Nitrobenzene (CASRN 98-95-3)

Reference Dose for Chronic Oral Exposure (RfD)

0079

Nitrobenzene; CASRN 98-95-3

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Nitrobenzene

File First On-Line 01/31/1987

<table>
<thead>
<tr>
<th>Category (section)</th>
<th>Status</th>
<th>Last Revised</th>
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<td>Oral RfD Assessment (I.A.)</td>
<td>on-line</td>
<td>01/01/1991</td>
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<tr>
<td>Inhalation RfC Assessment (I.B.)</td>
<td>no data</td>
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<tr>
<td>Carcinogenicity Assessment (II.)</td>
<td>on-line</td>
<td>02/01/1995</td>
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_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Nitrobenzene
CASRN — 98-95-3
Last Revised — 01/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also 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.

NOTE: The Oral RfD for nitrobenzene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

_I.A.1. Oral RfD Summary
**Critical Effect**

Hematologic, adrenal, renal and hepatic lesions

Rat/Mouse Subchronic Inhalation Study

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### Experimental Doses*

<table>
<thead>
<tr>
<th>NOAEL: none</th>
<th>UF</th>
<th>MF</th>
<th>RfD</th>
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<tbody>
<tr>
<td>LOAEL: 25 mg/cu.m (mice) converted to 4.6 mg/kg/day</td>
<td>10,000</td>
<td>1</td>
<td>5E-4 mg/kg/day</td>
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</table>

*Conversion Factors: 6 hour/24 hour, 5 days/7 days, 0.039 cu.m/day/0.03 kg (mice breathing rate/body weight) and 0.8 absorption factor; thus, 25 mg/cu.m x 6 hour/24 hour x 5 days/7 days x 0.039 cu.m/day / 0.03 kg x 0.8 = 4.6 mg/kg/day

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#### I.A.2. Principal and Supporting Studies (Oral RfD)


The CIIT 90-day inhalation study provides the most appropriate data currently available to derive an RfD. Ten animals/sex/species/dose group were administered nitrobenzene at 1 of 3 doses. Other than increased incidence of hemolytic anemia in rats at 25 mg/cu.m and vacuolization of adrenal cortical cells in female mice at 25 mg/cu.m and higher, adverse effects of nitrobenzene exposure in mice and rats were comparable to unexposed controls at this dose. Mice and rats exposed to nitrobenzene at 81 mg/cu.m showed increased incidence and severity of liver and kidney lesions.

Data regarding the effects of nitrobenzene in humans are limited to symptoms and observations in workers, including headaches, vertigo, and methemoglobinemia (ACGIH, 1980). The potential "safe" level derived from the TLV appears adequate to protect workers from such adverse effects; however, the effects of occupational exposure to nitrobenzene on the liver and/or kidneys have not been adequately evaluated. The CIIT (1984) study indicates that the liver and kidney may be target organs of chronic/subchronic nitrobenzene exposure, and an acceptable level based on the TLV may not be protective for the toxic effects of nitrobenzene on the liver and/or kidney. Therefore, until more definitive chronic data are available, the RfD of 0.0005 mg/kg/day is recommended to protect against adverse health effects of nitrobenzene.

#### I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 10,000 represents two 10-fold factors for both intra- and interspecies variability to the toxicity of this chemical in lieu of specific data, a 10-fold factor for estimating a chronic effect level, from its subchronic equivalent, and a 10-fold factor for estimating an RfD from a LOAEL rather than a NOAEL.

MF — None

#### I.A.4. Additional Studies/Comments (Oral RfD)

None.

#### I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

Medium to low confidence in the study is recommended because it is not an oral study, a limited number of animals/sex/dose were tested, and a NOAEL for the critical toxic effect (i.e., adrenal toxicity) was not determined, although two species were used and many parameters were measured. Low confidence in the database is recommended because chronic reproductive and teratology data are missing. Low confidence in the RfD follows.

#### I.A.6. EPA Documentation and Review of the Oral RfD

**I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or hotline.iris@epa.gov (internet address).

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

Substance Name — Nitrobenzene  
CASRN — 98-95-3

Not available at this time.

**II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Nitrobenzene  
CASRN — 98-95-3  
Last Revised — 02/01/1995

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.

NOTE: The carcinogenicity assessment for nitrobenzene may change in the near future pending the outcome of a further review now being conducted by the Carcinogen Risk Assessment Verification Endeavor Work Group.

**II.A. Evidence for Human Carcinogenicity**

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

Classification — D; not classifiable as to human carcinogenicity  
Basis — Based on no data concerning carcinogenicity in humans or animals.

**II.A.2. Human Carcinogenicity Data**

None.

**II.A.3. Animal Carcinogenicity Data**

None.
II.A.4. Supporting Data for Carcinogenicity

In Salmonella/microsomal mutagenicity assays with strains TA92, TA94, TA97, TA98, TA100, TA1535, TA1537 and TA1538, nitrobenzene was not positive (Garner and Nutman, 1977; Chiu et al., 1978; Shimizu et al., 1983; Ho et al., 1981; Haworth et al., 1983; Anderson and Styles, 1978; Miyata et al., 1981). These assays were conducted with and without liver homogenates by plate incorporation, spot test and in one study (Hughes et al., 1984), by the vapor exposure method.

Nitrobenzene was mutagenic in the presence of liver homogenate and norharman in S. typhimurium strain TA98 but not in strain TA100 (Suzuki et al., 1983). Nitrobenzene did not cause an increase in unscheduled DNA synthesis in hepatocytes isolated from gavage-treated rats (Mirsalis et al., 1982). Fel'dt (1985) reported that oral administration of nitrobenzene did not produce micronucleus or chromosome aberrations in bone marrow cells or dominant lethal mutations in mice.

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

None.

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

None.

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

II.D.1. EPA Documentation


The 1985 Health and Environmental Effects Profile for Nitrobenzene and the 1987 Health Effects Assessment for Nitrobenzene have received OHEA review.

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


Verification Date — 11/08/1989

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

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]
VI. Bibliography

Substance Name — Nitrobenzene  
CASRN — 98-95-3  
Last Revised — 12/01/1990

VI.A. Oral RfD References


VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References


Hughes, T.J., C. Sparacino and S. Frazier. 1984. Validation of chemical and biological techniques for evaluation of vapors in ambient air/mutagenicity testing of twelve (12) vapor-phase compounds. EPA 600/1-84-005. NTIS PB 84-164219.


_VII. Revision History_

Substance Name — Nitrobenzene
CASRN — 98-95-3

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<td>IV.</td>
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<td>EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.</td>
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<td>04/01/1997</td>
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_VIII. Synonyms_

Substance Name — Nitrobenzene  
CASRN — 98-95-3  
Last Revised — 01/31/1987

- 98-95-3  
- Benzene, Nitro-  
- Essence of Mirbane  
- Essence of Myrbane  
- Mirbane Oil  
- NCI-C60082  
- Nitrobenzene  
- Nitrobenzol  
- Oil of Mirbane  
- Oil of Myrbane
Data
• Animal Carcinogenicity Data
• Supporting Data for Carcinogenicity

Quantitative Estimate of Carcinogenic Risk from Oral Exposure
• Summary of Risk Estimates
• Dose-Response Data
• Additional Comments
• Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure
• Summary of Risk Estimates
• Dose-Response Data
• Additional Comments
• Discussion of Confidence
• EPA Documentation, Review and, Contacts

Bibliography
Revision History
Synonyms