Evaluation of the Health Risk of Ordnance Disposal Waste in Drinking Water (1982)

Pages
58

Size
8.5 x 11

ISBN
0309328888

Subcommittee on Ordnance Disposal Waste; Committee on Toxicology; Board on Toxicology and Environmental Health Hazards; Assembly of Life Sciences; National Research Council

EVALUATION OF THE HEALTH RISKS OF ORDNANCE DISPOSAL WASTE IN DRINKING WATER

prepared for the

Department of the Navy

by the

COMMITTEE ON TOXICOLOGY

Board on Toxicology and Environmental Health Hazards
Assembly of Life Sciences
National Research Council

National Academy Press
Washington, D.C.

February 1982

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The National Research Council was established by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and of advising the federal government. The Council operates in accordance with general policies determined by the Academy under the authority of its Congressional charter of 1863, which establishes the Academy as a private, nonprofit, self-governing membership corporation. The Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in the conduct of their services to the government, the public, and the scientific and engineering communities. It is administered jointly by both Academies and the Institute of Medicine. The National Academy of Engineering and the Institute of Medicine were established in 1964 and 1970, respectively, under the charter of the National Academy of Sciences.

Prepared under Contract N00014-80-C-0161 between the National Academy of Sciences and the Office of Naval Research.

Subcommittee on Ordnance Disposal Waste

Lawrence Fishbein, National Center for Toxicological Research, Jefferson, Arkansas
Roger O. McClellan, Inhalation Toxicology Research Institute, Albuquerque, New Mexico
Robert Snyder, Rutgers University College of Pharmacy, Piscataway, New Jersey

COMMITTEE ON TOXICOLOGY

Roger O. McClellan, Inhalation Toxicology Research Institute, Albuquerque, New Mexico, Chairman
Lawrence Fishbein,* National Center for Toxicological Research, Jefferson, Arkansas
Ian T. Higgins, University of Michigan Medical Center, Ann Arbor, Michigan
Wendell W. Kilgore, University of California, Davis, California
Leonard T. Kurland, Mayo Clinic, Rochester, Minnesota
Howard Maibach, University of California, San Francisco, California
H. George Mandel, George Washington University School of Medicine, Washington, D.C.
Joseph V. Rodricks, Clement Associates, Inc., Arlington, Virginia
Ronald C. Shank, University of California, Irvine, California
Carl M. Shy,* University of North Carolina, Chapel Hill, North Carolina
Edward A. Smuckler, University of California, San Francisco, California
Robert Snyder, Rutgers University College of Pharmacy, Piscataway, New Jersey
Peter Spencer, Albert Einstein College of Medicine, Bronx, New York
Philip G. Watanabe, Dow Chemical U.S.A., Midland, Michigan

National Research Council Staff

Gary R. Keilson, Staff Scientist
Gordon W. Newell, Staff Scientist
Norman Grossblatt, Editor
Brenda Spears, Secretary

*Member of the Committee until July 31, 1981.

INTRODUCTION

The U.S. Department of the Navy's Bureau of Medicine and Surgery (BUMED) has responsibility for suggesting environmental-health criteria for pollutants peculiar to the Navy when standards or guidelines are not available from federal agencies with primary responsibility, such as the Environmental Protection Agency (EPA). Ordnance waste presents a problem to the Navy, because it can enter drinking-water supplies and pose health risks to affected communities. The EPA has not issued environmental-health standards for many of the chemicals in ordnance waste. BUMED is therefore engaged in a program to assess the distribution and fate of selected pollutants, to provide advice on their toxicity, and to establish criteria for their concentrations in drinking water.

Five constituents of ordnance-disposal waste are of particular concern as potential contaminants of drinking water: ammonium picrate, picramic acid (2-amino-4,6-dinitrophenol), 1,3,5-trinitro-1,3,5-triazacyclohexane (RDX), propylene glycol dinitrate (a component of Otto Fuel II), and trinitrotoluene (TNT). For each of these compounds, BUMED has established a target interim maximal contaminant level (TIMCL) for drinking water.

In an effort to get outside expert opinion on its recommendations, BUMED has asked the Committee on Toxicology of the National Research Council's Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, to evaluate the available literature on the compounds in question, to comment on the appropriateness of the TIMCLs, and to suggest additional research that could provide a stronger data base on which to derive TIMCLs.

This report reviews and evaluates the pertinent literature on the five contaminants identified by BUMED and suggests drinking-water criteria on them. The criteria are intended as guidelines in estimating the health risks of the contaminants associated with exposure from drinking water. They are not standards or maximal contaminant concentrations, such as are suggested by the EPA, and would not guarantee absolute safety. The criteria were derived on the basis of health considerations; the feasibility of achieving the suggested concentrations in drinking water was not taken into account. If the data on a particular compound were sparse, the Committee has identified research that would provide a better basis for suggesting health criteria.

AMMONIUM PICRATE

BACKGROUND INFORMATION

Chemical Name: 2,4,6-Trinitrophenol, ammonium salt
Common Names: Ammonium picrate; Picric acid, ammonium salt; Obeline picrate; Picratol; Explosive D
CAS Number: 131-74-8
Physical and Chemical Properties: See Table 1

Ammonium picrate is used in explosives. Although relatively little has been done to study its toxicity, some aspects of the toxicity of picric acid (2,4,6-trinitrophenol) have been described. In biologic systems, ammonium picrate would be expected to dissociate to yield picrate ion, so it is appropriate to summarize the literature on picric acid and its anion and to point out the studies that involved its ammonium salt.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

The toxicology of picric acid has been reviewed by Berkowitz (1979). Asymptomatic microscopic hematuria was observed among 245 men after they drank (on a ship) water that contained picric acid at an unknown concentration. Ingestion may result in nausea, vomiting, diarrhea, abdominal pain, oliguria, anuria, yellow staining of the skin, pruritus, skin eruptions, stupor, convulsions, and death (Windholz *et al.*, 1976). Gosselin *et al.* (1976) reported that the lowest lethal human dose after ingestion is about 5 mg/kg. Exposure to picric acid produces an increase in metabolic rate similar to that caused by dinitrophenol. This may be taken to mean that picric acid is an uncoupler of oxidative phosphorylation.

The literature on the cutaneous effects of ammonium picrate is sparse. Sunderman *et al.* (1945) reported dermatitis in munitions workers exposed to airborne ammonium picrate at 0.009-0.194 mg/m^3 for 2-13 mo. Schwartz (1944) reported that workers exposed to ammonium picrate had dermatitis characterized by edema, papules, vesicles, and desquamation. The well-known effects of related compounds such as picric acid, are also of potential relevance in assessing the risks of dermal exposure of ammonium picrate, and are discussed here. Melinite, an explosive prepared from picric acid, induced sensitization in workers at French arsenals (Foussereau *et al.*, 1982). When melinite contained traces of dinitrophenol, dermatitis was frequent. Another related compound, trinitrotoluene, is also an allergen and trinitroanisole (methyl picrate) is considered a highly potent allergen (Bandmann and Dohn, 1967). Berkowitz (1979) described skin sensitization from picric acid, and Schwartz (1944) reported dermatitis similar to that described for ammonium picrate. Although appropriate test concentrations for the diagnosis of allergic contact

dermatitis have been established for several related compounds, this must still be determined for ammonium picrate (Bandmann and Dohn, 1967).

EFFECTS ON ANIMALS

Acute Exposure

There are no data on acute toxicity of ammonium picrate, but some values on the lethal doses of picric acid have been reported and are summarized in Table 2.

Berkowitz (1979) reported that picric acid potentiated the analgesic activity of several opiates and increased pentobarbital sleeping time in mice.

Cutaneous Effects

Sensitization of guinea pigs to picric acid develops slowly. It is first evident as discrete papules and vesicles and requires 2-3 d for maximal response. Inflammation in the form of scaling, erythema, and thickening can be seen a week after exposure (Berkowitz, 1979). Because of its high allergic potency, picric acid has been extensively studied as a model compound in guinea pig assays (Maguire and Chase, 1972).

Chronic Exposure

Sunderman et al. (1945) reported on experiments in which four rabbits and eight guinea pigs were exposed to ammonium picrate in a factory atmosphere for up to 12 mo. (There were no controls, and the numbers of animals were small; so the data must be considered no more than suggestive.) Of the eight guinea pigs, three were found dead at 1 wk, 3 wk, and 9 mo after starting exposure. The remainder survived the entire exposure period. Two of the rabbits were killed at 6 wk and the other two at 12 mo. Aside from inflammatory reactions to ammonium picrate, the major effect was the occurrence of brownish granules in kidney, heart, lung, and liver. The authors postulated that the granules were either phagocytes that had engulfed ammonium picrate and died or crystals of guanidine picrate.

Carcinogenicity

There are no data on the carcinogenic potential of ammonium picrate.

Teratogenicity and Reproductive Effects

There are no reports on the teratogenicity and reproductive effects of ammonium picrate.

Mutagenicity

Picric acid is mutagenic to Salmonella typhimurium TA98 (Yoshikawa et

al., 1976). Won (1977) reported that mutations were seen only after metabolic activation. Van Esch et al. (1957) were unable to detect tumors in male or female Wistar rats fed picric acid at 500 ppm in the diet for 2.5 yr.

EXPOSURE LIMITS

BUMED (1980) recommended a TIMCL for ammonium picrate of 0.001 mg/L. The primary basis of that recommendation was consideration of the taste threshold (0.5 mg/L) (Ruchhoft and Norris, 1946), to which an uncertainty factor was applied. Previously, the Navy (Fauth and Wheeler, 1977) had suggested a maximal drinking water limit of 0.05 mg/L, after applying an uncertainty factor of 10 to the taste threshold; 0.01 mg/L was stated as a desirable concentration.

COMMITTEE RECOMMENDATIONS

The toxicity data on ammonium picrate are sparse, and there are no data that indicate the effects of multiple dosing by ingestion. However, on the basis of the available information on ammonium picrate and acute toxicity information on picric acid in humans and animals, the Committee believes that the BUMED suggested concentration of 0.001 mg/L is a reasonable drinking-water criterion. Because there is uncertainty about potential health effects of exposure to ammonium picrate at the TIMCL or any other concentration, the Committee has identified several kinds of research that should be considered. These include detailed study of the effects of chronic exposure, preferably by ingestion, at various concentrations. Valuable information can also be obtained from a 90-d exposure study, which would include investigation of the toxicokinetics and mechanisms of action of ammonium picrate. In addition, because of the potential for skin contact with ammonium picrate, there is justification for developing at least a partial profile of dermatotoxicologic effects. This would include appropriate guinea pig sensitization assays and a determination of non-irritant concentrations for diagnostic patch testing in humans.

Pending evaluation of toxicity data on ammonium picrate still to be obtained, the drinking-water concentration of 0.001 mg/L should be considered as an interim criterion.

Table 1. Some Physical and Chemical Properties of Ammonium Picrate

Molecular weight:	246.14
Solubility:	1 g/100 ml of water at 20°C; slightly soluble in alcohol
Conversion factors in air:	1 ppm = 10 mg/m^3 1 mg/m^3 = 0.1 ppm

Table 2. Lethality Data on Picric Acid[a]

Species	Route of Administration	LD_{Lo}[b] mg/kg
Pigeon	Subcutaneous	200
Frog	Subcutaneous	200
Dog	Subcutaneous	60
Cat	Oral	250
Rabbit	Oral	120
Guinea pig	Oral	100

[a]From NIOSH, 1979.
[b]Lowest reported lethal dose.

REFERENCES

Bandmann, H.J., and Dohn, W. 1967. Die Epicutantestung. Munchen: J.F. Bergmann. p. 291-292.

Berkowitz, J.B. 1979. Appendix B. Chemistry, toxicology, and potential environmental effects of picric acid. In: Literature review -- Problem Definition Studies on Selected Chemicals. Monthly Progress Report No. 21. Contract No. DAMD17-C-7037. Cambridge, MA.: Arthur D. Little, Inc. p. 8-27.

Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 1980. Letter to the Committee on Toxicology, National Research Council, Washington, D.C., February 11, 1980. 5 p.

Fauth, M.I., and Wheeler, P.P. 1977. Guidelines and analytical methods for selected explosives in potable and waste waters. Indian Head, MD.: Ordnance Environmental Support Office, Naval Ordnance Station. [15 p.]

Foussereau, J., Benezra, C., and Maibach, H. 1982. Occupational Dermatology. Copenhagen: Munksgaard. p. 71-74.

