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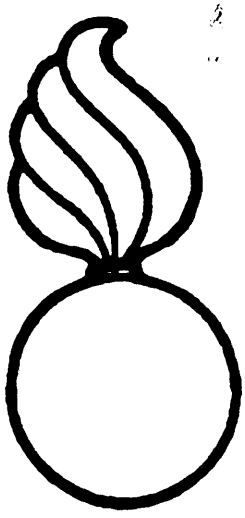
Overview Of The Health Effects Of Selected Munitions Chemicals



Overview of the Health Effects of Selected Munitions Chemicals

W.C. Roberts, B.J. Commons, H.T. Bausum,
C.O. Abernathy, J.J. Murphy, K. Khanna, and E.V. Ohanian

EPA

Overview of the Health Effects of Selected Munitions Chemicals*

W.C. Roberts[1], B.J. Commons[2], H.T. Bausum[3], C.O. Abernathy[4], J.J. Murphy[5], and K. Khanna[4]

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* The opinions and conclusions expressed in this document are those of the authors and do not necessarily reflect those of the U.S. Army or the U.S. Environmental Protection Agency.

PREFACE

In 1985, the United States Environmental Protection Agency (EPA) (Assistant Administrator for Water) and the United States Department of the Army (Deputy for Environment, Safety, and Occupational Health) established a Memorandum of Understanding (MOU) to develop EPA Drinking Water Health Advisories (HAs) for Army environmental contaminants (MOU, 1991). This collaboration has resulted in a review of the toxicological data base for selected munitions chemicals and the development of recommended exposure limits for specific durations (1-day, 10-day, longer-term [7 years], and lifetime [70 years]). Both cancer and noncancer endpoints of toxicity have been considered in these munitions assessments. This document is a brief review of some toxicological endpoints considered in the assessment of selected munitions chemicals.

Additional information on munitions chemicals or other drinking water compounds can be obtained by calling the EPA Safe Drinking Water Hotline (1-800-426-4791).

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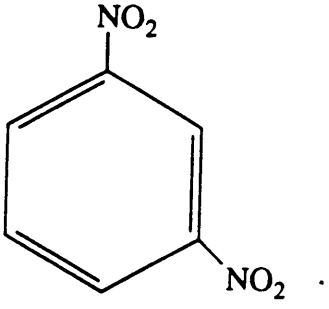

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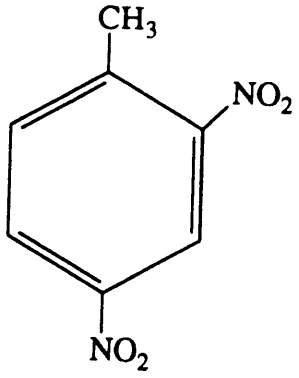

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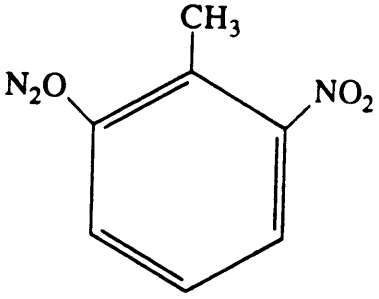

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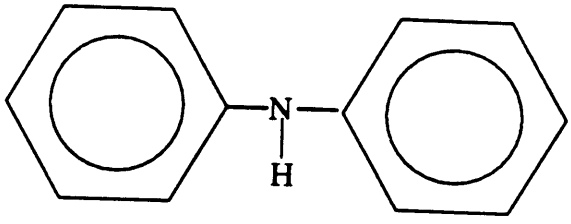

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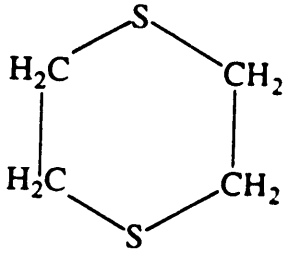

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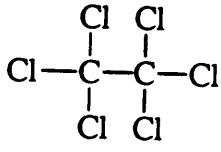

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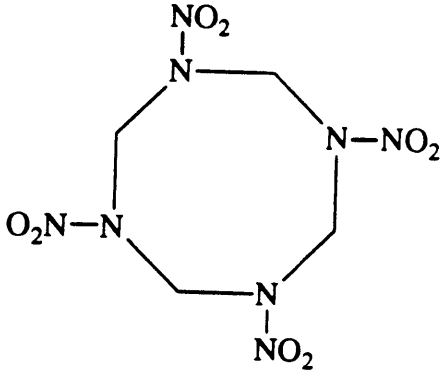

HMX
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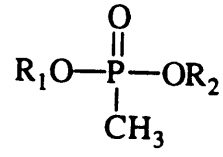
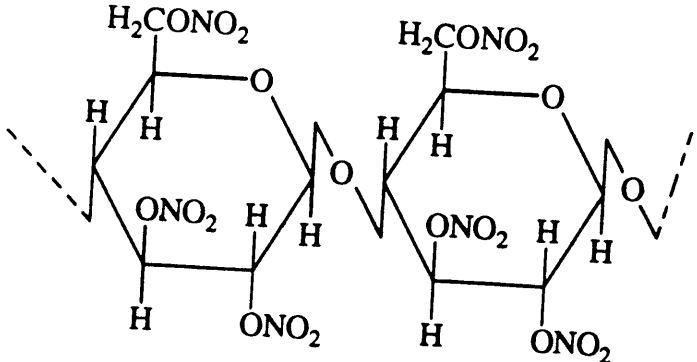
1,3,5,7-tetrazocine)



Methyl Phosphonates*
(*See pages 21, 36, 38, and 54 for individual structures.)

