2,4,6-Trinitrotoluene (TNT); CASRN 118-96-7

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 TNT

File First On-Line 09/26/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/26/1988
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7
Last Revised — 09/26/1988

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
Liver effects **26-Week Dog Feeding Study** **U.S. DOD, 1983**	NOEL: none LOAEL: 0.5 mg/kg/day	1000	1	5E-4 mg/kg/day

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed dog food consumption)

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

U.S. Department of Defense (DOD). 1983. AD-A157 002. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

The U.S. Department of Defense (U.S. DOD, 1983) commissioned a study to determine the effects of TNT (approximately 99% pure) administered daily by gelatin capsule, containing a mix of TNT with Purina Certified Rodent Chow, to groups of six beagle dogs/sex at 0, 0.5, 2, 8, or 32 mg/kg/day for 25 weeks. Animals were approximately 6.5 months old at the start of the TNT dosing schedule. Animals were observed several times daily, before and after dosing, for toxic signs and were examined weekly by palpation for detectable masses. Body weight and food intakes were recorded weekly. Other toxicologic endpoints included a comprehensive clinical chemistry and hematological evaluation, urinalyses, and periodic electrocardiography (ECG) and ophthalmic examinations. During week 27 all animals were fasted for 16 to 18 hours and were sacrificed by injection of intravenous pentobarbital sodium. Major organs were weighed and all organs were collected and fixed for microscopic examination. Statistical analyses were performed.

Several indications of liver injury were observed upon gross and histologic examination. Male (8 and 32 mg/kg/day) and female (32 mg/kg/day) dogs had significant increases in relative and/or absolute liver weight accompanied by moderate to marked hepatocytic cloudy swelling and

hepatocytomegaly. The hepatic swelling and hepatocytomegaly was observed at all dose levels, but to a greater degree in the high-dose group; lesions at the low dose (0.5 mg/kg/day) were described as trace to mild. No such lesions were seen in the control animals. Microscopic evidence of cirrhosis was seen, primarily in males, at the 8 and 32 mg/kg/day dose levels. Hemosiderosis of the liver was seen in the majority of dogs at 2 and 8 mg/kg/day (the two highest levels) as well as in one female at the 2 mg/kg/day level. None of these microscopic lesions were seen in the two females necropsied prior to termination of this study. The 0.5 mg/kg/day test level is the LOAEL for liver effects. The histopathology at this level is trace to mild and is unsupported by effects on the liver enzymes and organ weight.

In a rat study (U.S. DOD, 1984a), groups of 75 animals/sex (approximately 6 to 7 weeks old) received TNT (about 99% pure), mixed in a diet of Purina rodent chow meal, at dose levels of 0.0, 0.4, 2, 10, or 50 mg/kg/day for 24 months. A NOAEL of 0.4 mg/kg/day is based on the absence of systemic effects of TNT on the spleen, kidney, bone marrow, and bladder.

The effects of feeding experiments with TNT was studied by the U.S. DOD (1978) in Swiss-Webster mice, Sprague-Dawley rats, and beagle dogs. Dogs appeared to be the most sensitive species tested during the subchronic studies, with 0.2 mg/kg/day having no observable effects and 2 mg/kg/day showing some effects. In rats, a concentration in feed giving 7.4 mg/kg/day to females and 7 mg/kg/day to males caused toxic effects. No observable toxic effects were found at 1.4 mg/kg/day for female or male rats. In mice, a dose in feed giving approximately 37.8 mg/kg/day and 35.7 mg/kg/day to females and males, respectively, caused toxic effects. No observable effects were found at 8 mg/kg/day and 7.5 mg/kg/day for female and male mice, respectively.

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

UF — The UF of 1000 allows for uncertainties in laboratory animal-to-man dose extrapolation, interindividual sensitivity, subchronic-to-chronic extrapolation, and LOAEL-to-NOAEL extrapolation.

MF — None

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

The U.S. DOD (1981) conducted a 13-week study in which Fischer 344 rats (10/sex/dose level) were administered TNT (about 99% pure) in the diet at 1, 5, 25, 125, or 300 mg/kg/day. Thirty animals/sex were used as controls and received the same rodent chow used to prepare the test diets. A NOAEL of 5 mg/kg/day is indicated by the absence of testicular degeneration and effects on the spleen at this dose level.

The U.S. DOD (1974a) conducted a 90-day study with cynomolgus monkeys to evaluate the toxicity of TNT administered by gastric intubation as a suspension in a 1% aqueous solution of methyl cellulose. Daily dosages were 0.02, 0.1, or 1 mg/kg. A NOAEL or LOAEL could not be determined for this study because of the small numbers of animals evaluated and the lack of statistical evaluation.