Gosselin, R.E., Hodge, H.C., Smith, R.P., and Gleason, N.M. 1976. Clinical Toxicology of Commercial Products, 4th ed. Baltimore, MD.: Williams & Wilkins.

Maguire, H.C., Jr., and Chase, M. W. 1972. Studies on the sensitization of animals with simple chemical compounds. XIII. Sensitization of guinea pigs with picric acid. J. Exp. Med. 135:357-375.

National Institute for Occupational Safety and Health. 1979. Registry of Toxic Effects of Chemical Substances. R.J. Lewis, Sr., and R.L. Tatkin, eds. Cincinnati, OH.: U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health.

Ruchhoft, C.C., and Norris, F.I. 1946. Estimation of ammonium picrate in wastes from bomb- and shell-loading plants. Some reactions of ammonium picrate in water and sewage. Ind. Eng. Chem. Anal. Ed. 18:480-483.

Schwartz, L. 1944. Dermatitis from explosives. J. Am. Med. Assoc. 125:186-190.

Sunderman, F.W., Weidman, F.D., and Batson, O.V. 1945. Studies of the effects of ammonium picrate on man and certain experimental animals. J. Ind. Hyg. Toxicol. 27:241-248.

Van Esch, G.J., Vink, H.H., and Van Genderen, H. 1957. Influence of hexanitrodiphenylamine on the incidence of neoplasms in the mammary tissue of rats. Nature 180:509-510.

Windholz, M., Budavari, S., Stroumtsos, L.Y., and Fertig, M.N., eds. 1976. The Merck Index: An Encyclopedia of Chemicals and Drugs. Ninth ed. Rahway, NJ.: Merck & Co., Inc.

Won, W.D. 1977. Picric acid and its biodegradation products as mutagens. Abstr. Annu. Meet. Am. Soc. Microbiol. 77:276.

Yoshikawa, K., Uchino, H., and Kurata, H. 1976. Studies on mutagenicity of hair dye. Eisei Shikenjo Hokoku (Bull. Nat. Inst. Hyg. Sci.) No. 94:28-32. [CA 88:164999a, 1978].

PICRAMIC ACID

BACKGROUND INFORMATION

Chemical Names: 2-Amino-4,6-dintrophenol; 2,4-Dinitro-6-aminophenol
Common Names: Picramic acid, C.I. Oxidation Base 21, Fourrine 4R, Fourrine 93, Furro 4R, Zoba 4R
CAS Number: 96-91-3
Physical and Chemical Properties: See Table 3

Picramic acid is prepared from picric acid, concentrated ammonium hydroxide, and hydrogen sulfide followed by neutralization with acetic acid. It is used in the manufacture of azo dyes, as a reagent for albumin, and as an indicator (yellow with acids, red with alkalies). Picramic acid is a major metabolite of picric acid, which has been used as the explosive in detonating fuses and as a bursting-charge explosive.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

There are no published reports of the effects of picramic acid on humans.

EFFECTS ON ANIMALS

Acute Exposure

The oral LD_{50} of picramic acid in mice was reported to be 378 mg/kg (Stetka, 1979a).

Chronic Exposure

There are no published reports of chronic exposure of animals to picramic acid.

Carcinogenicity

There are no published reports on the carcinogenic potential of picramic acid in animals.

Teratogenicity and Reproductive Effects

The teratogenic effects of picramic acid have not been reported.

The only report of possible reproductive effects of picramic acid referred to a dominant lethal assay in mice (Stetka, 1979b). Male CD-1 mice were given picramic acid in corn oil by gavage for 5 d at 7.56, 25.2, and 75.6 mg/kg. They were then mated with virgin females for the entire spermatogenic cycle (7 wk). Compared with controls,

there were no effects on fertility, average number of implantations, number of resorptions per pregnant female, number of females with one or more dead implants, or number of dead implants per total implants.

Mutagenicity

Picramic acid was negative in the sister chromatid exchange assay with L5178Y mouse lymphoma cells (Stetka, 1979c), in the mouse dominant lethal assay (Stetka, 1979b), and in cytogenic analysis of mouse bone marrow (Stetka, 1979a). In Salmonella typhimurium strains TA 1538, 98, 1535, and 100, picramic acid was mutagenic without activation by liver S-9 (Wyman et al., 1979). Concentrations ranged from 1 to 200 µg/plate, with the highest being cytotoxic in TA 100. A related compound, 2-amino-5-nitrophenol, had direct-acting mutagenicity in TA 98 (Chiu et al., 1978). Picric acid (2,4,6-trinitrophenol) was mutagenic in Salmonella typhimurium strains TA 98 and 100 at 10 µg in the presence of rat liver S-9 (Wyman et al., 1979; Chiu et al., 1978)

COMPARATIVE TOXICOLOGY

Little information is available on picramic acid, but 2,4-dinitrophenol and other structurally related compounds, have been studied more extensively. Most nitrophenol compounds are uncouplers of oxidative phosphorylation, this being a primary mechanism of their toxicity. Leader and Whitehouse (1966) measured uncoupling activity of various compounds in rat liver mitochondria respiring on succinate. 2,4-Dinitrophenol at 9 mg/L was a powerful uncoupler (on the basis of ability to decrease the ratio of phosphorus to oxygen). Picramic acid at about 22 mg/L was also a powerful uncoupler, while picric acid at 57 mg/L had no effect.

The fatal human oral dose of 2,4-dinitrophenol is about 1-3 g (Gosselin et al., 1976). To prevent toxicity, blood concentrations should not exceed 10 µg/g of blood (Dreisbach, 1963). 2,4-Dinitrophenol can cause liver and kidney insufficiencies, is cataractogenic in humans on repeated exposure, is absorbed through intact skin, and is a contact allergen (Gosselin et al., 1976; Dreisbach, 1963). Nitrophenols in general are slowly eliminated from the body. Intoxication from picric acid is associated with blood concentrations above 20 µg/g of blood. Kidney and liver damage occur in acute poisoning. Picric acid is also absorbed through the skin, and skin sensitization and dermatitis result from direct contact or airborne exposure (Berkowitz, 1979; Schwartz, 1944).

EXPOSURE LIMITS

In 1977, the Navy (Fauth and Wheeler, 1977) suggested a guideline standard for picramic acid in drinking water of 0.05 mg/L, one-tenth of the reported taste threshold of 0.5 mg/L. It was stated that 0.05 mg/L should be considered a maximal acceptable limit, with 0.01 mg/L as a desired target concentration. BUMED (1980) has now suggested a TIMCL for picramic acid in drinking water of 0.001 mg/L.

COMMITTEE RECOMMENDATIONS

Information on picramic acid is severely limited, compared with that on structurally related compounds, such as 2,4-dinitrophenol. However, there does not appear to be any evidence to suggest that the BUMED recommendation of 0.001 mg/L is inappropriate as a drinking-water criterion for picramic acid. There is a need for further study of this compound, and the suggested criterion of 0.001 mg/L should be regarded as an interim one, pending review of further research. The effects of chronic exposure to picramic acid, preferably by ingestion, should be investigated. As a minimum, a 90-d study of the toxicity, toxicokinetics, and mechanisms of action would provide valuable information.

Table 3. Some Physical and Chemical Properties of Picramic Acid

Molecular weight:	199.12
Melting point:	168°C
Solubility:	0.065 g/100 ml of water at 22°C; soluble in alcohol, benzene, glacial acetic acid, aniline, and ether
Conversion factors in air:	1 ppm = 8.33 mg/m^3 1 mg/m^3 = 0.12 ppm

REFERENCES

Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 1980. Letter to the Committee on Toxicology, National Research Council, Washington, D.C., February 11, 1980. 5 p.

Berkowitz, J.B. 1979. Appendix B. Chemistry, toxicology, and potential environmental effects of picric acid. In: Literature review -- Problem Definition Studies on Selected Chemicals. Monthly Progress Report No. 21. Contract No. DAMD17-C-7037. Cambridge, MA.: Arthur D. Little, Inc. p. 8-27.

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

Dreisbach, R.H. 1963. Handbook of Poisoning: Diagnosis and Treatment, 4th ed. Los Altos, CA.: Lange Medical Publications.

Fauth, M.I., and Wheeler, P.P. 1977. Guidelines and analytical methods for selected explosives in potable and waste waters. Indian Head, MD.: Ordnance Environmental Support Office, Naval Ordnance Station. [15 p.]

Gosselin, R.E., Hodge, H.C., Smith, R.P., and Gleason, N.M. 1976. Clinical Toxicology of Commercial Products, 4th ed. Baltimore, MD.: Williams & Wilkins.

Leader, J.E., and Whitehouse, M.W. 1966. Uncoupling of oxidative phosphorylation by some salicylamide derivatives. Biochem. Pharmacol. 15:1379-1387.

Schwartz, L. 1944. Dermatitis from explosives. J. Am. Med. Assoc. 125:186-190.

Stetka, D. 1979a. Mutagenicity evaluation of picramic acid in the mouse bone marrow cytogenetic analysis. Segment report. LBI Project No. 21022. Kensington, MD.: Litton Bionetics, Inc. [21 p.]

Stetka, D. 1979b. Mutagenicity evaluation of picramic acid in the mouse dominant lethal assay. Segment report. LBI Project No. 21021. Kensington, MD.: Litton Bionetics, Inc. [23 p.]

Stetka, D. 1979c. Mutagenicity evaluation of picramic acid in the sister chromatid exchange assay in L5178Y mouse lymphoma cells. Segment report. LBI Project No. 20990. Kensington, MD.: Litton Bionetics, Inc. [10 p.]

Wyman, J.F., Guard, H.E., Won, W.D., and Quay, J.H. 1979. Conversion of 2,4,6-trinitrophenol to a mutagen by Pseudomonas aeruginosa. Appl. Environ. Microbiol. 37:222-226

PROPYLENE GLYCOL DINITRATE
(A MAJOR COMPONENT OF OTTO FUEL II)

BACKGROUND

Chemical Name: 1,2-Propanediol, dinitrate; 1,2-Propylene glycol dinitrate
Common Names: Propylene dinitrate, Propylene nitrate, Isopropylene nitrate, PGDN
CAS Number: 6423-43-4
Physical and Chemical Properties: See Table 4

Otto Fuel II, a liquid propellant used in torpedoes, is a mixture of three components. The main component is propylene glycol dinitrate (PGDN), which accounts for 90% of the mixture; the remainder of the mixture is 2-nitrodiphenylamine (a so-called desensitizer) and di-n-butylsebacate (a so-called stabilizer). This review is primarily confined to PGDN, the compound used as the basis for the TIMCL recommended by the Navy for Otto Fuel II, although available information on Otto Fuel II is also reviewed.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Rivera (1974) reviewed the health effects of PGDN, which is an analogue of the nitrate esters that are used as vasodilators. These compounds produce nasal congestion, headaches, dizziness, nausea, vasodilatation, decrease in blood pressure, and labored breathing. The nitrate esters act as methemoglin-formers, but experience with PGDN suggests that this is not one of its important activities. PGDN shares with the other nitrated esters the property of leading to rapid development of tolerance: headaches are common early in the workweek, but disappear as tolerance develops during the week and reappear at the start of the next workweek. It is possible that compensatory vasospasm on withdrawal from ester nitrate exposure may produce coronary insufficiency, which at its most severe may be fatal.

In controlled studies (Stewart et al., 1974), humans were exposed to PGDN at 0.03, 0.1, 0.2, 0.35, 0.5, and 1.5 ppm for 1-8 h. At 0.1 ppm and greater, most of the subjects developed headaches after 2 h; but some tolerated exposure for 1 h. Longer exposures at these concentrations invariably resulted in more severe headaches. Exposure at 0.5 ppm produced severe disequilibrium. These subjects were unable to perform normally in the Romberg test or in the heel-to-toe test after 6 h of exposure. They usually had severe headaches, but appeared to function normally in tests of intellectual ability and manual coordination. Exposure at 0.2 ppm and greater caused alteration in the visual evoked response. At 1.5 ppm, severe eye irritation was observed within 30-40 min, although no conjunctivitis was seen. Subjects exposed to PGDN 8 h/d for 5 d at 0.2 ppm developed a tolerance to headaches, but there was an alteration in the visual evoked response.

Otto Fuel II can be absorbed from the skin and lead to headaches, dizziness, and nausea (Rivera, 1974). Splashes into the eyes can cause severe irritation, and ingestion can cause disorders of the gastrointestinal tract, damage to mucosal membranes, dilatation of blood vessels, headaches, nausea, and dizziness.