Structures (continued)



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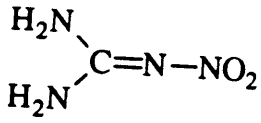

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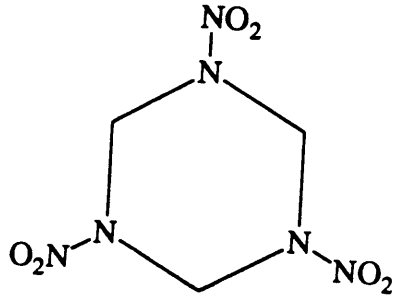

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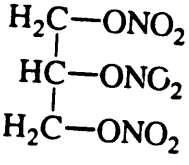

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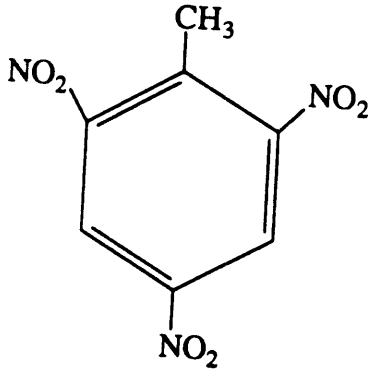

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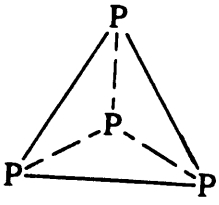
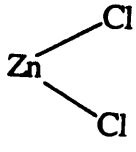


White Phosphorus



Zinc Chloride

Adverse Effects of the Munitions Chemicals Zinc (Zn), 1,4-Dithiane (D), Hexachloroethane (HCE), and White Phosphorous (WP) [1]

C.O. Abernathy [a], B.J. Commons [b], K.L. Khanna [a], W.C. Roberts [c], and H.T. Bausum [d]

[a/]Office of Water, U.S. Environmental Protection Agency, Washington, DC, [b/]U.S. Army Medical Department, Military District of Washington, Washington, DC, [c/]U.S. Army Materiel Command, Alexandria, VA, [d/]U.S. Army Biomedical Research and Development Laboratory, Frederick, MD.

Munitions chemicals such as Zn, D, HCE, and WP exert a wide array of toxic effects in biological systems. Although an essential element, Zn exerts deleterious effects at higher doses. At 4.4 mg/kg/day, it decreases LDL-cholesterol and impairs immune function. Lower doses (1 to 2 mg/kg/day) increase HDL-cholesterol and decrease erythrocyte superoxide dismutase activity. Zn can also affect reproduction. D has LD50s of 2,800 and 3,700 mg/kg for female and male rats, respectively. At 105 mg/kg/day in rats, D causes nasal lesions (both sexes), kidney (male), and liver (female) effects. HCE primarily affects the kidney and male rats are more susceptible than females. At higher doses, HCE induces liver necrosis. It causes renal adenomas and carcinomas in male rats and is classified as a Group C chemical by the U.S. EPA. Acute WP exposure leads to fatty liver and jaundice in humans, while longer-term exposure causes "phossy jaw", a destructive bone disease. Data gaps for these munitions chemicals include lack of adequate cancer bioassays for Zn, D, and WP; reproductive studies on D and HCE; and developmental assays for D and WP.

1/ Abstract # 1030 of the 32nd Annual Meeting of the Society of Toxicology (March 1993). *The Toxicologist* 13(1):272.

INTRODUCTION

The United States Department of Defense relies on numerous chemicals, many of which are unique to or related primarily to military operations, or used to conduct activities necessary for national defense and security. Among these potentially harmful chemicals are WP, HCE, 1,4-Dithiane, and Zn.

The U.S. Army and the U.S. EPA established a Memorandum of Understanding to cooperate in developing Health Advisories (HAs) for munitions chemicals that may occur in drinking water. HAs, developed by the U.S. EPA Office of Drinking Water, list nonregulatory concentrations of drinking water contaminants at which adverse health effects are not expected to occur over specific exposure durations. They are neither legally enforceable standards, nor are they issued as federal regulations. HAs may or may not lead to the issuance of national standards or Maximum Contaminant Levels (MCLs). Each HA also contains information on the nature of the adverse health effects associated with the contaminant in drinking water. They provide informal technical guidance that assists public health officials when contaminations occur. HAs are developed for One-day, Ten-day, Longer term (7 years or 10% lifetime) and Lifetime exposures based on systemic, noncarcinogenic toxicity. A threshold dose-response relationship is assumed. Lifetime HAs are not recommended for known or probable human carcinogens (EPA classes A and B, respectively). A potency value (unit risk), derived from the linearized multistage model with 95% upper confidence limits, is used to calculate risk for a lifetime exposure to carcinogens in drinking water. The munitions HAs are based on systemic, noncarcinogenic endpoints usually from effects observed in animal studies.

