# m-Dinitrobenzene; CASRN 99-65-0

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 m-Dinitrobenzene

**File First On-Line 08/22/1988**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | yes | 08/22/1988* |
| **Inhalation RfC (I.B.)** | not evaluated | |
| **Carcinogenicity Assessment (II.)** | yes | 03/01/1991* |

*A comprehensive review of toxicological studies was completed (05/27/05) - please see sections I.A.6. and II.D.2. for more information.

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — m-Dinitrobenzene
CASRN — 99-65-0
Last Revised — 08/22/1988

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.

### I.A.1. Oral RfD Summary

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|---|---|---|---|---|
| **Increased splenic weight**<br><br>**Rat Subchronic Oral Study**<br><br>**Cody et al., 1981** | NOAEL: 3 ppm (0.40 mg/kg/day)<br><br>LOAEL: 8 ppm | 3000 | 1 | 1E-4 mg/kg/day |

*Conversion Factors: Drinking water concentrations converted to dosages by investigators.

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

Cody, T.E., S. Witherup, L. Hastings, K. Stemmer and R.T. Christian. 1981. 1,3-Dinitrobenzene: Toxic effect in vivo and in vitro. J. Toxicol. Environ. Health. 7(5): 829-847.

Groups of 20 Carworth Farm rats of each sex were exposed to 0, 3, 8, or 20 ppm m-dinitrobenzene in drinking water for 16 weeks. Hematocrit, hemoglobin levels and white cell counts were measured on selected males in each group 5, 10, and 14 weeks after the start of the study. Body weights and food and water consumption were recorded throughout the experiment. At termination body and organ weights were measured and all major tissues were examined histopathologically. The concentration of 20 ppm m-dinitrobenzene decreased body weight gain in females, decreased hemoglobin concentrations and caused testicular atrophy in males, and was associated with splenic enlargement and hemosiderin deposits in both sexes of rats. Significantly increased spleen weights were also observed in both sexes of rats treated with 8 ppm. No effects considered to be treatment-related were found at 3 ppm m- dinitrobenzene.

Therefore, the 3 ppm dose is considered a NOAEL for oral exposure and the 8 ppm dose is a LOAEL. Based on water consumption data, Cody et al. (1981) stated that the 3 ppm dose level corresponded to a mean daily m-dinitrobenzene intake of 0.40 mg/kg in males. Therefore, the equivalent NOAEL of 0.40 mg/kg/day, when divided by an uncertainty factor of 3000, equals the RfD of 0.0001 mg/kg/day or 0.009 mg/day for a 70 kg man.

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

UF — 10 for extrapolation from subchronic to chronic exposure, 10 for extrapolation across species, 10 for sensitive human subgroups, and 3 for the lack of subchronic and reproductive toxicity data.

MF — None

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

In a behavioral rat study, 10 male rats/group were exposed to 0, 3, or 8 ppm m-dinitrobenzene in drinking water for 90 days. At both m-dinitrobenzene exposure levels, rats showed significantly increased running wheel activity and nonsignificant increases in activity platform counts. Because more traditional measures of toxicity were not affected by administration of 3 ppm m-dinitrobenzene, the change in running wheel activity should not, by itself, be considered an adverse effect (Cody et al., 1981).

Male and female rats were exposed to 50, 100, 200 ppm DNB in drinking water for 8-Weeks. Mortality was high at 200 ppm, hemoglobin concentrations were decreased at doses higher than 50 ppm. At 50 ppm and higher doses increased relative spleen weights and testicular (but not ovarian) atrophy, with accompanying decreased spermatogenesis. At 50 ppm or higher doses (females) and 100 ppm or higher doses (males), hexabarbital sleep time was significantly decreased, indicating acceleration of microsomal metabolism (Cody et al., 1981).

The ACGIH (1986) cited historical studies indicating that dinitrobenzene exposure is associated with methemoglobinemia, liver damage and ready skin absorption. No published reports were found either in man or animals; thus the ACGIH (1986) designated a TLV-TWA of 0.15 ppm (approximately 1 mg/cu.m) for all three dinitrobenzene isomers. They based this value on the comparative acute toxicities of similar polynitroaromatics, relative to the toxicities of mononitro derivatives.

There are currently no data on the reproductive effects of m-dinitrobenzene.

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

Study — Medium
Database — Low
RfD — Low

Study confidence was rated medium because both a NOAEL and a LOAEL were defined in subchronic drinking water studies using an adequate number of animals and suitable endpoints. Confidence in the data base is rated low because the only supporting evidence is a subchronic study at much higher concentration levels. Database confidence would be increased if reproductive and chronic toxicity bioassays were available and if more specific details regarding human exposure were provided. The resulting confidence in the RfD is rated low.

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

Source Document — U.S. EPA, 1985

Limited peer review and extensive Agency-wide review, 1985.

Other EPA Documentation — None

Agency Work Group Review — 03/19/1987, 04/20/1988

Verification Date — 04/20/1988

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for m-Dinitrobenzene and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

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

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).

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

Substance Name — m-Dinitrobenzene
CASRN — 99-65-0

Not available at this time.