EFFECTS ON ANIMALS

Acute Exposure

The data on acute lethality of PGDN in animals are in Table 5. The mouse is the least sensitive species studied, whereas the rat, monkey, cat, and guinea pig appear to display similar degrees of sensitivity; the cat may be the most sensitive animal.

Jones et al. (1972) observed the effects of PGDN in rabbits from dermal and occular exposure. The Draize test showed no skin irritation after 24 and 72 h. Instillation of PGDN in the eye produced conjunctival redness, which was gone within 24 h; no damage to the iris or cornea was observed. When the skin tests were extended to 20 d of treatment, a number of dose-dependent phenomena became apparent. At 1 g/kg, some skin irritation was observed. At 2 g/kg, the animals were weakened and cyanotic, and their breathing was shallow and rapid; one of these animals died and had a reduced hematocrit and hemoglobin concentration. At 4 g/kg, significant methemoglobinemia was observed.

Subchronic Exposure

In one study, rats were exposed to PGDN by inhalation 7 h/d, 5 d/wk, for 30 d at 10.8 ppm (65 mg/m^3) and showed no abnormalities (Jones et al., 1972). In a second study (Jones et al., 1972), 15 rats, 15 guinea pigs, 2 dogs, and 9 monkeys were each exposed to PGDN continuously for 90 d at 11 ppm (67 mg/m^3), 18 ppm (108 mg/m^3), or 39 ppm (236 mg/m^3). Equal numbers of animals were used as controls. One monkey exposed at 39 ppm died; no other deaths or signs of toxicity were noted in any of the other animals. At 39 ppm, iron deposits were found in the liver, kidneys, and spleen of monkeys and dogs; there was also liver damage in guinea pigs and focal hepatic necrosis and acute renal tubular necrosis in female rats. In addition, all animals had increased levels of methemoglobin at 39 ppm and dogs had decreased hemoglobin and hematocrit values. At 18 ppm, dogs had hemosiderin in their livers and epithelial cells lining the proximal renal tubules and guinea pigs had pulmonary hemorrhage. Fatty changes in the liver were noted in animals at all three concentrations.

There have been several reports of behavioral testing in monkeys exposed to PGDN. Jones et al. (1972) exposed rhesus monkeys to PGDN at 35 ppm for 90 d and reported no changes in avoidance behavior. Mattsson et al. (1975a, 1975b) and Young et al. (1976) exposed rhesus monkeys at 2-33 ppm for 1-125 d and used a variety of avoidance tests,

but were unable to demonstrate any deficits. There was, however, a slight decrease in the visual evoked response. No pathologic effects were observed at necropsy.

Chronic Exposure

There are no published reports of chronic exposure of animals to PGDN.

Carcinogenicity

There are no published reports investigating the carcinogenic potential of PGDN.

Teratogenicity and Reproductive Effects

There are no published reports on the teratogenicity and reproductive effects of PGDN.

Mutagenicity

Otto Fuel II was subjected to a series of mutagenicity tests at Litton Bionetics (1979a, 1979b, 1979c, 1979d). In the Ames *Salmonella* test, there were no indications of mutagenesis in strains TA 1535, 1537, 1538, 98, or 100; nor were mutations seen in yeast D4 cells with or without metabolic activation (Litton Bionetics, 1979a). Otto Fuel II was not found to be active in the dominant lethal test (Litton Bionetics, 1979b). Cytogenetic analysis in which aberrations were investigated did not demonstrate an effect of PDGN that was statistically significant, but some unusual chromosomal damage was observed that is not normally seen in the historical controls (Litton Bionetics, 1979c). These studies should be repeated. There was no evidence of increased sister chromatid exchange in the mouse lymphoma cell, although metabolic activation led to increased toxicity of PGDN metabolites to the cells (Litton Bionetics 1979d). These studies did not suggest a mutagenic potential for PGDN.

Toxicokinetics

The metabolism of PGDN was reviewed by Clark and Litchfield (1969) and Litchfield (1971). When it was administered to rats, blood nitrite and nitrate increase, and nitrate is a major urinary metabolite. Partial denitration yields either 1- or 2-nitropropylene glycol, but neither is found at 0.5% or more in the urine, because of further degradation. In the blood, the 2-nitro isomer predominates. Studies of PGDN metabolism *in vitro* have demonstrated that the red cell is the exclusive site of degradation in blood. Isomers are formed *in vitro*, but the 2- isomer predominates *in vitro* as it does *in vivo*. Further studies in the rat have demonstrated the complete removal of the nitro groups to yield the free glycol and the eventual breakdown of the glycol to CO_2. The latter steps are in part assumed, on the basis of analogy to ethylene glycol. The breakdown is apparently not complete since some of the glycol may appear in the urine.

Further mechanistic studies by Andersen and Smith (1973) suggested that oxyhemoglobin (HBO_2) is responsible for the oxidation of PGDN. The reaction is inhibited by CO. The authors suggested that PGDN reacts at or near the heme, the iron is oxidized, and the mononitrate is formed. The stoichiometry suggests that 1.5 mol of heme are oxidized to yield methemoglobin per nitro group released. It seems that there must be a reactive intermediate, and nitrite is thought to be this intermediate.

EXPOSURE LIMITS

ACGIH (1981) has proposed a threshold limit value-time weighted average (TLV-TWA) for PGDN in the workroom air of 0.05 ppm (0.3 mg/m^3). BUMED (1980) has suggested a TIMCL in drinking water of 0.05 mg/L for Otto Fuel II, assuming that PGDN is the most important component.

COMMITTEE RECOMMENDATIONS

The available data on derivation of a target interim concentration for PGDN in drinking water are limited. However, there does not appear to be any evidence to suggest that the BUMED recommendation of 0.05 mg/L is inappropriate as a drinking-water criterion for PGDN. The little reliable quantitative information that is available would tend to support this recommendation. In an inhalation study, dogs exposed intermittently at 10 ppm (100 mg/m^3) for 90 d had minimal effects and rats exposed at 10 ppm for 30 d had no observed effects. With these data, the following equation could be used to estimate a target concentration for PGDN in drinking water:

$$\frac{(100\ mg/m^3)(10\ m^3)}{(2\ L/d)\quad (1{,}000)} = 0.5\ mg/L$$

The assumptions made here are that a 70-kg adult inhales 10 m^3 of air and consumes 2 L of water per day, that PGDN is completely absorbed from the respiratory tract, and that an uncertainty factor of 1,000 would be appropriate. However, because animal data from a 90-d study are being used to estimate a criterion for lifetime exposure, because there is little supporting toxicity information, and because the extrapolation from inhalation to oral exposure has many uncertainties (such as the potential wide variability of the respiratory rate in a heterogeneous population that could be exposed to PGDN and the absence of data to estimate the absorption factor), the Committee believes it would be inappropriate at this time to modify the current suggested exposure limit of 0.05 mg/L. As additional information on PGDN becomes available, the drinking-water criterion should be reevaluated. Further examination of the effects of chronic exposure of PGDN at various concentrations that may be found in drinking water is particularly needed.

Table 4. Some Physical and Chemical Properties of Propylene Glycol Dinitrate

Molecular weight:	166.09
Boiling point:	92°C
Solubility:	0.13 g/100 ml of water
Conversion factors in air:	1 ppm = 7.14 mg/m^3
	1 mg/m^3 = 0.14 ppm

Table 5. Acute Lethality of Propylene Glycol Dinitrate[a]

Species	Route of Administration	LD_{50}, mg/kg
Rat	Oral	250
Rat	Subcutaneous	463
Rat	Intraperitoneal	479
Mouse	Subcutaneous	1,208
Mouse	Intraperitoneal	1,047
Monkey	Intravenous	410
Cat	Subcutaneous	200
Guinea pig	Intraperitoneal	402

[a]From NIOSH, 1978.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1981. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists. 94 p.

Andersen, M.E., and Smith, R.A. 1973. On the mechanism of oxidation of human and rat hemoglobin by propylene glycol dinitrate. Biochem. Pharmacol. 22:3247-3256.

Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 1980. Letter to the Committee on Toxicology, National Research Council, Washington, D.C., February 11, 1980. 5 p.

Clark, D.G., and Litchfield, M.H. 1969. The toxicity, metabolism, and pharmacologic properties of propylene glycol 1,2-dinitrate. Toxicol. Appl. Pharmacol. 15:175-184.

Jones, R.A., Strickland, J.A., and Siegel, J. 1972. Toxicity of propylene glycol 1,2-dinitrate in experimental animals. Toxicol. Appl. Pharmacol. 22:128-137.

Litchfield, M.H. 1971. Aspects of nitrate ester metabolism. J. Pharmaceut. Sci. 60:1599-1607.

Litton Bionetics Inc. 1979a. Mutagenicity evaluation of Otto Fuel #2 in the Ames Salmonella/microsome plate test. Segment report. Submitted to Office of Naval Res., Arlington, Va. LBI Project No. 20988. Kensington, Md.: Litton Bionetics, Inc. [11 p.]

Litton Bionetics, Inc. 1979b. Mutagenicity evaluation of Otto Fuel #2 in the mouse dominant lethal assay. Segment report. Submitted to Office of Naval Res., Arlington, Va. LBI Project No. 21021. Kensington, Md.: Litton Bionetics, Inc. [23 p.]

Litton Bionetics, Inc. 1979c. Mutagenicity evaluation of Otto Fuel in the mouse bone marrow cytogenetics analysis. Segment report. Submitted to Office of Naval Res., Arlington, Va. LBI Project No. 21022. Kensington, Md.: Litton Bionetics, Inc. [13 p.]

Litton Bionetics, Inc. 1979d. Mutagenicity evaluation of Otto Fuel #2 in the sister chromatid exchange assay in L5178Y mouse lymphoma cells. Segment report. Submitted to Office of Naval Res., Arlington, Va. LBI Project No. 20990. Kensington, Md.: Litton Bionetics, Inc. [10 p.]

Mattsson, J.L., Crock, J.W., Jr., and Jenkins, L.J., Jr. 1975a. Effects of propylene glycol 1,2-dintrate on Rhesus monkey visual evoked response and Sidman avoidance task. Bethesda, Md.: Armed Forces Radiobiol. Res. Inst., Defense Nuclear Agency. AFRRI Scientific Report SR75-41.

Mattsson, J.L., Young, R.W., Curran, C.R., Franz, C.G., Cowan, N.J., and Jenkins, L.H. 1975b. Acute and chronic propylene glycol dinitrate exposure in the monkey: Effects on conditioned avoidance behavior and visual evoked response. Bethesda, MD.: Armed Forces Radiobiol. Res. Inst. and Naval Medical Research Institute.

National Institute for Occupational Safety and Health. 1978. Registry of Toxic Effects of Chemical Substances, Lewis, R.J., Sr., ed. NIOSH, Cincinnati, OH. [DHEW (NIOSH) Publ. No. 79-100]. 1363 p.

Rivera, J.C. 1974. Otto Fuel II: Health hazards and precautions. U.S. Navy Med. 63:7-10.

Stewart, R.D., Peterson, J.E., Newton, P.E., Hake, C.L., Hosko, M.J., Lebrun, A.J., and Lawton, G.M. 1974. Experimental human exposure to propylene glycol dinitrate. Toxicol. Appl. Pharmacol. 30:377-395.

Young, R.W., Curran, C.R., Franz, C.G., and Jenkins, L.J., Jr. 1976. Effects of chronic inhalation of propylene glycol 1,2-dinitrate on the conditioned avoidance behavior of primates. Bethesda, MD.: Armed Forces Radiobiol. Res. Inst., Defense Nuclear Agency. AFRRI Sci. Rep. SR6-25.

RDX

BACKGROUND INFORMATION

Chemical Names: Hexahydro-1,3,5-trinitro-1,3,5-triazine; Hexahydro-1,3,5-trinitro-s-triazine; 1,3,5-Trinitro-1,3,5-triazacyclohexane
Common Names: RDX, Cyclonite, Cyclotrimethylenenitramine, Cyclotrimethylenetrinitramine, Hexogen, Hexogen 5W, T4
CAS Number: 121-82-4
Physical and Chemical Properties: See Table 6

RDX was first used on a large scale as a base charge for denonators and as an explosive for shells and bombs by all major participants in World War II (Stone et al., 1969). More recently, it has been incorporated in Composition C-4 (91% RDX, 2.1% polyisobutylene, 1.6% motor oil, and 5.3% di-(2-ethylhexyl) sebacate), a plastic explosive used by the military to level trees and to destroy enemy fortifications. Composition C-4 was the most common plastic explosive used by field units during the Vietnam War (Stone et al., 1969).