ZINC

Empirical Formula	Zn++
Synonyms	ZnCl: Zinc Chloride; $ZnSO_4 \cdot 7H_2O$: Zinc sulfate heptahydrate; ZnO: Zinc oxide
Genotoxicity	Zinc compounds were generally negative in *in vitro* reverse bacterial mutation assays with *Salmonella typhimurium*.
Reproductive and Developmental Effects	Administration of 150 mg/kg/day causes maternal toxicity as evidenced by a decrease in weight gain. In contrast, dietary administration during reproduction caused no toxic effects at levels up to 250 mg/kg/day.
Cancer Classification	Zinc chloride may be a teratogen. Mutagenicity studies produced mixed results in which some cytotoxicity was indicated. Other zinc compounds are addressed in the zinc chloride Health Advisory. There is an absence of toxicological evidence for classifying zinc as a potential carcinogen. Zinc and zinc salts are assigned to Group D; not classifiable as to human carcinogenicity.
Reference Dose	0.3 mg/kg/day

Conclusion - Zinc

Based on the available animal toxicity data, the HA for One-day and Ten-day is 5 mg/L for the 10 kg child. The Longer-term HA for the 10 kg child is 3 mg/L and for the 70 kg adult is 12 mg/L. The Lifetime HA is 2 mg/L. These values are considered protective against toxic effects for the sensitive members of the population. The essentiality of zinc was considered in the derivation of these HA values. Currently, available data to assess the carcinogenic risk of zinc are inadequate, but in view of its physical and chemical properties, and considering that zinc is an essential element, it seems unlikely that zinc chloride will present a carcinogenic risk to humans at the levels considered safe for consumption. Using the U.S. EPA criteria for classification of carcinogenic risk, zinc chloride, and other zinc compounds currently meet the criteria for Group D; not classifiable as to human carcinogenicity. This group is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

1,4-DITHIANE

Empirical Formula	$C_4H_8S_2$
Synonyms	Diethylene disulfide, Diethylene sulfide, *p*-Dithiane, 1-4-Dithiacyclohexane, Tetrahydro 1,4-Dithiin, Triethylene trisulfide (early 1920s misnomer), Tetramethylene 1,4-disulfide (German equivalent)
Genotoxicity	1,4-dithiane was not mutagenic in the Ames Salmonella/Mammalian Microsome Mutagenicity Assay.
Reproductive and Developmental Effects	No studies were available for evaluating potential reproductive and developmental effects.
Cancer Classification	EPA Group D; not classifiable as to human carcinogenicity.
Reference Dose	0.01 mg/kg/day

Conclusion - 1,4-Dithiane

No studies on the health effects of 1,4-dithiane in humans were reported in the literature. HAs for One-day and Ten-day exposures are not recommended; data judged to be unsuitable. The LOAEL of 105 mg/kg/day is used in the derivation of the Longer-term HA. It is based on a 90-day gavage rat study (Schieferstein, 1987), which is the only study of appropriate length that was found in the available literature. The longer-term HA value for a 10 kg child is 0.4 mg/L and 1.0 mg/L for a 70 kg adult. A Lifetime HA of 0.08 mg/L (80 µg/L) has been determined. This value is considered protective against toxic effects for the sensitive members of the population. No studies on the potential carcinogenicity of 1,4-dithiane were found in the literature. Therefore, no estimation of excess cancer risk has been made. 1,4-dithiane was not mutagenic in Salmonella assays with and without metabolic activation. Using the U.S. EPA criteria for classification of carcinogenic risk, 1,4-dithiane meets the criteria for Group D; not classifiable as to human carcinogenicity. This group is for agents with inadequate human and animal evidence of carcinogenicity or for which no data is available.

HEXACHLOROETHANE (HCE)

Empirical Formula	C_8Cl_4
Synonyms	Carbon hexachloride, Perchloroethane, Ethanehexachloride, 1,1,1,2,2,2-Hexachloroethane, Hexachloroethylene, Avlothane, Distokal, Distopan, Distopin, Egitol, Falkitol, Fasciolin, Hexoram, Phenohep
Genotoxicity	HCE did not induce genetic effects in *in vitro Salmonella typhimurium* and *Saccharomyces cerevisiae* assays
Reproductive and Developmental Effects	No reproductive studies were found. A developmental effects study in rats orally exposed to HCE indicated that it is not teratogenic. Although gestation time was reduced, the number of viable fetuses was decreased, and there was an increase in fetal resorption.
Cancer Classification	EPA Group C; possible human carcinogen based on hepatocellular carcinomas in $B6C3F_1$ mice of both sexes.
Reference Dose	0.001 mg/kg/day

Conclusion - Hexachloroethane

Based on the available animal data, the HA for One-day and Ten-day exposures for a child is 5 mg/L. The Longer-term HA for the child is 130 µg/L and for the adult is 450 µg/L. Evidence is presented that HCE may meet the U.S. EPA criteria for Group C; possible human carcinogen based on animal data. The DWEL for HCE is 40 µg/L for lifetime exposure. The Lifetime HA is 1 µg/L assuming a 20% Relative Source Contribution (RSC) and equivocal evidence of carcinogenicity (Group C).

WHITE PHOSPHOROUS

Empirical Formula	P_4
Synonyms	WP; Yellow Phosphorous; Elemental Phosphorous
Genotoxicity	Negative results in *Salmonella typhimurium* with and without activation.
Reproductive and Developmental Effects	In a two-litter, one generation reproduction study with rats, increased mortality of parental females was attributed to difficulties during parturition. No information was found in the available literature regarding possible developmental effects.
Cancer Classification	EPA Group D; not classifiable as to human carcinogenicity.
Reference Dose	0.00002 mg/kg/day

Conclusion - White Phosphorus

Based on the available human and animal toxicity data, and considering the extreme toxicity of WP following oral exposure, HAs for One-day, Ten-day, and Longer-term exposures are not recommended. A Lifetime HA of 0.1 µg/L has been determined. This value is considered protective against toxic effects for the most sensitive members of the population. There are no currently available data adequate to assess the carcinogenic risk or developmental effects of WP. In view of the toxic effects of WP on the bone, it is recommended that screening studies be undertaken to assess the teratogenic potential of WP. Using the U.S. EPA criteria for classification of carcinogenic risk, WP meets the criteria for Group D; not classifiable as to human carcinogenicity. This group is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