The U.S. DOD (1974b) also conducted a 90-day toxicity study in purebred beagle dogs administered TNT in the diet (consisting of ground dog chow supplemented with commercial canned dog food) at dosage levels of 0.02, 0.1, or 1 mg/kg/day. Three dogs/sex/dosage level were used. A slight increase in hemosiderosis of the bone marrow in the high-dose group could not be properly assessed because of the small group size. The small number of animals evaluated precludes the determination of a NOAEL or LOAEL.

In a 24-month study conducted by the U.S. DOD (1984b) in B6C3F1 hybrid mice, TNT (>99% pure) was administered in a diet of ground Purina chow to groups of 75 mice/sex/group at dosage levels of 0.0, 1.5, 10, or 70 mg/kg/day. No noncarcinogenic effects were seen at the LDT. Noncancer effects included anemia and hepatomegaly without microscopic alterations at the high-dose level.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The principal study is a well-designed subchronic dog study, but the method of administration (capsule) is not ideal and a NOAEL was not established. Other studies (dog subchronic, rat chronic) are somewhat supportive of the magnitude of the RfD, but effects on the hematopoetic system are observed in other species at generally higher doses. Data on reproductive toxicology are lacking. The RfD is therefore given a medium confidence rating for these reasons.

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

Source Document — U.S. EPA, 1988

Other EPA Documentation — None

Agency Work Group Review — 06/11/1986, 01/20/1988, 04/20/1988

Verification Date — 04/20/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 2,4,6-Trinitrotoluene 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.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 — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7
Last Revised — 06/01/1989

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 — C; possible human carcinogen

Basis — Evidence of human carcinogenicity is inadequate. Urinary bladder papilloma and carcinoma were observed in female Fischer 344 rats. Mutagenic activity was observed in Salmonella with and without metabolic activation.

II.A.2. Human Carcinogenicity Data

None. There are extensive human toxicity data, but they are not useful in the evaluation of carcinogenicity.

II.A.3. Animal Carcinogenicity Data

Limited. The carcinogenic potential of TNT was evaluated in 24-month studies in Fischer 344 rats (U.S. DOD, 1984a) and in hybrid B6C3F1 mice (U.S. DOD, 1984b).

In the rat, TNT was administered at 0, 0.4, 2, 10, and 50 mg/kg/day by diet to groups of 75 rats/sex. Ten rats/sex/dose were sacrificed following 6 and 12 months on test, and surviving animals were sacrificed after 24 months of treatment. Based on the observation of splenic congestion, increased amounts of pigment deposition in the kidneys, bone marrow fibrosis and decrease in body weight gain at doses of 2.0 mg/kg/day or greater, the MTD was achieved. Toxic effects on the urogenital system, primarily seen for high dose (50 mg/kg/day) animals, include hyperplasia of the renal pelvis with lymphocytic infiltration of renal tissue, and for females, urinary bladder hyperplasia, papilloma and carcinoma. The tumor incidence for combined transitional cell papilloma and carcinoma of the urinary bladder in females was 0/54, 0/54, 0/55, 1/55, and 17/55 for the control, 0.4, 2.0, 10.0, and 50.0 mg/kg/day dose groups, respectively. In addition to the above mentioned neoplasms, hepatocellular (male rats), renal and urinary bladder hyperplasia (female rats) seen at doses of 10 mg/kg/day or greater support the conclusion that TNT is a carcinogen in F344 rats under the conditions of the study. Neoplastic lesions in the urinary bladder were considered rare by the study authors.

In the mouse study, TNT was administered in the diet for up to 24 months. Groups of 75 mice/sex received TNT at doses of 0, 1.5, 10, or 70 mg/kg/day. Ten mice/sex/dose were killed

following 6 and 12 months on test; surviving animals killed after 24 months of treatment. The major systemic effects observed in the high-dose group included anemia with hepatotoxicity, indicating the MTD was achieved. The study authors reported that the incidence of all types of malignant lymphoma combined with lymphocytic and granulocytic leukemia in the spleen of females increased with dose and was statistically significant at 70 mg/kg/day. However, when all types of malignant lymphomas and lymphocytic leukemia were counted in all animal tissues combined rather than for a single organ (McConnell et al., 1986), the incidence of tumors by sex or for both sexes combined was not statistically significantly elevated nor was there a significant trend. These neoplasms were, therefore, not considered to be treatment-related.