RDX is manufactured by two procedures: the Woolwich or direct process, in which hexamine is nitrated with nitric acid yielding 70-75% RDX; and the Bachmann process, used exclusively in the United States, in which hexamine is mixed with nitric acid, ammonium nitrate, and acetic anhydride to yield 80-84% RDX, of which about 10% is cyclotetramethylenetetranitramine (HMX) (Lindner, 1980). Nitromethane and methylnitrate are volatile byproducts formed during cleavage of hexamethylenetetramine by the latter process (Thompson et al., 1979).

RDX is desensitized by mixing with trinitrotoluene (TNT) to form cyclotols or by coating with waxes, synthetic polymers, and elastomeric binders. Most of the RDX made in the United States is converted to Composition B (60% RDX, 40% TNT, and 1 part wax) and Composition A3 (91% RDX and 9% wax) (Lindner, 1980).

In 1972, the production of RDX in U.S. Army plants was estimated at over 80,000 tons (Small and Rosenblatt, 1974).

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Barsotti and Crotti (1949) reported 17 cases of toxic reactions that occurred between 1939 and 1942 in Italian workers handling powdered RDX in the drying, cooling, sieving, and packing processes of its manufacture. Ten workers experienced generalized convulsions of a clonic-tonic type followed by postictal coma, four had loss of consciousness without convulsions, two had vertigo, and one had vomiting and confusion. These either occurred without prodromal symptoms or were preceded by several days of insomnia, restlessness, irritability, or anxiety. Recovery in all cases was complete. Similar symptoms of toxicity were described by Vogel (1951) in German

workers handling fine RDX powder.

Five cases of illness in workers handling RDX in an explosives plant in the United States were described by Kaplan et al. (1965). All the cases occurred in the workers exposed to RDX in its finely powdered form. Inhalation, ingestion, and skin absorption were considered the probable modes of entry into the body. The typical symptoms in the 5 cases reported as RDX intoxication were sudden convulsion and unconsciousness without convulsion. There were few or no premonitory symptoms, some of the subjects experiencing only short periods of headache, dizziness, nausea, or vomiting. No abnormal physical findings were noted other than those related to the CNS, and no changes were evident in the complete blood count or urinalysis. Treatment was supportive, and recovery was complete with no sequelae.

No fatalities have been experienced in RDX facilities (Hathaway and Buck, 1977). Reported toxic effects of RDX in man have been limited to the CNS and have been manifested as epileptoid seizures (Barsotti and Crotti, 1949; Kaplan et al., 1965).

A cross-sectional epidemiologic study was conducted by Hathaway and Buck (1977) to investigate the effects of RDX following a report of a cluster of three cases of systemic lupus erythematosus at one munitions plant. Of the 2,022 employees selected from 5 U.S. Army ammunition plants, 1,491 participated (73.7%). Of these, 69 were exposed to RDX alone, 70 were exposed to TNT alone, 24 were exposed to RDX and HMX, 465 were exposed to RDX and TNT, and 863 were not exposed to explosives. The study demonstrated no excess of autoimmune disease and failed to identify any hematologic, hepatic, or renal abnormalities in employees with 8-h time-weighted exposures to RDX at up to 1.57 mg/m^3 (average exposure, 0.28 mg/m^3). Tables 7-9 list the mean laboratory values for RDX-exposed and -nonexposed employees and the proportions of abnormal laboratory determinations by RDX exposure category in males and females.

A number of serious intoxications have been reported in persons who ingested Composition C-4 to produce a "high" similar to that of ethanol (Stone et al., 1969). Ingestion of Composition C-4 by six military personnel was followed in a few hours by multiple generalized seizures, hematuria, severe nausea and vomiting, twitching, and mental changes. The six people were hospitalized and were treated by gastric lavage, maintenance of airways, control of seizures, and maintenance of fluid and electrolyte balance. All six survived. Army physicians recognized Composition C-4 intoxication as by far the most common cause of recurring generalized seizures in Vietnam (Stone et al., 1969).

Convulsions have also been reported in factory workers who handle and pack Composition C-4, and inhalation of the dust was incriminated (Merrill, 1968).

After ingestion of Composition C-4 or long exposure to the fumes from its burning, patients had signs of CNS, renal, and gastrointestinal toxicity (Hollander and Colbach, 1969; Merrill, 1968; Stone et al., 1969). Ketel and Hughes (1972) reviewed 18 cases of toxic encephalopathy with seizures secondary to ingestion of Composition C-4. The CNS signs, which appear sequentially, are confusion, marked hyperirritability, myoclonic seizures, and major

motor seizures with prolonged postictal confusion and amnesia. The toxic effects involving the CNS were completely reversible, often within weeks and occasionally over several months, both clinically and electroencephalographically.

EFFECTS ON ANIMALS

Acute Exposure

The LD_{50} of RDX is approximately 200 mg/kg in nonfasting rats and 50-100 mg/kg in fasting rats (von Oettingen *et al.*, 1949). Other lethal doses have been reported:

Skin, guinea pig LD_{Lo}	465 mg/kg	McNamara et al., 1974
Oral, rat LD_{50}	200 mg/kg	von Oettingen *et al.*, 1949
Oral, mouse LD_{50}	500 mg/kg	Sklyanskaya and Pozhariskii, 1944
Intraperitoneal, rat LD_{Lo}	10 mg/kg	McNamara et al., 1974
Intravenous, rat LD_{Lo}	18 mg/kg	McNamara et al., 1974
Intravenous, mouse LD_{50}	19 mg/kg	McNamara et al., 1974
Intravenous, guinea pig LD_{50}	25 mg/kg	McNamara et al., 1974
Intravenous, dog LD_{Lo}	40 mg/kg	McNamara et al., 1974

Schneider *et al.* (1977) reported that the acute LD_{50} of RDX depends on its physical form and on the method used to suspend or dissolve it. Hence, caution must be exercised in comparing results among various laboratories, to ensure that what appear to be different LD_{50} values for RDX are not due primarily to differences in the RDX solutions or suspensions. For example, the oral LD_{50} of more finely powdered RDX whose saline slurry was more stable was equivalent to the oral LD_{50} of dimethyl sulfoxide solutions of RDX (about 100 mg/kg), but about one-third of the LD_{50} of granular RDX (approximately 300 mg/kg) in the rat.

Sklyanskaya and Pozhariskii (1944) described the acute effects of RDX administered by gavage in aqueous and oil suspensions in mice, rabbits, and cats. The severity of neuromuscular excitation depended on dose and ranged from mild hyperreflexia to severe convulsions and eventual death. The 100-mg/kg dose, harmless to mice, was fatal in cats.

Sunderman *et al.* (1944) reported that RDX injected intraperitoneally caused convulsions and death in rats in 9-121 min; subcutaneous and intravenous injections also caused a rapid onset of convulsions. Doses as low as 10 mg/kg intraperitoneally and 18 mg/kg intravenously caused death.

Subchronic Exposure

Repeated daily oral administration of RDX at 25, 50, or 100 mg/kg to rats for 3 mo produced hyperirratibility, convulsions, and a mortality of 40-86.6%. RDX at 15 mg/kg did not cause outright symptoms or deaths (von Oettingen *et al.*, 1949). Repeated daily exposure to RDX at 15, 25, 50, or 100 mg/kg did not cause significant cytologic blood changes in rats.

Rats given RDX by gavage at 20 mg/kg per day for up to 90 d did not have convulsions or overt neurologic signs characteristic of RDX toxicity. However, 8 of the 30 treated rats died, apparently from exacerbation of chronic respiratory disease (Schneider et al., 1978).

Feeding of RDX to dogs at 50 mg/kg per day for 6 wk produced hyperirratibility, convulsions, and weight loss, but did not materially affect the cytologic picture. The gross and microscopic changes in the organs and tissues of rats and dogs fed RDX daily were negligible (von Oettingen et al., 1949).

Sklyanskaya and Pozhariskii (1944) reported that mice given RDX at 20 mg/kg per day for up to 30 d became progressively more debilitated and died, but had no clinical signs of neurotoxicity.

Three of six rhesus monkeys given RDX at 10 mg/kg per day for 90 d had at least one severe convulsive episode, and five of the six developed tremors and had frequent episodes of emesis (Martin and Hart, 1974). Dogs were unaffected at this dosage, except for occasional emesis (Hart, 1974). The only effect observed at 1 and 0.1 mg/kg per day was emesis.

Chronic Exposure

Male and female Sprague-Dawley rats fed RDX in their diets at 1.0, 3.1, and 10 mg/kg for 2 yr had no increase in mortality and no overt signs of toxicity (Hart, 1976).

Carcinogenicity

No published reports were available investigating the carcinogenic potential of RDX. However, long-term studies are currently underway (Jorgenson and Spanggord, 1981; Lish, 1981), which should be evaluated by the Navy as soon as the results become available.

Teratogenicity and Reproductive Effects

There are no published reports of teratogenic or reproductive effects of RDX.

Mutagenicity

RDX was nonmutagenic when tested in the Ames Salmonella test with strains TA 1535, 1537, 1538, 100, and 98 with and without metabolic activation (Whong et al., 1980).

Toxicokinetics

The metabolism and distribution of RDX after administration of single oral doses in the rat and miniature swine have been determined by Schneider et al. (1977). In rats given RDX intraperitoneally at 500 mg/kg, the mean times to first seizure and to death were 23.8 and 171 min, respectively, and the mean plasma RDX concentrations at seizure and death were 5.2 and 13.8 μg/ml, respectively. After an oral dose of 100 mg/kg, the plasma concentration was 2.1 μg/ml at 4 h and 3.0

μg/ml at 24 h, and the urinary concentration was 5.5 μg/ml at 4 h and 6.9 μg/ml at 24 h. Four days after an oral dose of 50 mg/kg, less than 0.6% of the original dose remained in the rat. Only 3% had been excreted unchanged, mostly in the urine; the remainder had been metabolized, and the metabolites excreted in the urine or exhaled (as CO_2). The reactions involved in RDX metabolism appear to be catalyzed by microsomal enzyme systems and occur primarily in the liver (French et al., 1976; Bradley, 1977).

In miniature swine given RDX orally at 100 mg/kg, the plasma concentration was 1.6 μg/ml at 2 h and 4.7 μg/ml at 24 h, and the urinary concentration was 2.0 μg/ml at 2 h and 3.6 μg/ml at 24 h (Schneider et al., 1977).

In the studies reported by Schneider et al. (1977), irrespective of dosage or route of administration, the RDX concentration was greatest in kidney, varied most widely in liver (site of RDX metabolism), and did not accumulate in brain. In miniature swine given 100 mg/kg orally, the concentrations of RDX in brain, heart, liver, renal cortex, renal medulla, and fat at 24 h were between 4.4 and 9.1 μg/g. Rats convulsed within the first several hours after receiving RDX, but miniature swine convulsed 12-24 h after receiving RDX (Schneider et al., 1977); the latter is comparable with the latent period preceding RDX convulsions in humans (Merrill, 1968; Stone et al., 1969; Knepshlied and Stone, 1972; Ketel and Hughes, 1972) and consistent with the time course of RDX in swine plasma (Schneider et al., 1977).

In a subchronic study in which rats were given unlabeled RDX or [^{14}C]RDX by gavage at 20 mg/kg per day for up to 90 d or allowed free access to drinking water that was saturated with unlabeled RDX or [^{14}C]RDX (50-70 μg/ml) for up to 90 d, RDX was also found to be extensively metabolized (Schneider et al., 1978). About one-third of the total label was exhaled as $^{14}CO_2$, and a similar amount was excreted in the urine. The amount of parent compound in the urine accounted for only 3-5% of the total urinary radioactivity, and the remainder was associated with unidentified metabolites. RDX did not accumulate significantly in any of the tissues examined. Residual carcass radioactivity was about 2.5 times greater after 13 wk of drinking [^{14}C]RDX-saturated water than it was after 1 wk, but the carcass RDX concentration was only about 1.5 times as great. Metabolism of RDX produced various one-carbon intermediates, e.g., CO_2, bicarbonate ion, and formic acid (Schneider et al., 1977, 1978). Incorporation of these intermediates into various long-lived cellular constituents was believed to be the cause of the slight increase in body burden of radioactivity after 13 wk (Scheider et al., 1978).