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## II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — m-Dinitrobenzene
CASRN — 99-65-0
Last Revised — 03/01/1991

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 — D; not classifiable as to human carcinogenicity

Basis — Based on no data in humans and animals.

#### II.A.2. Human Carcinogenicity Data

None.

### II.A.3. Animal Carcinogenicity Data

None.

### II.A.4. Supporting Data for Carcinogenicity

m-Dinitrobenzene was mutagenic in Salmonella typhimurium strains TA98 and TA100 with and without metabolic activation (Spanggord et al., 1982; McGregor et al., 1980; Kawai et al., 1987). Chiu et al. (1978) found m-DNB to be mutagenic in TA98 but not in TA100. Testing was done with only three concentrations and without metabolic activation. m-DNB was mutagenic in TA1538 with and without metabolic activation (Spanggord et al, 1982; McGregor et al., 1980; Garner and Nutman, 1977). Spanggord et al. (1982) found that m- DNB was mutagenic in TA98 and TA100 but was not mutagenic in TA1535, TA1537 and TA100 NR3 (nitroreductase negative strain), with and without metabolic activation. McGregor et al. (1980) found only slight activity in TA1537 and no mutagenicity in TA1535.

Probst et al. (1981) reported that m-DNB did not increase unscheduled DNA synthesis in cultivated hepatocytes at concentrations from 0.5 to 1000 nmoles/mL. m-DNB induced mutations in S. typhimurium strains TA1538, TA98, TA100 and D3052 tested over a 10,000-fold concentration range with and without metabolic activation; the minimum concentration was 0.6 mmoles/mL.

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

None.

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

None.

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

### II.D.1. EPA Documentation

Source Document — U.S. EPA, 1989

The Health Advisory for 1,3-Dinitrobenzene has received Agency and external review.

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

Agency Work Group Review — 06/15/1990

Verification Date — 06/15/1990

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for m-Dinitrobenzene and a change in the assessment is not warranted at this time. For more information, IRIS users may contact 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 — m-Dinitrobenzene
CASRN — 99-65-0

### VI.A. Oral RfD References

ACGIH (American Conference of Government Industrial Hygienists). 1986. Threshold limit values for dinitrobenzenes. ACGIH, Cincinnati, OH. p. 214.

Cody, T.E., S. Witherup, L. Hastings, K. Stemmer and R.T. Christian. 1981. 1,3-Dinitrobenzene: Toxic effects in vivo and in vitro. J. Toxicol. Environ. Health. 7(5): 829-847.

U.S. EPA. 1985. Health and Environmental Effects Profile on Dinitrobenzenes (o-, m-, p-). 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. NTIS PB 88-173638.

## VI.B. Inhalation RfC References

None

## VI.C. Carcinogenicity Assessment References

Chiu, C.W., L.H. Lee, C.Y. Wang, G.T. Bryan. 1978. Mutagenicity of some commercially available nitro compounds for Salmonella typhimurium. Mutat. Res. 58: 11-22.

Garner, R. and C.A. Nutman. 1977. Testing of some azo dyes and their reduction products for mutagenicity using Salmonella typhimurium TA 1538. Mutat. Res. 44: 9-19.

Kawai, A., S. Goto, Y. Matsumota and H. Matsushita. 1987. Mutagenicity of aliphatic and aromatic nitro compounds. Japan J. Ind. Health. 29: 34-54.

McGregor, D.B., C.G. Riach, R.M. Hastell and J.C. Dacre. 1980. Genotoxic activity in microorganisms of tetryl, 1,3-dinitrobenzene and 1,3,5- trinitrobenzene. Environ. Mutagen. 2(4): 531-541.

Probst, G.S., R.E. McMahon, L.E. Hill, C.Z. Thompson, J.K. Epp and S.B. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3(1): 11-32.

Spanggord, R.J., K.E. Mortelmans, A.F. Griffin and V.F. Simmon. 1982. Mutagenicity in Salmonella typhimurium and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. Environ. Mutagen. 4(2): 163-179.

U.S. EPA. 1989. Drinking Water Health Advisory for 1,3-Dinitrobenzene. Office of Drinking Water, Washington, DC. (Draft)

## VII. Revision History

Substance Name — m-Dinitrobenzene
CASRN — 99-65-0

| Date | Section | Description |
|---|---|---|
| **08/22/1988** | I.A. | Oral RfD summary on-line |
| **03/01/1991** | II. | Carcinogenicity assessment on-line |
| **10/28/2003** | I.A.6., II.D.2. | Screening-Level Literature Review Findings message has been added. |
| **06/22/2005** | I.A.6., II.D.2. | Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions. |

## VIII. Synonyms

Substance Name — m-Dinitrobenzene
CASRN — 99-65-0
Last Revised — 08/22/1988

- 99-65-0
- benzene, 1,3-dinitro-
- benzene, m-dinitro-
- binitrobenzene
- 1,3-dinitrobenzene
- 2,4-dinitrobenzene
- Dinitrobenzene, m-
- 1,3-dinitrobenzol
- dwunitrobenzen
- UN 1597