Review of the Oral Toxicity of the Munitions Chemicals 2,4- and 2,6-Dinitrotoluene

J.J. Murphy [a], C.O. Abernathy , K.L. Khanna [b], W.C. Roberts [c], and H.T. Bausum [d]

[a]/Oncology Branch, Office of Toxic Substances, U. S. Environmental Protection Agency, Washington, DC; [b]/Human Risk Assessment Branch, Office of Water, U. S. Environmental Protection Agency, Washington, DC.; [c]/U.S Army Materiel Command, Alexandria, VA; [d]//U.S. Army Biomedical Research and Development Laboratory, Frederick, MD

Dinitrotoluene (DNT) is used in making dyes, chemicals, and explosives. Technical-grade (tg)-DNT is composed of 75% 2,4-isomer, 20% 2,6-isomer, and 5% other isomers. Humans exposed to DNT have reported vertigo, paralysis, nausea, and diarrhea. Acute toxicity studies in rodents indicate moderate toxicity. Subchronic oral studies in dogs, rats, and mice showed central neural lesions, methemoglobinemia, and testis damage at 25-400 mg/kg/day of 2,4-DNT, and similar effects with 2,6-DNT at 20-300 mg/kg/day. EPA Reference Doses (RfDs) are 0.002 mg/kg/day for 2,4-DNT and 0.001 mg/kg/day for 2,6-DNT. Both are considered to be B2 (probable human) carcinogens; therefore, no Lifetime Drinking-Water Health Advisory has been proposed.

(Individual opinions expressed are not necessarily those of the U.S. EPA or the U.S. Army.)

1/ Abstract # 1049 of the 32nd Annual Meeting of the Society of Toxicology (March 1993). *The Toxicologist* 13(1): 277.

INTRODUCTION

The U.S. Army and the U.S. EPA established a Memorandum of Understanding to cooperate in developing Health Advisories (HAs) for munitions chemicals that may occur in drinking water. HAs, developed by the U.S. EPA Office of Drinking Water, list nonregulatory concentrations of drinking water contaminants at which adverse health effects are not expected to occur over specific exposure durations. They are not legally enforceable standards, nor are they issued as federal regulations. HAs may or may not lead to the issuance of national standards of Maximum Contaminant Levels (MCLs). Each HA also contains information on the nature of the adverse health effects associated with the contaminant in drinking water. They provide informal technical guidance that assists public health officials when contaminations occur. HAs are developed for One-day, Ten-day, Longer-Term (7 years or 10% lifetime) and Lifetime exposures based on systemic, noncarcinogenic toxicity. A threshold dose-response relationship is assumed. Lifetime HAs are not recommended for known or probable human carcinogens (EPA classes A and B, respectively). A potency value (unit risk), derived from the linearized multistage model with 95% upper confidence limits, is used to calculate risk for a lifetime exposure to carcinogens in drinking water. The munitions HAs are based on systemic, noncarcinogenic endpoints usually from effects observed in animal studies.

In this paper, available health effects data were reviewed and evaluated. The HA values were determined using EPA methodology.

REFERENCE DOSE AND HEALTH ADVISORY VALUES OF 2,4- AND 2,6 DNT

Compound	2,4-Dinitrotoluene	2,6-Dinitrotoluene
RfD	0.002 mg/kg/day	0.001 mg/kg/day
1-Day HA for Drinking Water	0.5 mg/L	0.4 mg/L
10-Day HA	0.5 mg/L	0.4 mg/L
Longer-term HA (child)	0.3 mg/L	0.4 mg/L
Longer-term HA (adult)	1.0 mg/L	1.0 mg/L
Lifetime HA	Not applicable	Not applicable

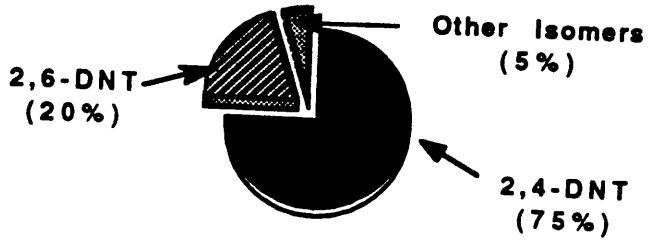
The U.S. EPA has classified 2,4- and 2,6-Dinitrotoluene in Group B2 (probable human carcinogen). The 1E-6 risk level is 5 micrograms of DNT in 1 liter of drinking water.

DNT USES

Industrial
- Dyes
- Toluenediamine synthesis (polyurethane production)

Military
- Explosives
  - Plasticizer
  - TNT Production

Technical Grade DNT Composition



SYSTEMIC HEALTH EFFECTS IN EXPERIMENTAL ANIMAL STUDIES—2,4-DNT

	Dog	Rat	Mouse
Acute (oral)	Not Studied	LD_{50} = 500 mg/kg Ataxia, Cyanosis	LD_{50} = 1640 mg/kg Ataxia, Cyanosis
Subchronic (13 wk, diet)	Neurotoxicity Hematological Testicular	Neurotoxicity Hematological Testicular	Neurotoxicity Hematological Testicular
Chronic/Lifetime (12-24 mo, diet)	Neurotoxicity Hematological Liver & Kidney	Testicular Reproduction	Hematological Testicular Liver & Spleen