In the studies in which rats were given RDX by gavage at 20 mg/kg per day for 90 d, the plasma RDX never exceeded 2.08 μg/ml. There were no convulsions or overt neurologic signs characteristic of RDX toxicity at the plasma concentrations observed in this study (Schneider et al., 1978).

Urine:plasma and tissue:plasma RDX ratios were consistently greater in oral-administration than in drinking-water studies. Administration in drinking water would allow a slower, but continuous, absorption, permitting more efficient hepatic metabolism and decreased urinary excretion of the parent compound (Schneider et al., 1978).

EXPOSURE LIMITS

The threshold limit value-time weighted average (TLV-TWA) for RDX in workroom air is 1.5 mg/m^3 (ACGIH, 1981). BUMED (1980) has established a TIMCL for RDX in drinking water of 0.05 mg/L. USAMBRDL (1980) has recommended an RDX limit of 0.03 mg/L for drinking water.

On the basis of the absence of observable bioaccumulation in rats given RDX by gavage at 20 mg/kg per day or allowed free access to RDX-saturated drinking water (50-70 μg/ml) for up to 90 d (Schneider et al., 1978), the absence of toxicity in rhesus monkeys given RDX at 1 mg/kg per day for 90 d (Martin and Hart (1974), and the absence of toxicity in rats given RDX in food at 10 mg/kg per day for 2 yr (Hart, 1976), Schneider et al. (1978) stated that an ingestion limit of approximately 0.1 mg/kg per day would appear appropriate, regardless of the mode of ingestion. Assuming that a 70-kg man consumes 3 L of water per day, Schneider et al. (1978) suggested an acceptable concentration of RDX in drinking water of 2-3 mg/L.

COMMITTEE RECOMMENDATIONS

The most relevant data for evaluating the effects of long-term exposure of RDX are from Martin and Hart (1974) and Hart (1974, 1976). In these studies, 10 mg/kg per day for 90 d or 2 yr produced little effect in dogs or rats, respectively, and 1 mg/kg per day produced little effect in monkeys. After evaluating the toxicity data on RDX, the Committee has concluded that there is no strong indication that the current BUMED recommendation of 0.05 mg/L should be modified. Although the data already cited could be used to support raising the drinking-water criterion, the Committee believes that that would not now be prudent, given the limited data base on effects of chronic exposure to RDX. Long-term exposure to RDX is now being studied, and the Committee suggests that the drinking water criterion be reevaluated when data from current studies become available.

Table 6. Some Physical and Chemical Properties of RDX

Molecular weight:	222.26
Melting point:	202°C
Solubility:	Insoluble in water (0.0076 g/100 g water at 25°C), ethanol (0.105 g/100 g ethanol at 20°C), isopropyl alcohol, carbon tetrachloride, and carbon disulfide Slightly soluble in methanol, ether, ethyl acetate, and glacial acetic acid Soluble in acetone (1 g in 25 ml), cyclohexanone, dimethyl sulfoxide, hot aniline, phenol, and nitrobenzene
Conversion factors in air:	1 ppm = 10 mg/m^3 1 mg/m^3 = 0.1 ppm

Table 7. Mean Laboratory Values for RDX-Exposed and -Nonexposed Employees at Five Army Munition Plants[a]

LABORATORY DETERMINATION	MALE			FEMALE		
	Nonexposed	RDX Exposed		Nonexposed	RDX Exposed	
		Undetected[b]	0.01 mg/m^3 or over		Undetected[b]	0.01 mg/m^3 or over
No. of people	237	22	45	101	1	25
LDH	173	191	174	184	167	184
Alk. Phos.	82	78	80	70	88	67
SGOT	22	25	21	21	10	20
SGPT	21	26	18	13	10	12
Bilirubin	0.5	0.4	0.4	0.4	0.4	0.4
Hb	15.2	14.7	15.2	13.8	13.9	13.8
Hct	47	45.6	47	41.7	43.3	41.4
Reticulocyte count	0.7	0.9	0.7	1	0.3	1.1
Total protein	7.2	7.2	7.3	7.3	7.6	7.2
BUN	15.5	15.6	16.4	13.2	8	12.6
Glucose	94	91	93	92	67	92
Cholesterol	212	202	208	212	206	227

[a]Reprinted with permission from Hathaway and Buck, 1977.
[b]Some exposure was thought to exist, on the basis of professional judgement, but no RDX was detected with breathing-zone sampling.

Table 8. Proportion of Abnormal Laboratory Determinations by RDX Exposure Category in Male Workers at Five Army Munition Plants[a]

DETERMINATION[b]	RDX EXPOSURE[c]		
	None	Undetected	0.01 mg/m^3 or over
Hb (< 14)	15/237	3/22	4/45
Hct (< 40)	1/237	1/22	1/45
Reticulocyte count (> 1.5)	18/237	3/22	2/45
LDH (> 250)	2/237	1/22	0/45
Alk. Phos. (> 105)	34/237	1/22	6/45
SGOT (> 35)	15/237	2/22	0/45
SGPT (> 35)	20/237	4/22	2/45
Bilirubin (> 1.0)	5/237	1/22	1/45

[a]Reprinted with permission from Hathaway and Buck, 1977.
[b]Abnormal values in parentheses.
[c]Proportion of abnormal results to total number of persons in exposure category.

Table 9. Proportion of Abnormal Laboratory Determinations by RDX Exposure Category in Female Workers at Five Army Munition Plants[a]

DETERMINATION[b]	RDX EXPOSURE[c]		
	None	Undetected	0.01 mg/m^3 or over
Hb (<12)	2/101	0/1	0/25
Hct (<37)	4/101	0/1	0/25
Reticulocyte count (>1.5)	19/101	0/1	5/25
LDH (>250)	11/101	0/1	1/25
Alk. Phos. (>105)	11/101	0/1	0/25
SGOT (>35)	4/101	0/1	1/25
SGPT (>35)	3/101	0/1	0/25
Bilirubin (>1.0)	4/101	0/1	0/25

[a]Reprinted with permission from Hathaway and Buck, 1977.
[b]Abnormal values in parentheses.
[c]Proportion of abnormal results to total number of persons in exposure category.

REFERENCES

American Conference of Governmental Industrial Hygienists. 1981. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists. 94 p.

Barsotti, M., and Crotti, G. 1949. Attacchi epilettic come manifestazione di intossicazine professionale da trimetilentrinitroamina (T4). (Epileptiform attacks as manifestations of professional poisoning with trimethylenetrinitramine (T-4)). Med. Lav. 40:107-111. [CA 43: 8682C, 1949]

Bradley, S.L. 1977. The role of mixed function oxidases in the metabolism of cyclotrimethylenetrinitramine (RDX). M.S. Thesis in Biology. American University, Washington, DC. 38 p.

Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 1980. Letter to the Committee on Toxicology, National Research Council, Washington, D.C., February 11, 1980. 5 p.

French, J.E., Bradley, S.L., Schneider, N.R., Andersen, M.E., and Jenkins, L.J., Jr. 1976. Cyclotrimethylenetrinitramine (RDX)-induced ultrastructural changes in rat liver and kidney. Toxicol. Appl. Pharmacol. 37:122, abstr. no. 73.

Hart, E.R. 1974. Subacute toxicity of RDX and TNT in dogs. Final Report. Contract No. N00014-73-C-0162. Kensington, MD.: Litton Bionetics. 8 p.

Hart, E.R. 1976. Two-year feeding study in rats. Final Report. Contract No. N00014-73-C-0162, Task No. NR 202-043. Kensington, MD.: Litton Bionetics. 6 p.

Hathaway, J.A., and Buck, C.R. 1977. Absence of health hazards associated with RDX manufacture and use. J. Occup. Med. 19:269-272.

Hollander, A.I., and Colbach, E.M. 1969. Composition C-4 induced seizures: A report of five cases. USARV Med. Bull. Pamph. No. 40-14:31-35.

Jorgenson, T.A., and Spanggord, R.J. 1981. Determination of the chronic mammalian toxicological effects of LAP wastewaters. Toxicol. Res. Projects Directory 7(2).

Kaplan, A.S., Berghout, C.F., and Peczenik, A. 1965. Human intoxication from RDX. Arch. Environ. Health. 10:877-883.

Ketel, W.B., and Hughes, J.R. 1972. Toxic encephalopathy with seizures secondary to ingestion of composition C-4: A clinical and electroencephalographic study. Neurology 22:871-876.

Knepshield, J.H., and Stone, W.J. 1972. Toxic effects following ingestion of C-4 plastic explosive. IN Keup, W., ed. Drug Abuse: Current Concepts and Research. Springfield, Ill.: Charles C. Thomas. p 296-301.

Lindner, V. 1980. Explosives and propellants. IN Kirk-Othmer Encyclopedia of Chemical Technology, Third Edition. Volume 9:561-671. NY.: John Wiley & Sons.

Lish, P.M. 1981. Determination of the chronic mammalian toxicological effects of RDX. Toxicol. Res. Projects Directory 6(5).

Martin, D.P., and Hart, E.R. 1974. Subacute toxicity of RDX and TNT in monkeys. Final Report. Contract No. N00014-73-C-0162, NR 108-985. Kensington, MD.: Litton Bionetics. 19 p.

McNamara, B. P., Averill, H.P., Owens, E.J., Callahan, J.F., Fairchild, D.G., Ciuchta, H.P., Rengstorff, R.H., and Biskup, R.K. 1974. The toxicology of cyclotrimethylenetrinitramine (RDX) and cyclotetramethylenetetranitramine (HMX) solutions in dimethylsulfoxide (DSMO), cyclohexanone, and acetone. Department of the Army, Headquarter, Edgewood Arsenal, Aberdeen Proving Ground, MD. Technical Rep. EB-TR-73040. [Also issued as AD-780 010]. 112 pp.

Merrill, S.L. 1968. Ingestion of an explosive material, composition C-4: A report of two cases. USARV Med. Bull. Pam. No. 40-8:5-10.

Schneider, N.R., Bradley, S.L., and Andersen, M.E. 1977. Toxicology of cyclotrimethylenetrinitramine: Distribution and metabolism in the rat and the miniature swine. Toxicol. Appl. Pharmacol. 39:531-541.

Schneider, N.R., Bradley, S.L., and Andersen, M.E. 1978. The distribution and metabolism of cyclotrimethylenetrinitramine (RDX) in the rat after subchronic administration. Toxicol. Appl. Pharmacol. 46:163-171.

Sklyanskaya, R.M., and Pozhariskii, F.I. 1944. Toxicity of hexogen. Farmakol. Toksikol. 7:43-47. [CA 39:3073, 1945].

Small, M.J., and Rosenblatt, R.H. 1974. Munitions production products of potential concern as waterborne pollutants. Phase II. Technical Report 7404. Aberdeen Proving Ground, MD.: U.S. Army Medical Bioengineering Research and Development Laboratory. 96 p.

Stone, W.J., Paletta, T.L., Heiman, E.M., Bruce, J.I., and Knepshield, J. H. 1969. Toxic effects following ingestion of C-4 plastic explosive. Arch. Intern. Med. 124:726-730.

Sunderman, F.W., Clark, J.K., and Bills, E.S. 1944. Compilation of Informal Monthly Reports on Hazards to Health of Individuals Working With RDX, May 1943-June 1944. National Defense Research Committee of the Office of Scientific Research and Development, NORC Contract No. OEM sr-962. (unclassified). [Arch. Environ. Health 10:883, 1965].

Thompson, C.R., Kats, G., and Lennox, R.W. 1979. Phytotoxicity of air pollutants formed by high explosive production. Environ. Sci. Technol. 13:1263-1268.

United States Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD. 1980. Interim Environmental Criteria for Munitions Compounds. [25] p.

Vogel, W. 1951. Uber hexogen-vergiftongen beim menschen. (Hexogen poisoning in human beings). Zbl. Arbeitsmed. 1:51-54. [Arch. Environ. Health 10:883, 1965].

von Oettingen, W.F., Donahue, D.D., Yagoda, H., Monaco, A.R., and Harris, M.R. 1949. Toxicity and potential dangers of cyclotrimethylenetrinitramine (RDX). J. Ind. Hyg. Toxicol. 31:21-31.

Whong, W.-Z., Speciner, N.D., and Edwards, G.S. 1980. Mutagenic activity of tetryl, a nitroaromatic explosive, in three microbial test systems. Toxicol. Letters 5:11-17.

