.77 ± 0.62 | 13.67 ± 0.58[c] |
| Urea (mg/dL) | 45.41 ± 2.50 | 58.45 ± 4.91[c] |
| Creatinine (mg/dL) | 0.410 ± 0.05 | 0.888 ± 0.10[c] |

[a]Mittal et al. (2007).
[b]Values are presented as means ± standard deviation
[c]Statistically significantly different from control at $p < 0.01$

Interpretation of this study (Mittal et al., 2007) is confounded by the cholesterol-rich diet, severely reduced feed intake in the treated animals, and incomplete reporting of results. Given the experimental conditions, it cannot be concluded with confidence that the observed changes were due to the administration of *N*-nitrosopyrrolidine alone. In addition, effect levels and dose-response can not be identified. This study is not considered further for the assessment of noncancer endpoints.

***Inhalation Exposure***

No pertinent data were located regarding effects of *N*-nitrosopyrrolidine in animals following inhalation exposure.

**Other Studies**

***Other Routes***

Female Wistar-derived rats (number not unspecified) were administered *N*-nitrosopyrrolidine (99% purity) subcutaneously at 0−30 mg/kg-day for up to 12 weeks and sacrificed at 4-week intervals (Hendy and Grasso, 1977). Body weights were recorded weekly. The livers of sacrificed animals were weighed, fixed, and examined microscopically. Staining was employed to ascertain the activity of glucose-6-phosphatase and lysosomal acid phosphatase in liver sections. Liver tissues were subject to histopathological examination. No other toxicological evaluations were performed.

Mortality, body weights, and liver weights were not reported. After treatment with 30 mg/kg-day *N*-nitrosopyrrolidine for 4 weeks, inflammatory cell infiltrate and necrosis were detected in the liver tissues of sacrificed animals (Hendy and Grasso, 1977). Enlarged nuclei and the presence of an iron-containing, PAS-positive pigment were detected in affected hepatocytes. Centrilobular loss of glucose-6-phosphatase and lysosomal phosphatase activities were reported. Hypertrophy of the Golgi apparatus and SER were noted, and relative liver weights increased (actual weights not specified). Histopathological observations from animals sacrificed after 8 weeks of treatment showed enlarged hepatocytes with small lysosomes. By 12 weeks, bile duct proliferation and individual cell necrosis were apparent. Lysosomes were present, and glucose-6-phosphatase activity was markedly reduced. Relative liver weights sharply increased (data not shown). In rats treated with 10 mg/kg-day for up to 12 weeks, the same histochemical, ultrastructural, and cytochemical liver changes were noted—but to a lesser degree. Rats administered 3 mg/kg-day for up to 12 weeks had decreased relative liver weights, but did not otherwise differ from control animals.

## DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *N*-NITROSOPYRROLIDINE

Provisional RfD values for *N*-nitrosopyrrolidine cannot be derived because of the lack of suitable oral toxicity data. Chronic oral studies were conducted as cancer bioassays primarily and do not provide suitable endpoints for noncancer assessment. The 4-week study (Mittal et al., 2007) in hypercholesterolemic rats is not useful in the derivation of the RfD because of the short duration (28 days) with only one dose group. No effect levels could be identified due to the lack of dose-response relationship. In addition, the Mittal et al. (2007) study is confounded by the cholesterol-rich diet with "mild to severe pathological changes among the control and experimental groups," severely reduced feed intake in the treated animals, and incomplete reporting of results.

## DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *N*-NITROSOPYRROLIDINE

Provisional RfC values for *N*-nitrosopyrrolidine cannot be derived because no inhalation data are available.

## PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *N*-NITROSOPYRROLIDINE

Due to the presence of a quantitative cancer assessment for *N*-nitrosopyrrolidine on IRIS (U.S. EPA, 2009), no provisional cancer assessment is necessary or performed in this document.

## REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2008) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

Anderson, LM; Carter, JP; Driver, CL; et al. (1993) Enhancement of tumorigenesis by *N*-nitrosodiethylamine, *N*-nitrosopyrrolidine and N6-(methylnitroso)-adenosine by ethanol. Cancer Lett 68:61−66.

ATSDR (Agency for Toxic Substances and Disease Registry). (2009) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service. Available online at http://www.atsdr.cdc.gov/toxprofiles/index.asp.

Berger, MR; Schmahl D; Zerban, H. (1987) Combination experiments with very low doses of three genotoxic nitrosamines with similar organotropic carcinogenicity in rats. Carcinogen 8:1635−1643.

Berger, MR; Schmahl D. (1988) Combination effects of low doses of genotoxic carcinogens with similar organotropism. In: Schmahl, D; ed. Combination effects in chemical carcinogenesis. New York, NY: VCH Publishers, pp. 93-123.

CalEPA (California Environmental Protection Agency). (2009a) Search chronic RELs. Office of Environmental Health and Hazard Assessment. Available online at http://www.oehha.ca.gov/air/chronic_rels/index.html.

CalEPA (California Environmental Protection Agency). (2009b) Search toxicity criteria database. Office of Environmental Health and Hazard Assessment. Available online at http://www.oehha.ca.gov/risk/ChemicalDB/index.asp.

CalEPA (California Environmental Protection Agency). (2009c) Hot spots unit risk and cancer potency values. Available online at http://www.oehha.ca.gov/air/hot_spots/pdf/TSDlookup2002.pdf.

Chung, FL; Tanaka, T; Hecht, SS. (1986) Induction of liver tumors in F344 rats by crotonaldehyde. Cancer Res 46:1285−1289.