II.A.4. Supporting Data for Carcinogenicity

Mutagenic activity for TNT was reported by the U.S. DOD (1978a). As little as 10 ug/plate dissolved in DMSO, with or without metabolic activation, was mutagenic in Salmonella typhimurium strains TA98, TA1538 and TA1537. At 30 ug/plate TNT was mutagenic in TA100 as well as the other three strains. In vivo cytogenetic analyses on bone marrow from Sprague-Dawley rats treated for 28 days with TNT at 190.4 or 1.8 mg/kg/day in feed were negative for genetic damage (U.S. DOD, 1978b). Ashby et al. (1985) reported TNT gave negative response in the mouse bone marrow micronucleus assay and in an in vivo/in vitro rat liver assay for unscheduled DNA synthesis (UDS).

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

II.B.1. Summary of Risk Estimates

Oral Slope Factor: 3.0E-2/mg/kg/day

Drinking Water Unit Risk: 9.0E-7/ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

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

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

Tumor Type: urinary bladder, transitional cell papilloma and transitional squamous cell carcinomas
Test animals: rat/Fischer 344, female
Route: diet
Reference: U.S. DOD, 1984a

Administered Dose (ppm)	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0.0	0	0/54
0.4	0.065	0/54
2.0	0.325	0/55
10.0	1.623	1/55
50.0	8.117	17/55

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

Five of the 17 urinary bladder tumors were benign neoplastic changes (i.e., papillomas). The human equivalent dose was determined using a standard surface area correction factor. The

animal study dose is divided by the ratio of the human weight (70 kg) to the rat weight (0.30 kg) raised to the 1/3 power.

The unit risk should not be used if the water concentration exceeds 1E+4 ug/L. Above this concentration the slope factor may differ from that stated.

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

Both rat and mouse studies (U.S. DOD, 1984a,b), were well conducted with appropriate number of animals per sex per dose.

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, 1988

The Health Advisory for trinitrotoluene received Agency Review.

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

Agency Work Group Review — 07/27/1988, 08/15/1988, 09/22/1988

Verification Date — 09/22/1988

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 2,4,6-Trinitrotoluene 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.

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 — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7

VI.A. Oral RfD References

U.S. Department of Defense. 1974a. AD-A44 650. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1974b. AD-A035 717. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1978. AD-A080 957. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1981. AD-A108 447. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1983. AD-A157 082. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1984a. AD-A168 637. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. Department of Defense. 1984b. AD-A168 754. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. EPA. 1988. Drinking Water Health Advisory for 2,4,6-Trinitrotoluene. Office of Drinking Water, Washington, DC. (Draft)

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

Ashby, J., B. Burlinson, P.A. Levre and J. Topham. 1985. Non-genotoxicity of 2,4,6-trinitrotoluene (TNT) to the mouse bone marrow and the rat liver. Implications for its carcinogenicity. Arch. Toxicol. 58: 14-19.

McConnell, E.E., H.A. Solleveld, J.A. Swenberg and G.A. Boorman. 1986. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76(2): 283-289.

U.S. DOD (U.S. Department of Defense). 1978a. AD-A069 333. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703) 274-7633.

U.S. DOD (U.S. Department of Defense). 1978b. AD-A080 957. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703) 274-7633.

U.S. DOD (U.S. Department of Defense). 1984a. AD-A168637. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703) 274-7633.

U.S. DOD (U.S. Department of Defense). 1984b. AD-A168754. Available from Defense Technical Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703) 274-7633.

U.S. EPA. 1988. Health Advisory on Trinitrotoluene. Office of Drinking Water, Washington, DC.

VII. Revision History

Substance Name — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
06/01/1989	II.	Carcinogen summary on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2,4,6-Trinitrotoluene (TNT)
CASRN — 118-96-7
Last Revised — 09/26/1988

- 118-96-7
- BENZENE, 2-METHYL-1,3,5-TRINITRO-
- ENTSUFON
- NCI-C56155
- TNT
- alpha-TNT
- TNT-TOLITE
- TOLIT
- TOLITE
- 2,4,6-TRINITROTOLUEEN
- TRINITROTOLUENE
- 2,4,6-Trinitrotoluene
- Trinitrotoluene, 2,4,6-
- s-TRINITROTOLUENE
- sym-TRINITROTOLUENE

- 2,4,6-TRINITROTOLUOL
- s-TRINITROTOLUOL
- sym-TRINITROTOLUOL
- TRITOL
- TRITON
- TROJNITROTOLUEN
- TROTYL
- TROTYL OIL
- UN 0209