TRINITROTOLUENE (TNT)

BACKGROUND INFORMATION

Chemical Names: 2,4,6-Trinitrotoluene; 2-Methyl-1,3,5-trinitrobenzene
Common Names: Trinitrotoluene, TNT, Tolite, α-TNT, Trotyl, Tritol, Trilit
CAS Number: 118-96-7
Physical and Chemical Properties: See Table 10

TNT was discovered in 1863 and by 1902 had assumed importance in Germany as the principal constituent in many explosives. It was widely used by itself or in combination with other materials during World War I (McConnell and Flinn, 1946). TNT has been the most commonly used explosive in the munitions industry since World War I and continues to be used extensively in shells, bombs, and mines and as a bursting charge (Goodwin, 1972; Morton et al., 1976; Hathaway, 1977). It is made in either a batch or a continuous process (Rinkenbach, 1965; Lindner, 1980). Toluene is nitrated with nitric acid and mixed with sulfuric acid in a 3-stage operation by using increasing temperatures and mixed-acid concentrations to introduce nitro groups successively to form mononitrotoluene (MNT), dinitrotoluene (DNT), and TNT. Numerous other compounds are formed, including unsymmetric isomers of TNT and such oxidation products as tetranitromethane, nitrobenzoic acid, nitrocresol, and partially nitrated toluenes. Purified TNT can be obtained in the Sellite process, in which crude TNT is treated with 16% sodium sulfite and then reacts preferentially with asymmetric meta isomers to form the water-soluble sodium salts of the corresponding sulfonic acids. The formation of isomeric impurities and reaction byproducts and the losses in selliting reduce the theoretical yield of α-TNT to about 85-88%. The chief impurities in crude TNT are 2,3,4-trinitrotoluene (β-TNT; m.p., 112°C), small amounts of trinitrobenzoic acid, trinitrobenzene, and tetranitromethane (Rinkenbach, 1965).

TNT production can result in air pollutants, such as nitrotoluene (as ortho, meta, and para isomers, which are dissolved in spent acids and are released to the air during the reprocessing of acids) and tetranitromethane (formed during the destructive oxidation of a byproduct, 3,5-dinitrotoluene) (Thompson et al., 1979).

Substantial quantities of waste are generated during the processes necessary for the production, purification, and loading of munitions (Walsh et al., 1973; Won et al., 1974; Smock et al., 1976; Leggett, 1977). The main wastewater problem originates from TNT finishing, shell washout, and equipment and building washdown, in which TNT is dissolved in the washwater and is chemically transformed into a complex of various compounds and isomers, collectively referred to as "pink water" (Smock et al., 1976). The waste formed when partially purified TNT is finally water-washed after sellite purification is also referred to as "pink water" (Walsh et al., 1973). "Red water" is the waste formed during the sellite purification of TNT.

In the finishing process, TNT is dried, flacked, and packaged with considerable amounts of water (e.g., as much as 500,000 gal can be

generated at a single plant) to clean equipment and the interior of finishing-plant buildings. It is usually beyond the capacity of a munitions plant to incinerate such volumes of water in addition to the large amounts of red and pink water normally incinerated. Hence, the finishing-plant wastewater is usually disposed of by discharge into nearby rivers or streams (Walsh et al., 1973). The finishing-plant water consists mostly of α-TNT, with smaller amounts of dinitrotoluenes and isomers of TNT. Owing to exposure to sunlight and neutralization of the wastewater before disposal, some of these nitro compounds are chemically transformed into highly colored compounds whose identities and toxicities are largely unknown (Walsh et al., 1973; Smock et al., 1976). Studies by Walsh et al. (1973) have suggested that in neutral and basic solutions the chemical conversion of α-TNT may be as high as 95%; hence, the main pollutant in neutralized finishing-plant wastewater is most likely not α-TNT, but rather the colored conversion species.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Hathaway (1977) reviewed the scientific and medical literature on TNT, with emphasis on studies that provided correlation between work exposures and adverse health effects. During World Wars I and II, many TNT workers reportedly died of aplastic anemia or toxic hepatitis; the nature of these toxic effects was reported mostly between 1920 and 1955 (Voegtlin et al., 1922; Hart et al., 1944; Cone, 1944; McConnell and Flinn, 1946; Crawford, 1954). There were 475 deaths in about 17,000 cases of TNT poisoning in the United States in a period of about 7.5 mo of World War I--in sharp contrast with the total experience in the United States during World War II (e.g., a rate of less than three occupational-disease deaths per 100,000 operating employees per year) (McConnell and Flinn, 1946). Since World War II, there have been only occasional reports of deaths due to TNT poisoning, and there have been very few reports in the English-language literature of any problems related to TNT use in the last 20 yr (Morton et al., 1976). Goodwin (1972) reported reversible liver damage in a small percentage of workers in a shell-loading plant in a period of over 20 yr.

Occupational exposure to TNT has been reported to occur by inhalation, ingestion, and skin absorption. Commonly reported medical problems include gastritis, dermatitis, and anemia (Voegtlin et al., 1922; Cone, 1944; Lawrence, 1942); hemolytic anemia (Djerassi and Vitany, 1975); nose and throat irritation (Fairhill, 1957); red-blood-cell destruction (Cone, 1944); methemoglobinemia (Cone, 1944); leukopenia and leukocytosis (Fairhill, 1957); peripheral neuritis (Soboleva, 1969); myocardial irregularities (Soboleva, 1969); pancreatic dysfunction (Kleiner et al., 1974); and cataract formation (Hassman and Juran, 1971).

In a series of 22 TNT fatalities in the United States in World War II, summarized by McConnell and Flinn (1946), eight persons died of toxic hepatitis and 13 of aplastic anemia; one partially recovered from hepatitis and later died of aplastic anemia or a combination of the two

conditions. Only one-third of the 22 were exposed to TNT at average concentrations over 1.5 mg/m^3. In this series, hepatitis occurred more frequently among the younger persons (average age, 30 yr) and aplastic anemia among the older (average age, 45 yr). The pathologic findings in the clinical hepatitis cases invariably included degenerative damage to the liver, usually with great reduction in size and weight.

Airborne concentrations of TNT required to cause death were reported to be considerably higher than 1.5 mg/m^3, the current workplace standard (OSHA, 1981). With respect to concentrations near the OSHA standard, effects have varied. Cone (1944) reported that at 0.5-2.0 mg/m^3 no hematologic abnormalities occurred, but liver function was not evaluated. However, a case of aplastic anemia has been reported in connection with exposure to TNT at much less than 1.5 mg/m^3 (Eddy, 1944).

Older reports of adverse health effects generally did not include information on workplace concentrations of TNT, particularly for nonfatal effects. In an uncontrolled study (Ermakov et al., 1969), it was reported that 122 of 574 employees had chronic TNT poisoning with an average TNT concentration of 1 mg/m^3; work exposures ranged from 6 to 25 yr. Most of the affected workers had functional disorders of the CNS, 22% (27) had chronic anemia and leukopenia, 20% (24) had cataracts, and 12% (15) had symptoms of hepatitis. There were no comparisons with unexposed control populations or breakdowns of individual TNT exposure.

A number of case reports of aplastic anemia from various sources have included the extent of exposure and are shown in Table 11.

Several reports of controlled studies have provided information on early and subclinical effects of TNT exposure (Stewart et al., 1945; El Ghawabi et al., 1974; Friedlander et al., 1974; Hathaway, 1974; Morton et al., 1976; Buck and Wilson, 1975). The most striking finding in these epidemiologic studies is the occurrence of hematologic and hepatic abnormalities at TNT concentrations well below 1.5 mg/m^3. The most persistent findings are mild reductions in the hemoglobin and hematocrit concentrations and red-blood-cell counts of exposed people--the findings are attributed mostly to the destruction of red cells by hemolysis (Cone, 1944; Voegtlin et al., 1922) and are direct toxic effects of TNT or its metabolites (Hathaway, 1977).

In one study, statistically significant increases in serum glutamic oxaloacetic transaminase and lactic dehydrogenase occurred after exposure to TNT at 0.8 mg/m^3 and persisted at 0.6 mg/m^3 (Morton et al., 1976). A study to determine a threshold for effects involved 533 employees exposed to TNT and 865 employees not exposed to explosives (Buck and Wilson, 1975). Of the 533 exposed workers, 58 were exposed to both TNT and RDX. Concomitant exposure to RDX was not thought to influence the effect of TNT exposure on hematologic or hepatic function (Hathaway and Buck, 1976). Mild biologic effects, particularly reduction in hemoglobin concentration or red-blood-cell count, were noted at exposures as low as 0.2 mg/m^3. Table 12 illustrates the relationship between hemoglobin and TNT exposure for all participants. Reticulocyte counts varied greatly in both exposed and nonexposed workers. Many workers had low reticulocyte counts (below 0.5%), and many had high counts (above 1.5%). Both low and high counts tended to

be more frequent in exposed workers, and mean counts were higher after greater TNT exposures.

Toxicokinetics

The main route of absorption of TNT into the human body is the skin, but ingestion and absorption through the respiratory tract must also be considered (Goodwin, 1972). The relative importance of routes of exposure appears to be variable and probably depends on the nature of the work operation, the physical state of TNT, and the personal hygiene and work practices of individual employees (Hathaway, 1977). Because skin absorption and accidental ingestion of TNT occurs, it is acknowledged to be extremely difficult to formulate dose-response relationships for TNT and observe toxic effects in man (Hathaway, 1977).

Ether-extractable pigments in urine from munition workers exposed to TNT consisted of 60-75% dinitrotoluidines, 10-25% nitrotoluylene-diamines, and 10-15% aminonitrocresols. The dinitrotoluidine fraction consisted mainly of 4-amino-2,6-dinitrotoluene, with smaller amounts of 2-amino-4,6-dinitrotoluene. Trace amounts of 4-hydroxylamino-2,6-dinitrotoluene were detected, but no azoxy compounds were found (Lemberg and Callaghan, 1944).

EFFECT ON ANIMALS

Acute Exposure

The following are some data on lethal doses of TNT:

Oral, rabbit LD_{Lo}	500 mg/kg	Wyon, 1921
Oral, rat LD_{Lo}	700 mg/kg	" "
Oral, cat LD_{Lo}	1,850 mg/kg	" "
Subcutaneous, cat LD_{Lo}	200 mg/kg	" "
Subcutaneous, rabbit LD_{Lo}	500 mg/kg	" "

Acute-toxicity studies of TNT wastewater were reported by Sasmore et al. (1976). Synthetic and authentic TNT wastewater residues were irradiated to 50 and 100% TNT degradation levels at pH values of 5, 7, and 9.4, lyophilized to solid residues, and administered orally as a suspension in corn oil to male and female Swiss Webster mice to determine acute oral LD_{50} values. An LD_{50} of 1.3 g/kg was found for nonirradiated material containing 9% TNT. On irradiation at pH 5, it was 2.2 g/kg at 50% TNT degradation and 4.9 g/kg at 100% TNT degradation. The toxicity of the discharges decreased as a function of irradiation time.

Subchronic Exposure

In one study, dogs were given TNT daily by capsule for 90 d at 0, 0.2, 2.0, or 20 mg/kg body weight; rats received TNT in their diet daily for 90 d at 0, 0.002, 0.01, 0.05, or 0.25% (0, 1.42, 7.18, 35.56, and 162.18 mg/kg body weight, respectively); and mice received TNT in their diet daily for 90 d at 0, 0.001, 0.005, 0.025, or 0.125% (0, 1.56, 7.76,

36.77, and 188.61 mg/kg body weight, respectively) (Dilley et al., 1977; Dilley et al., 1978a). All three species receiving the high dose had anemia, with reduced numbers of red cells, reduced hemoglobin, and reduction in spleen size. A marked reduction in the size of the testes was observed in the rats and mice receiving the high dose and to a lesser extent in those receiving the second highest dose. The primary toxicity of TNT appeared to be toward the erythroid cells and the developing germinal cells of males.