Crampton, RF. (1980) Carcinogenic dose-related response to nitrosamines. Oncology 37:251−254.

Druckrey, H; Preussmann, R; Ivankovic, S. (1969) *N*-nitroso compounds in organotropic and transplacental carcinogenesis. Ann N Y Acad Sci 163:676−696.

Gray, R; Peto, R; Brantom, P; et al. (1991) Chronic nitrosamine ingestion in 1040 rodents: the effect of the choice of nitrosamine, the species studied, and the age of starting exposure. Cancer Res 51:6470−6491.

Greenblatt, M; Lijinsky, W. (1972a) Nitrosamine studies: Neoplasms of liver and genital mesothelium in nitrosopyrrolidine-treated MRC rats. J Natl. Cancer Inst. 48(6):1687−1696.

Greenblatt, M; Lijinsky, W. (1972b) Failure to induce tumors in Swiss mice after concurrent administration of amino acids and sodium nitrite. J Natl. Cancer Inst. 48(5):1389−1392.

Habs, M; Habs, H; Schmahl, D. (1980) Effect of the intermittent administration of *N*-nitrosopyrrolidine on the tumor incidence in Sprague-Dawley rats. Int J Cancer 26:47−51.

Hendy, R; Grasso, P. (1977) Hepatotoxic response to single or repeated injections of n-nitrosopyrrolidine in the rat. Chem Biol Interact 18:309−326.

Hoos, A; Habs, M; Schmahl, D. (1985) Comparison of liver tumor frequencies after intermittent oral administration of different doses of *N*-nitrosopyrrolidine in Sprague-Dawley rats. Cancer Lett 26:77−82.

IARC (International Agency for Research on Cancer). (1978). Some N-Nitroso Compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Lyon, France. 17: 226−255.

IARC (International Agency for Research on Cancer). (2009) Search IARC monographs. Available online at http://monographs.iarc.fr/index.php.

Ketkar, MB; Schneider, P; Preussmann, R; et al. (1982) Carcinogenic effect of low doses of *N*-nitrosopyrrolidine administered in drinking water to Syrian Golden hamsters. J Cancer Res Clin Oncol 104:75−79.

Lijinsky, W; Taylor, HW. (1976) The effect of substituents on the carcinogenicity of *N*-nitrosopyrrolidine in Sprague-Dawley rats. Cancer Res 36:1988−1990.

Mittal, G; Vadhera, S; Brar, A; et al. (2007) Protective role of dietary fibre on *N*-nitrosopyrrolidine-induced toxicity in hypercholesterolemic rats. Hum Exp Toxicol 26:91−98.

NIOSH (National Institute for Occupational Safety and Health). (2009) NIOSH pocket guide to chemical hazards. Index by CASRN.

NTP (National Toxicology Program). (2005) 11th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. Available online at http://ntp-server.niehs.nih.gov.

NTP (National Toxicology Program). (2009) Management status report. Available online at http://ntp.niehs.nih.gov/index.cfm?objectid=78CC7E4C-F1F6-975E-72940974DE301C3F.

OSHA (Occupational Safety and Health Administration). (2009) OSHA Standard 1910.1000 Table Z-1. Part Z, toxic and hazardous substances. Available online at https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9992.

Peto, R; Gray, R. (1984) Nitrosamine carcinogenesis in 5120 rodents: chronic administration of 16 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, or hamsters). IARC Sci Publ 57:627−665.

Preussmann, R; Eisenbrand, G; Schmahl, D. (1976) Carcinogenicity testing of low doses of nitrosopyrrolidine and of nitrosobenzthiazuron and nitrosocarbaryl in rats. IARC Sci Publ. 14:429−433.

Preussmann, R; Schmahl, D; Eisenbrand, G. (1977) Carcinogenicity of *N*-nitrosopyrrolidine: Dose-response study in rats. Z. Krebsforsch. 90:161−166.

Takatori, K; Mori, H; Kato, T; et al. (1977) Research on the carcinogenic activities of *N*-nitrosopyrrolidine, *N*-nitroso-2-pyrrolidone, and *N*-nitroso-5-methyl-2-pyrrolidone. Yakugaku Zasshi 97:320−323.

U.S. EPA (Environmental Protection Agency). (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.

U.S. EPA (Environmental Protection Agency). (1986a) 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.

U.S. EPA (Environmental Protection Agency). (1986b) Guidelines for carcinogen risk assessment. Washington, DC.

U.S. EPA (Environmental Protection Agency). (1991a) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (Environmental Protection Agency). (1991b) Integrated Risk Information System (IRIS). IRIS Summary of *N*-Nitrosopyrrolidine (CASRN 930-55-2). Office of Research and Development, National center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/.

U.S. EPA (Environmental Protection Agency). (1994) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (Environmental Protection Agency). (1997) Health Effects and Assessment Summary Tables. FY-1997 update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC; EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA (Environmental Protection Agency). (2006) 2006 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA 822-R-06-013. Available online at http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf.

U.S. EPA (Environmental Protection Agency). (2009) Integrated Risk Information System (IRIS). Office of Research and Development, National center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/.

WHO (World Health Organization). (2009) Online catalogs for the Environmental Health Criteria series. Available online at http://www.who.int/ipcs/publications/ehc/ehc_alphabetical/en/index.html.

Zerban, H; Bannasch, P. (1983) Spongiosis hepatis in rats treated with low doses of hepatotropic nitrosamines. Cancer Lett 19:247−252.