SYSTEMIC HEALTH EFFECTS IN EXPERIMENTAL ANIMAL STUDIES—2,6-DNT

	Dog	Rat	Mouse
Acute (oral)	Not Studied	LD_{50} = 500 mg/kg Ataxia, Cyanosis	LD_{50} = 800 mg/kg Ataxia, Cyanosis
Subchronic (13 wk/diet)	Neurotoxicity Hematological Testicular	Hematopoietic Hematological Testicular	Hematopoietic Testicular
Chronic/Lifetime (12-24 mo/diet)	Not Studied	Not Studied	Not Studied

CRITICAL HEALTH EFFECTS—SYSTEMIC

2,4-DNT [Dog, 2 year study (Ellis et al., 1985)]

- Neurotoxicity and Hematological Effects
- LOAEL: 1.5 mg/kg/day
- NOAEL: 0.2 mg/kg/day

2,6-DNT [Dog, 13 week study (Lee et al., 1976)]

- Neurotoxicity, Hematological Effects, Mortality
- LOAEL: none
- NOAEL: 4 mg/kg/day
- FEL: 20 mg/kg/day

LOAEL: Lowest-Observed-Adverse-Effect-Level
NOAEL: No-Observed-Adverse-Effect-Level
FEL: Frank-Effect-Level

HUMAN HEALTH EFFECTS
(BASED ON INHALATION AND DERMAL EXPOSURES TO TG-DNT)

No reports of effects on exposure to pure isomers

General Effects

- Neurological (paralysis, unconsciousness, vertigo)
- Acute Toxic Hepatitis
- Ischemic Heart Disease
- Vomiting
- Hematological Effects
- Nausea
- Diarrhea

CARCINOGENICITY

- Human
  - No conclusive evidence in epidemiological studies
  - Slight increase in mortality from liver and bile duct cancer (Stayner et al., 1993)

- Animal
  - 2,4-DNT: Hepatocellular and mammary gland carcinomas in rats (Ellis et al., 1979)
  - Potency Factor: 6.8E-1/(mg/kg/day)—Derived from the Linearized Multistage model
  - 2,6-DNT: Hepatocellular carcinoma (Leonard et al., 1987)
  - tg-DNT: Hepatocellular carcinoma (Leonard et al., 1987)

PHYSICAL AND CHEMICAL PROPERTIES 2,4-DNT

CAS No.	121-14-2
Synonyms	2,4-Dinitrotoluol, 1-methyl-2,4-dinitrobenzene, NIOSH/OSHA (1985)
Chemical Formula	$CH_3C_6H_3(NO_2)_2$; NIOSH/OSHA (1985)
Molecular weight	182.14; NIOSH/OSHA (1985)
Melting point	70°C; NIOSH/OSHA (1985)
Boiling point	Decomposes (300°C); NIOSH/OSHA (1985)

PHYSICAL AND CHEMICAL PROPERTIES 2,6-DNT

CAS No.	606-20-2
Synonyms	2,6-Dinitrotoluol; 1-methyl-2,6-dinitrobenzene; NIOSH/OSHA (1985)
Chemical formula	$CH_3C_6H_3(NO_2)_2$; NIOSH/OSHA (1985)
Molecular weight	182.14; NIOSH/OSHA (1985)
Boiling Point	Decomposes (260°C); NIOSH/OSHA (1985)

CONCLUSIONS - 2,4/2,6-DNT

1. 2,4- and 2,6-DNT are isomers having similar toxic effects and potency.

2. The acute median lethal dose of 2,4- or 2,6-DNT in rodents is in the moderately toxic range.

3. 2,4- and 2,6-DNT have been classified as B2 carcinogens (probable human carcinogens).

4. Repeated administration has adverse effects on a variety of target organs, including liver, kidney, spleen, blood, testis, and nervous system at 25-400 mg/kg/day of 2,4-DNT and 20-300 mg/kg/day of 2,6-DNT.

Review of the Oral Toxicity of Selected Methylphosphonic Acids[1]

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Since the phosphonates, diisopropyl methylphosphonic acid (DIMP), dimethyl methylphosphonic acid (DMMP), isopropyl methylphosphonic acid (IMPA), and methylphosphonic acid (MPA), are potential or actual drinking water contaminants, a review of their oral toxicity is appropriate. Reported human effects are limited to mild and moderate DMMP-induced skin irritation. In animals, the acute oral toxicity of these phosphonates is slight to moderate (LD_{50}s $\geq$ 800 mg/kg) characterized by depressed activity, ataxia, and other neurological effects. DIMP did not demonstrate any treatment-related toxicity or developmental and reproductive effects in studies that ranged from 14 days to 26 weeks with doses up to 315 mg/kg/day. Other than acute rodent information, the toxicological data for IMPA is limited to a 90-day study with rats; there were no gross or histological organ effects nor were body weight or hematological parameters affected at doses up to 399 mg/kg/day. DMMP's major effects—testicular, epididymal, spermic, and reproductive toxicity—were demonstrated in several rat studies at exposures $\geq$ 250 mg/kg/day for 13 weeks. Genotoxicity studies are reported only for DIMP and DMMP; neither was mutagenic in non-mammalian assay systems, but they were mutagenic or genotoxic in some mammalian *in vivo* and *in vitro* systems. The only cancer bioassay is on DMMP; it caused renal transitional cell papilloma and carcinoma and mononuclear cell leukemia in male rats only. Toxicological data for MPA is limited to acute LD_{50} studies in rats and mice. U.S. EPA drinking water advisory levels are established for DIMP, DMMP, and IMPA.