Dilley et al. (1978a, 1978b) fed rats, mice, and dogs TNT or 1.6:1 TNT-RDX mixtures in their diet for 90 d. The mixture was representative of untreated wastewater from Army ammunition plants conducting load and assemble-and-pack operations. During the treatment, the highest-dose rats and mice (0.25 and 0.125% TNT, respectively, and 0.5% TNT-RDX for both species) had weight loss, reduced food intake, and red urine. Dogs on the highest dose (by capsule--TNT at 20 mg/kg per day or the mixture at 50 mg/kg per day) had weight loss, ataxia, nystagmus, and other neurologic signs, as well as orange urine. Hematologic changes in all three species (high dose only) included a reduced red blood cell count, hemoglobin, and hematocrit and increased red-cell volume with increased reticulocyte count. Clinical-chemistry changes included increased cholesterol and decreased serum glutamate pyruvate transaminase activity in rats and dogs. Histopathologic findings included increased hemosiderosis of the spleen and sometimes the liver in all three species receiving the highest dose. Testicular atrophy with focal interstitial cell hyperplasia was found in the rats receiving 0.25% TNT in their diets, rats receiving 0.5% TNT-RDX, and dogs receiving TNT-RDX at 50 mg/kg per day. Female rats given 0.5% TNT-RDX had a hypoplasia of the uterus. The no-observed-adverse-effect levels of TNT in the diets of rats and mice were 0.002% (1.42 mg/kg body weight) and 0.005% (7.76 mg/kg body weight); for TNT-RDX the no-observed-adverse-effect level was 0.005% for both rats and mice (3.57 and 8.28 mg/kg body weight for rats and mice, respectively). In dogs, the no-observed-adverse-effect level was 0.2 mg/kg per day for TNT and 0.5 mg/kg per day for TNT-RDX. In general, the TNT content of the TNT-RDX mixture was dominant in producing toxicity.

Dogs given daily doses of TNT at 0.02, 0.1, or 1 mg/kg for 90 d developed no signs of toxicity other than temporary episodes of emesis, to which tolerance apparently developed (Hart, 1974). Laboratory diagnostic procedures and both gross and microscopic postmortem examinations revealed no important differences from controls. Dogs treated with TNT administered subcutaneously at 7 mg/kg twice a week for 9 mo had renal pathologic changes, particularly damage of the tubular portion of the nephrons (Dynnik et al., 1977).

Rhesus monkeys (3 animals of each sex in each dosage group) were treated orally, once daily, 7 d/wk for 90 d with TNT at 1, 0.1, and 0.02 mg/kg (Martin and Hart, 1974). The high dosage group had increases in number of degenerate or necrotic megakaryocytes in bone marrow sections and increased iron-positive material in liver cord cytoplasm. The toxicologic importance of these two findings is uncertain.

Information available on the toxicity of TNT in mammals was extensively reviewed by Dacre and Rosenblatt (1974) and summarized by Hathaway (1977). The toxic effects in experimental animals included

hemolysis of red blood cells, development of anemia, central and peripheral nervous system impairment (including peripheral neuropathy), gastritis, disturbances in pancreatic function, fatty degeneration of the liver, hemosiderosis of the spleen, inhibition of phagocytosis, and increased cholesterol concentration in bile. There was wide species variability, but cats and dogs appeared to be more susceptible to TNT than rabbits and rats. Hematologic and liver function abnormalities have occurred in all species.

Chronic Exposure

There are no published reports of the effects of chronic exposure of TNT.

Carcinogenicity

There are no published reports of the carcinogenic potential of TNT in animals. Long-term studies are currently underway (Jones, 1981; Jorgenson and Spanggord, 1981; Lee, 1980; Lish, 1981), which should be evaluated by the Navy as soon as the results become available.

Teratogenicity and Reproductive Effects

Teratogenic and reproductive effects of TNT have not been reported in the literature.

Mutagenicity

TNT was detected as a frameshift mutagen that significantly accelerated the reversion rate of Salmonella typhimurium strain TA 98. In contrast, the major microbial metabolites of TNT (e.g., 2,6-dinitro-4-hydroxyaminotoluene, 2,6-dinitro-4-aminotoluene, 2-nitro-4,6-diaminotoluene, 2,4-dinitro-6-hydroxy-aminotoluene, 2,4-dinitro-6-aminotoluene, 2,2',4,4'-tetranitro-6,6'-azoxytoluene, and 2,2',6,6'-tetranitro-4,4'-azoxytoluene) appeared to be nontoxic and nonmutagenic (Won et al., 1976). When TNT was activated with microsomal enzymes, the mutagenic effect on strain TA 98 was not increased. This suggested that enzymatic oxidation of TNT in vitro yields nonreactive, nonmutagenic intermediates.

No cytogenic aberrations were found in bone-marrow cells from rats that were treated for 28 d with 0.25% and 0.002% TNT in the diet (Dilley et al., 1978a, 1978b).

Toxicokinetics

When rats were treated orally with TNT at 5-40 mg, 15-20% of the TNT was excreted unchanged in the urine in the first 24 h. Repeated dosing did not alter the excretion pattern; that suggested that there was no storage of TNT or metabolites. In rat urine, the diazotizable compounds were predominantly nitrotoluylenediamines (50-60%), with 25% dinitrotoluidines and about 18% aminonitrocresols. The latter fractions yielded 4-amino-2,6-dinitrotoluene and 5-nitro-m-phenylenediamine. No hydroxylamino or azoxy compounds were found (Lemberg and Callaghan, 1944).

2,6-Dinitro-4-aminotoluene and 2,6-dinitro-4-aminotoluene (15-20%) were found in the urine of dogs receiving TNT orally at 50 mg/kg per day. No evidence of 2,4-diamino-6-nitrotoluene, 2,4,6-triaminotoluene, 2,4,6-trinitrotoluene, 2,4,6-trinitrobenzylalcohol, 2,4,6-trinitrobenzaldehyde, or 2,4,6-trinitrobenzoic acid was found (Snyder, 1946).

In the rabbit, 47% of orally administered TNT was excreted in the urine as glucuronides and 30% as aromatic amino compounds, the latter estimated by measuring 4-amino-2,6-dinitrotoluene. The aromatic amino compounds included not only dinitroaminotoluenes, but possibly dinitroaminobenzyl alcohol conjugated with glucuronic acid, and as trinitrobenzylglucuronide. Doses of TNT up to 150 mg/kg were eliminated in 24 h; larger doses required up to 48 h. The isolation of 2,6-dinitro-4-hydroxylaminotoluene and 4-amino-2,6-dinitrotoluene showed the existence of a reduction mechanism. The formation of dinitrohydroxylaminotoluene was suggested by Channon et al. (1944) to explain partially the toxic action of TNT after oral, cutaneous, and intratracheal administration to rabbits.

After administration of [^{14}C]TNT (50 mg/kg), male rats excreted 59.5% of the oral dose in urine and 10.8% in feces after 24 h; 21.0% remained in the gastrointestinal tract. Female rats excreted 42.5% in urine and 2.2% in feces; 35.5% remained in the gastrointestinal tract. TNT was slowly absorbed after cutaneous application; e.g., male rats eliminated 17.4% in urine and 1.3% in feces after 24 h and 3.1% was recovered in the gastrointestinal tract. Absorption and elimination were faster after intratracheal administration. In 4 h, 17.5% was excreted in urine and 19.8% in bile. After oral administration, these values were 12.7% and 14.5%, respectively. Rats without bile cannulas excreted most of the dose in urine--an indication of considerable enterohepatic circulation. The urine and bile contained large amounts of glucuronides, but no sulfate conjugates were detected. The urine of rats contained diaminomononitrotoluenes and smaller amounts of TNT and dinitromonoaminotoluenes, with no dihydroxylamines or azoxytoluenes. Qualitative differences in metabolic products after oral, cutaneous, and intratracheal administration to rats were not apparent (El-hawari et al., 1978).

Hodgson et al. (1977) studied the comparative absorption, distribution, excretion, and metabolism of labeled TNT and isomers of dinitrotoluene (DNT) in rats. The nitrotoluenes were well absorbed after oral administration in the rat. The absorption was essentially complete in 24 h (60-90%). The extent of absorption was in the following order: 2,4-DNT, 3,4-DNT > 3,5-DNT, TNT, 2,5-DNT > 2,3-DNT, 2,6-DNT. Most of the absorbed radioactivity was eliminated in the urine, and the liver, kidneys, and blood contained small amounts of radioactivity. Negligible amounts of carbon-14 were recovered in the expired air; that indicated that the aromatic ring was not extensively metabolized. When ^{14}C-labeled nitrotoluenes were administered to bile-duct-cannulated rats, 10.3-27.3% of the carbon-14 was recovered in the bile--a suggestion that biliary excretion is also an important elimination pathway.

EXPOSURE LIMITS

The following workroom standards have been adopted by various countries for TNT: United States, 0.15 ppm or 1.5 mg/m^3; Czechoslovakia, 0.1 ppm or 1 mg/m^3; West Germany, 0.15 ppm or 1.5 mg/m^3; East Germany, 0.15 ppm or 1.5 mg/m^3; and U.S.S.R., 0.1 ppm or 1 mg/m^3 (Verschueren, 1977). The ACGIH (1981) has proposed a threshold limit value-time weighted average (TLV-TWA) for TNT of 0.5 mg/m^3 and a 15-min short-term exposure limit (STEL) of 3 mg/m^3.

BUMED (1980) has established a TIMCL for TNT in drinking water of 0.05 mg/L (0.05 ppm). The limit for TNT in drinking water recommended by the U.S. Army (USAMBRDL, 1978) is 0.03 mg/L. Earlier, the U.S. Army had established limits of 1 mg/L in drinking water and 5 mg/L in water used by fish and wildlife (Smock et al., 1976). USAMBRDL (1980) has recommended a TNT limit of 0.01 mg/L in wastewater, and the USSR has set 1 mg/L as the maximal permissible concentration in surface water (McKee and Wolf, 1963).

Dilley et al. (1978a) estimated maximum concentrations of TNT in drinking water on the basis of 90-d toxicity studies. The no-observed-adverse-effect concentrations were 0.2, 1.42, and 7.76 mg/kg per day for dogs, rats, and mice, respectively. Assuming a 70-kg man drinks 2 L of water per day and consumes 0.0187 kg of fish per day and using an uncertainty of 1,000 in extrapolating from animals to humans, Dilley et al. (1978a) calculated the TNT concentrations in water for human consumption to be 0.0063, 0.0447, and 0.245 mg/L, from dog, rat, and mouse data, respectively.

Studies of the toxic effects of TNT and its primary degradation product (pink water) on two species of algae and the fathead minnow indicated that there was no response to TNT at 0.05 mg/L or pink water at 0.07 mg/L (Smock et al., 1976). The authors suggested that these concentrations may be appropriate as necessary stream standards (with the caveat that that should be verified by long-term chronic-toxicity tests).

COMMITTEE RECOMMENDATIONS

No long-term exposure studies of TNT are available for evaluation. The most appropriate data for derivation of a drinking-water criterion were reported by Dilley et al. (1978a, 1978b), from which a concentration of TNT in water for human consumption was calculated to be in the range of 0.006-0.245 mg/L. These data support the current BUMED drinking-water criterion of 0.05 mg/L, and the Committee concludes that there are insufficient data to suggest a modification of the BUMED recommendation now. The Committee is concerned about some of the data that suggest that exposure to TNT may produce aplastic anemia (see Table 11), especially in the absence of any long-term studies of TNT. Use of an uncertainty factor of 1,000 in deriving the current drinking-water criterion should provide a reasonable margin of protection. Nevertheless, the Committee encourages the Navy to reassess the criteria for TNT as soon as the results of the current long-term studies are available for evaluation.

Table 10. Some Physical and Chemical Properties of TNT

Molecular weight:	227.13
Melting point:	80.1°C
Boiling point:	240°C
Solubility:	Very sparingly soluble in water (10.013 g/100 g water at 20°C) Soluble in acetone, benzene, ether, alcohol, and toluene
Conversion factors in air:	1 ppm = 10 mg/m^3 1 mg/m^3 = 0.1 ppm

Table 11. Case Reports of Aplastic Anemia[a]

No. Cases	Exposure to TNT, mg/m^3	Skin Contact	Other Exposure	References
13	b	Yes	?	Voegtlin et al., 1922
1	1.1-4.2	Yes	None	Eddy, 1944
1	2.1-3.4	Yes	None	Eddy, 1944
1	< 0.5	Yes	? benzene	Eddy, 1944
1	0	?	sulfanilamide	Sievers et al., 1946
1	1.0-3.5	?	acetophenetidin	Sievers et al., 1946
1	1.0-3.5	?	None	Sievers et al., 1946
1	1.1-7.0	Yes	None	Cone, 1944
1	3.7-10.7	Yes	None	Cone, 1944
1	4.2	Yes	None	Cone, 1944
1	5.3-7.0	Yes	None	Cone, 1944

[a]Reprinted with permission from Hathaway, 1977.
[b]One-third of persons exposed to TNT at over 1.5 mg/m^3. Remaining two-thirds exposed to TNT at less than 1.5 mg/m^3. Exact exposures were not reported.