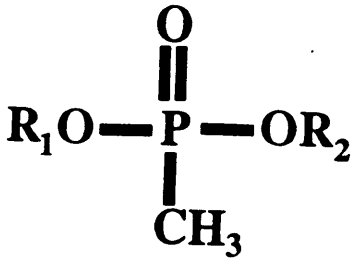
1/ Abstract # 1050 of the 32nd Annual Meeting of the Society of Toxicology (March 1993). *The Toxicologist* 13(1):277.

INTRODUCTION

The methylphosphonic acids used in munitions chemicals production have entered the environment in some areas. Thus, the production, use, and storage of these munitions are a concern of federal and local public health agencies. Some drinking water contamination may result from production, wastewater discharge, and/or seepage from storage facilities.

To recognize and deal with potential risks from methylphosphonic acids exposure, their potential human health effects must be understood. Accordingly, we have reviewed the health effects of selected methylphosphonic acids. The U.S. Army Medical Research and Development Command (USAMRDC) and the U.S. EPA have been collaborating through an Interagency Agreement (IAG) to study the effects of long-term exposure to methylphosphonic acids. The U.S. EPA has recommended Drinking Water Health Advisory (HA) levels to protect the public.

STRUCTURES



Compound	R1	R2
Methylphosphonic Acid	H	H
Dimethyl Methylphosphonate	CH_3	CH_3
Isopropyl Methyphosphonic Acid	H	$CH(CH_3)_2$
Diisopropyl Methyphosphonate	$CH(CH_3)_2$	$CH(CH_3)_2$

DIMETHYLPHOSPHONATE (DMMP)

Genotoxicity	Negative in *in vitro Salmonella typhimurium* assays; positive mutagen in mouse lymphoma cells and Chinese Hamster Ovary (CHO) cells with and without metabolic activation; induced sex-linked recessive lethal mutations in *Drosophila* and positive results in dominant-lethal assays in mice and rats.
Reproductive and Developmental Effects	Toxic to the male reproductive system. Decreased numbers of live fetuses and increased resorptions in female rats. Not found to be a teratogen.
Cancer Classification	Group C; possible human carcinogen based on the occurrence of mononuclear cell leukemia and kidney transitional cell papillomas and carcinomas in male F344 rats.
Reference Dose	0.2 mg/kg/day; based on adverse reproductive effects (resorptions) in untreated female rats mated with males gavaged with 179 mg/kg/day DMMP for 90 days.
Drinking Water Equivalent Level	7 mg/L

Health Advisory Values:

One-day	2 mg/L
Ten-day	2 mg/L
Longer-term (10kg child)	2 mg/L
Longer-term (70kg adult)	6 mg/L
Lifetime	0.1 mg/L

Cancer Risk Estimates

q1* (LMS)	5E-3/(mg/kg/day)
Drinking Water Unit Risk	1E-7/(µg/L)

Risk Level	Drinking Water Concentration
E-4 (1 in 10,000)	7E + 2 µg/L
E-5 (1 in 100,000)	7E + 1 µg/L
E-6 (1 in 1,000,000)	7E + 0 µg/L

METHYLPHOSPHONIC ACID (MPA)

The available literature on MPA is not sufficient to determine Drinking Water Health Advisory Values.

ISOPROPYL METHYLPHOSPHONIC ACID (IMPA)

Genotoxicity	Negative in in vitro *Salmonella typhimurium* (Ames) tests with and without metabolic activation
Reproductive and Developmental Effects	No information was found in the available literature regarding the reproductive or developmental effects of IMPA.
Cancer Classification	Group D; not classifiable as to human carcinogenicity. No information was found in the available literature regarding the carcinogenic potential of IMPA.
Reference Dose	0.1 mg/kg/day based on absence of systemic effects in rats given up to 278.9 mg/kg/day IMPA in drinking water for 90 days
Drinking Water Equivalent Level	4 mg/L

Health Advisory Values

One-day	30 mg/L
Ten-day	30 mg/L
Longer-term (10kg child)	30 mg/L
Longer-term (70 kg adult)	100 mg/L
Lifetime	0.7 mg/L

DIISOPROPYL METHYLPHOSPHONATE (DIMP)

Genotoxicity	Negative in *in vitro Salmonella typhimurium* and *Saccharomyces cerevesiae* assays with and without metabolic activation.
Reproductive and Developmental Effects	Significant decrease in viability of F3a and F3b Sprague-Dawley rat pups in a 3-generation drinking water study. No other reproductive or developmental effects were found. The results of a mink study were inconclusive.
Cancer Classification	Group D; not classifiable as to human carcinogenicity.
Reference Dose	0.08 mg/kg/day based on absence of systemic effects in dogs given up to 75 mg/kg/day IMPA in the diet for 90 days.
Drinking Water Equivalent Level	3 mg/L

Health Advisory Values

One-day	8 mg/L
Ten-day	8 mg/L
Longer-term (10kg child)	8 mg/L
Longer-term (70 kg adult)	30 mg/L
Lifetime	0.6 mg/L

CONCLUSIONS - Methylphosphonic Acids

- The U.S. EPA has determined that there is sufficient toxicological information to establish drinking water HAs for IMPA, DIMP, and DMMP; available data is not sufficient for MPA.

- The critical effects (i.e., basis for U.S. EPA advisory values) differ among these methylphosphonic acids. There are no significant effects noted in studies with IMPA and DIMP. DMMP appears to have substantial adverse reproductive effects in males and is a possible human carcinogen based on equivocal observations in male rats.

- All lifetime HAs assume that water contributes only 20% to the overall body burden, i.e., Relative Source Contribution (RSC) = 20%.

- Of these methylphosphonic acids, DMMP has the most extensive experimental data base with systemic and carcinogenic effects noted in several animal species. DMMP also induces the formation of alpha-2u-microglobulin renal effects in male rats, which were considered in the risk assessment of this chemical.

The views expressed in this presentation do not necessarily represent the opinions or official positions of the U.S. EPA or of the Department of the Army.

REVIEW OF THE GENETIC AND CARCINOGENIC ACTIVITY OF THE NITRATED MUNITIONS CHEMICALS 1/

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Recent public interest in munitions chemicals indicates that a review of the genotoxicity and carcinogenicity of these chemicals is appropriate. Accordingly, we have examined the effects of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), nitrocellulose (NC), nitroguanidine (NQ), trinitroglycerol (TNG), 1,3-dinitrobenzene (1,3-DNB) and 2,4,6-trinitrotoluene (TNT). RDX, NC, NQ and TNG had little or no activity in a variety of test systems, but both 1,3-DNB and TNT were mutagenic in the *Salmonella* assay. No carcinogenic data are available for NQ and 1,3-DNB, and NC exerted no carcinogenic effects in rats, mice or dogs. TNG and RDX exerted hepatocarcinogenic effects (EPA Classification - Group C [possible carcinogen]) in rats and mice, respectively. On the other hand, TNT (also classified as a Group C chemical) caused urinary bladder carcinoma in rats. Comparison of various mechanisms that may be involved in the expression of the toxicity of TNG, RDX and TNT will be discussed.

Partially supported by an Interagency Agreement (IAG) between the U.S. EPA and the U.S. Army. The conclusions in this abstract are those of the authors and not necessarily those of the U.S. EPA or of the U.S. Army.

1/ Abstract # 292 of the 31st Annual Meeting of the Society of Toxicology (February 1992). *The Toxicologist* 12(1): 95.

Introduction

The nitrated munitions chemicals have played and continue to play a significant role in history. Since these chemicals have been produced and used in large quantities, it is inevitable that environmental contamination occurs. Sources of contamination include incomplete combustion of the munitions, wastewater discharge from manufacturing plants, seepage from sedimentation sites, and atmospheric release. In addition, workplace exposure also occurs during manufacture. The primary sources of drinking water contamination come from wastewater discharge and seepage.

To recognize and deal with the potential risks from exposure to the nitrated munitions chemicals, it is necessary to understand the potential human health effects of these compounds. Accordingly, we have reviewed and catalogued the health effects of the nitrated munitions. The U.S. Army Medical Research and Development Command (USAMRDC) and the U.S. Environmental Protection Agency (EPA) have been collaborating through an Interagency Agreement (IAG) to study the effects of long term exposure to these substances in drinking water. This poster focuses on potential carcinogenic risk after exposure to nitrated munitions chemicals.

Mutagenicity and Genotoxicity

	DNB[a]	HMX	NC	NQ	RDX	TNG	TNT
Assays Performed With and Without Metabolic (S9) Activation							
• *Salmonella typhimurium*	+[b]	-	-	-	-	-	+
• *Saccharomyces cerevisiae*	-	-		-	-	-	-
• *Escherichia coli*	-		-				-
Metabolic Activation Not Evaluated or Not Appropriate for Assay							
• Unscheduled DNA Synthesis:							
° Rat Hepatocytes (in vitro)	-						
° Rat Hepatocytes (in vivo/ in vitro)							-
° Human Lung Fibroblasts						-	
				-	-		-
• Chromosome/Chromatid in vivo Assays:							
° Kidney Cells (Dog & Rat)			-				
° Lymphocytes (Dog & Rat)						-	
° Bone Marrow Cells (Rat)			-			-	
° Fibroblasts (Chinese hampster)			-	-		-	
• Sister Chromatid Exchange (CHO Cells)				-			
• Mouse Lymphoma Cell Forward Mutation Assay				-			
• Mouse Bone Marrow Micronucleus Assay				-			
• CHO-K1 Cell Single Gene Mutation Assay							-
• Dominant Lethal Assay (Rat and/or Mouse)						-	
				-	-	-	

NOTES:

a/ ABBREVIATIONS: 1,3-Dinitrobenzene (DNB), Octahydro-1,3,5,7-tetranitro-3,5,7-tetrazocine (HMX), Nitrocellulose (NC), Nitroguanidine (NQ), Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), Trinitroglycerol (TNG), and 2,4,6-Trinitrotoluene (TNT)

b/ Positive results are indicated by "+". Negative results are indicated by "-". Blank spaces indicate that an assay was not performed.

Carcinogenicity

1,3-Dinitrobenzene, HMX, Nitroguanidine

- No human epidemiological or animal carcinogenic studies found in the literature.
- Classified in EPA Group D, Not Classifiable as to Human Carcinogenicity.

Nitrocellulose

- Negative in studies with Beagle dogs, rats, and CD-1 mice in feeding studies up to 24 months duration.
- Not Yet Classified by EPA.