Table 12. Relationship between Hemoglobin (Hb) and TNT Exposure in Workers at Several Army Munition Plants[a]

TNT Exposure, mg/m^3	No. Abnormal[b]	No. Normal	Relative Odds[c]
None	78	785	1.0
$\leq$ 0.01	24	191	1.3
0.02-0.09	10	63	1.6
0.10-0.19	18	80	2.3
0.20-0.29	4	20	2.0
0.30-0.39	5	5	10.1
0.40-0.49	14	33	4.3
0.50-0.99	11	21	5.3
1.00-1.49	3	5	6.1
$\geq$ 1.50	1	1	10.1

[a]Reprinted with permission from Hathaway, 1977.
[b]Males: Hb at less than 14 g/100 ml of blood;
Females: Hb at less than 12 g/100 ml of blood.
[c]An estimate of relative risk of abnormal Hb with increasing exposure to TNT. In all cases the odds are relative to those not exposed. Example for TNT exposure of 0.10-0.19 mg/m^3:

$$\text{Relative Odds} = \frac{18 \times 785}{80 \times 78} = 2.3$$

REFERENCES

American Conference of Governmental Industrial Hygienists. 1981. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, Ohio: American Conference of Governmental Industrial Hygientists. 94 p.

Buck, C.R., and Wilson, S.E., Jr. 1975. Adverse health effects of selected explosives (TNT, RDX). Occupational Health Special Study No. 32-049-75/76. Aberdeen Proving Ground, MD.: U.S. Army Environmental Hygiene Agency. [105 p.]

Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 1980. Letter to the Committee on Toxicology, National Research Council, Washington, D.C., February 11, 1980. 5 p.

Channon, H.J., Mills, G.T., and Williams, R.T. 1944. The metabolism of 2:4:6-trinitrotoluene (α -T.N.T.). Biochem. J. 38:70-85.

Cone, T.E., Jr. 1944. A review of the effect of trinitrotoluene (TNT) on the formed elements of blood. J. Ind. Hyg. Toxicol. 26:260-263.

Crawford, M.A.D. 1954. Aplastic anemia due to trinitrotoluene intoxication. Br. Med. J. 2:430-437.

Dacre, J.C., and Rosenblatt, D.H. 1974. Mammalian toxicology and toxicity to aquatic organisms of four important types of waterborne munitions propellants-an extensive literature evaluation. Final report, June 1973-March 1974. Technical Report No. 7403. Aberdeen Proving Ground, MD.: U.S. Army Medical Bioengineering Research and Development Laboratory. [AD-778 725] 166 pp.

Dilley, J.V., Newell, G.W., Schobert, S., Palmer, D., Dacre, J., and Shiotsuka, R. 1977. The subacute oral toxicity of trinitrotoluene in rats, mice, and dogs. Toxicol. Appl. Pharmacol. 41:220, abstr. no. 210.

Dilley, J.V., Tyson, C.A., and Newell, G.W. 1978a. Mammalian toxicological evaluations of TNT wastewaters. Volume II. Acute and subacute mammalian toxicity of TNT and the LAP mixture. SRI Project LSU-5028, Contract No. DAMD17-76-C-6050. Menlo Park, CA.: SRI International. 491 p.

Dilley, J.V., Tyson, C.A., Sasmore, D.P., Spanggord, R.J., Newell, G.W., and Dacre, J.C. 1978b. Subacute oral toxicity of TNT and a TNT/RDX mixture to dogs and rodents. Toxicol. Appl. Pharmacol. 45:256, abstr. no. 86.

Djerassi, L.S., and Vitany, L. 1975. Haemolytic episode in G6 PD deficient workers exposed to TNT. Br. J. Ind. Med. 32:54-58.

Dynnik, V.I., Ostrovskaya, I.S., Prilipsky, Y.V., and Baturina, T.S. 1977. The influence of chemical and physical factors on the state of the kidneys. Urol. Nefrol. No. 4:19-23. [English summary].

Eddy, J.H., Jr. 1944. Aplastic anemia following trinitrotoluene exposure. A report of three cases. J. Am. Med. Assoc. 125:169-172.

El Ghawabi, S.H., Harooni, A. El R., Ibrahim, G.A., Mansoor, M.B., Gaber, M.F., El Owny, R., and Soudi, M.M. 1974. Trinitrotoluene exposure. Ain Shams Med. J. 25:545-549.

El-hawari, A.M., Hodgson, J.R., Shiotsuka, R.N., and Lee, C.C. 1978. Disposition and metabolism of 2,4,6-trinitrotoluene (TNT), after oral, dermal and intratracheal dosing to rats. Pharmacologist 20:255, abstr. no. 548.

Ermakov, E.V., Aizenshtadt, V.S., and Ventsenostev, B.B. 1969. Chronic trinitrotoluene poisoning (clinical picture and pathogenesis of neuro-vegetative disturbances). Sovet Med. 32(7):119-122. [English summary].

Fairhill, L.T. 1957. Industrial Toxicology, 2nd ed. Baltimore: Williams and Wilkins. p. 352-354.

Friedlander, B.R., Vorpahl, K.W., Glenn, R.E., and Jordan, P.T. 1974. Occupational Health Special Study No. 99-020-74, APE 1300 Wash-out Plant, Letterkenny Army Depot, Chambersburg, Pa., 14-15 March. Aberdeen Proving Ground, MD.: U.S. Army Environmental Hygiene Agency. 17 p.

Goodwin, J.W. 1972. Twenty years handling TNT in a Shell-loading plant. Am. Ind. Hyg. Assoc. J. 33:41-44.

Hart, E.R. 1974. Subacute toxicity of RDX and TNT in dogs. Final Report. Contract No. N00014-73-C-0162. Kensington, MD.: Litton Bionetics, Inc. 8 p.

Hart, W.L., Ley, E.B., Scroggie, V.D., Johnson, E.A., and Eddy, J.H. 1944. A report of four cases of aplastic anemia occurring among munitions workers. Ind. Med. 13:896-899.

Hassman, P., and Juran, J. 1971. Trinitrotoluol-star. Sb. Ved. Pr. Lek. Fak. Karlovy Univ. 14:261-274. [In German].

Hathaway, J.A. 1974. Occupational Health Special Study No. 32-005-75. TNT Washout Facility, Letterkenny Army Depot, Chambersburg, Pa., 20 June, 24 June, and 12 November. Aberdeen Proving Ground, MD.: U.S. Army Environmental Hygiene Agency. 7 p.

Hathaway, J.A. 1977. Trinitrotoluene: A review of reported dose-related effects providing documentation for a workplace standard. J. Occup. Med. 19:341-345.

Hathaway, J.A., and Buck, C.R. 1976. Report of absence of health hazards associated with RDX manufacture and use in Shell-loading plants. Alexandria, Va.: Department of Defense Explosives Safety Seminar, 14-15 Sept. p. 689-692.

Hodgson, J.R., Hwang, S.W., Dacre, J.C., and Lee, C.C. 1977. Comparative absorption, distribution, excretion, and metabolism of 2,4,6-trinitrotoluene (TNT) and isomers of dinitrotoluene (DNT) in rats. Fed. Proc. 36:996, abstr. no. 3826.

Jones, D.C. 1981. Mammalian toxicological evaluations of TNT wastewaters. Toxicol. Res. Projects Directory 6(6).

Jorgenson, T.A., and Spanggord, R.J. 1981. Determination of the chronic mammalian toxicological effects of LAP wastewaters. Toxicol. Res. Projects Directory 7(2).

Kleiner, A.L., Vasilenko., N.M., Sonkin, I.S., Ostrovskaya, I.S., Yashina, L.N., and Liss, N.L. 1974. Functional disturbances of the pancreas of toxico-chemical etiology. Gig. Tr. Prof. Zabol. No. 10:15-18. [English summary].

Lawrence, R.D. 1942. Discussion on trinitrotoluene poisoning. Proc. Roy. Soc. Med. 35:553-560.

Lee, C.C. 1980. Mammalian toxicity of munitions compounds. Toxicol. Res. Projects Directory 5(9).

Leggett, D.C. 1977. Determination of 2,4,6-trinitrotoluene in water by conversion to nitrate. Anal. Chem. 49:880.

Lemberg, R., and Callaghan, J.P. 1944. Metabolism of symmetrical trinitrotoluene. Nature 154:768-769.

Lindner, V. 1980. Explosives and propellants. IN Kirk-Othmer Encyclopedia of Chemical Technology, Third Edition. Volume 9:561-671. NY.: John Wiley & Sons.

Lish, P.M. 1981. Determination of the chronic mammalian toxicological effects of TNT. Toxicol. Res. Projects Directory 6(6).

Martin, D.P., and Hart, E.R. 1974. Subacute toxicity of RDX and TNT in monkeys. Final Report. Contract No. N00014-73-C-0162, NR 108-985. Kensington, MD.: Litton Bionetics, Inc. 19 p.

McConnell, W.J., and Flinn, R.H. 1946. Summary of twenty-two trinitrotoluene fatalities in World War II. J. Ind. Hyg. Toxicol. 28:76-86.

McKee, J.E., and Wolf, H.W., eds. 1963. [Reprint, 1971]. Water Quality Criteria, 2nd ed. Publication No. 3-A. CA.: The Resources Agency of California, State Water Resources Control Board. 548 pp.

Morton, A.R., Ranadive, M.V., and Hathaway, J.A. 1976. Biological effects of trinitrotoluene from exposure below the threshold limit value. Am. Ind. Hyg. Assoc. J. 37:56-60.

Occupational Safety and Health Administration. 1981. Air Contaminants. 29 CFR 1910:1000.

Rinkenbach, W.H. 1965. Explosives. IN Kirk-Othmer Encyclopedia of Chemical Technology, Second Edition. Volume 8:581-658. NY.: John Wiley & Sons.

Sasmore, D.P., Spanggord, R.J., Kay, D.L., Ouchi, G.I., and Newell, G.W. 1976. Acute toxicity studies of TNT wastewaters. Toxicol. Appl. Pharmacol. 37:117-118, abstr. no. 62.

Sievers, R.F., Stump, R.L., and Monaco, A.R. 1946. Aplastic anaemia following exposure to trinitrotoluene. Occup. Med. 1:351-362.

Smock, L.A., Stoneburner, D.L., and Clark, J.R. 1976. The toxic effects of trinitrotoluene (TNT) and its primary degradation products on two species of algae and the fathead minnow. Water Res. 10:537-543.

Snyder, R.K. 1946. Metabolites of 2,4,6-trinitrotoluene (TNT) excreted in the urine of dogs. J. Ind. Hyg. Toxicol. 28:59-75.

Soboleva, L.P. 1969. State of the myocardium during chronic trinitrotoluene intoxication. Gig. Tr. Prof. Zabol. 13:47-48. [CA 72:93149e May 4, 1970.]

Stewart, A., Witts, L.J., Higgins, G., and O'Brien, J.R.P. 1945. Some early effects of exposure to trinitrotoluene. Br. J. Ind. Med. 2:74-82.

Thompson, C.R., Kats, G., and Lennox, R.W. 1979. Phytotoxicity of air pollutants formed by high explosive production. Environ. Sci. Technol. 13:1263-1268.

United States Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD. 1980. Interim Environmental Criteria for Munitions Compounds. [25] p.

Verschueren, K. 1977. Handbook of environmental data on organic chemicals. NY.: Van Nostrand Reinhold Co. p. 623.

Voegtlin, C., Hooper, C.W., and Johnson, J.M. 1922. Trinitrotoluene poisoning-its nature, diagnosis, and prevention. J. Ind. Hyg. 3:280-292.

Walsh, J.T., Chalk, R.C., and Merritt, C., Jr. 1973. Application of liquid chromatography to pollution abatement studies of munitions wastes. Anal. Chem. 45:1215-1220.

Won, W.D., DiSalvo, L.H., and Ng, J. 1976. Toxicity and mutagenicity of 2,4,6-trinitrotoluene and its microbial metabolites. Appl. Environ. Microbiol. 31:576-580.

Won, W.D., Heckley, R.J., Glover, D.J., and Hoffsommer, J.C. 1974. Metabolic disposition of 2,4,6-trinitrotoluene. Appl. Microbiol. 27:513-516.

Wyon, G.A. 1921. II. Experiments on the toxic effects of trinitrotoluene in animals. IN Medical Research Council Special Report No. 58. T.N.T. Poisoning and the Fate of T.N.T. in the Animal Body. Great Britain, London: H.M. Stationery Office. p. 32-48.