RDX

- Positive for hepatocellular carcinomas and adenomas in female B6C3F1 mice in a 24 month feeding study; negative for male mice.
- Negative in male and female Sprague-Dawley and Fischer 344 rats in 24 month feeding studies.
- Classified in EPA Group C, Possible Human Carcinogen.
- Potency Factor (Linearized Multistage Model): 1.1 E-1/(mg/kg/day)

Trinitroglycerol

- Positive for hepatocellular carcinoma in male and female Charles River CD rats in a 24 month feeding study.
- Negative in beagle dogs (12 month dosing via capsule) and CD-1 mice (24 month feeding study).
- Not Yet Classified by EPA (probable Group C, unverified).
- Potency Factor(Linearized Multistage Model): 1.66 E-2/(mg/kg/day)

2,4,6-Trinitrotoluene

- Positive for urinary bladder papillomas and carcinomas in female Fischer 344 rats in a 24 month feeding study; negative in males.
- Negative in B6C3F1 mice in a 24 month feeding study.
- Classified in EPA Group C, Possible Human Carcinogen.
- Potency Factor (Linearized Multistage Model): 3 E-2/(mg/kg/day)

Conclusions

1. A review of the genotoxic and carcinogenic effects of some nitrated munitions has not revealed a consistent pattern of effects. For example:

    a. TNG and RDX were not mutagenic in *Salmonella*, but induced liver cancer in rats and mice, respectively;

    b. Only TNT was mutagenic in *Salmonella* and carcinogenic (bladder cancer in rats only; and

    c. TNT and RDX did not cause cancer in both rats and mice and, therefore, are classified as Group C chemicals (possible carcinogens). TNG is similar to RDX in activity.

2. The lack of a discernable pattern among the nitrated munitions chemicals may be due to database deficiencies. Studies in the following areas would assist in the evaluation of these chemicals:

    a. Pharmacokinetic data on TNT, TNG, RDX, AND 1,3-DNB;

    b. Metabolic rates and patterns for the chemicals; and

    c. Carcinogenic studies for 1,3-DNB.

SURVEY OF LONG-TERM NONCARCINOGENIC TOXICITY OF NITRATED MUNITIONS CHEMICALS IN ANIMALS 1/

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1,3-Dinitrobenzene (DNB) produced splenic hemosiderosis, neurotoxic signs, and testicular damage at 6 mg/kg/day (mkd) for 12 weeks. Nitrocellulose (NC) seemed nontoxic in rats and dogs, but blocked the intestine in mice. Nitroguanidine (NQ), at doses up to 1000 mkd, increased water consumption and urine output. RDX (hexahydro-1,3,5-trinitro-1,3,5-triazine) caused hepatomegaly, renal necrosis and mortality at 40 mkd. Trinitroglycerol (TNG), at 1070 mkd, depressed weight gain and caused methemoglobinemia, while 2,4,6-trinitrotoluene (TNT) caused anemia and altered lipid metabolism at 50 mkd in rats.

Partially supported by an Interagency Agreement (IAG) between the U.S. EPA and the U.S. Army. The conclusions in this abstract are those of the authors and not necessarily those of the U.S. EPA or of the U.S. Army.

1/ Abstract # 293 of the 31st Annual Meeting of the Society of Toxicology (February 1992). *The Toxicologist* 12(1): 95.

Introduction

Nitrated munitions are reactive chemicals. These compounds exert pharmacological effects and may have health or environmental consequences. The U.S. Army Medical Research and Development Command (USAMRDC) and the U.S. Environmental Protection Agency (EPA) have been collaborating through an Interagency Agreement (IAG) to study the effects of long-term exposure to these substances in drinking water. This poster focuses on the chronic toxicity of selected nitrated munitions chemicals.

It will be noted that nitrated munitions affect a variety of target organs, including the liver, kidney, nervous system, cardiovascular and hematopoietic systems, and testis. Methemoglobinemia is a frequent, but not universal, consequence of exposure. Some of the effects that have been demonstrated in experimental animals may be mechanical (intestinal obstruction) or physiological (inducing diuresis) rather than toxic, *per se*.

Long-Term Noncarcinogenic Effects

1,3-Dinitrobenzene

EPA RfD derived from a NOAEL of 4E-1 mg/kg/day based on a rat study where the LOAEL was 1.14E+0 mg/kg/day for testicular and splenic effects.

- **Human**
  - Methemoglobinemia
  - Data Limited to Reports of Acute Occupational Exposure
- **Animal**
  - Splenic Effects - Increased Spleen Weight, Hemosiderin Deposition
  - Testicular Effects - Reduced Testicular Weight, Decreased Spermatogenesis, Atrophied Seminiferous Tubules
  - Neurotoxic Effects - Impaired Movement, Paresis, Loss of Equilibrium, Muscle Rigidity

HMX

EPA RfD derived from a NOAEL of 5E+1 mg/kg/day based on a rat study where the LOAEL was 1.5E+2 mg/kg/day for liver effects.

- **Human**
  - Research Data Limited to 2 Occupational Exposure Studies
- **Animal**
  - Liver Effects - Enlarged Centrilobular Cells
  - Renal Effects - Tubular Focal Atrophy and Dilitation

Nitrocellulose

- **Human**
  - No Toxic Effects
- **Animal**
  - Intestinal Impaction in Mice
  - Weight Loss

Nitroguanidine

EPA RfD derived from a NOAEL of 3.16E+2 mg/kg/day based on a rat study where the LOAEL was 1E+3 mg/kg/day for organ and body weight changes.

- **Human**
  - No Studies Found In The Literature
- **Animal**
  - Increased Water Consumption
  - Increased Urinary Output
  - Increased Heart Weight

Long-Term Noncarcinogenic Effects (Continued)

RDX

EPA RfD derived from a NOAEL of 3E-1 mg/kg/day based on a rat study where the LOAEL was 1.5E+0 mg/kg/day for prostate effects.

- **Human**
  - CNS Effects - Convulsions, Unconsciousness, Amnesia
  - Insomnia and Restlessness
  - Renal Effects - Oliguria, Hematuria, Elevated BUN
- **Animal**
  - CNS Effects - Convulsions
  - Anemia
  - Weight Loss
  - Testicular Atrophy
  - Hepatotoxicity/Increased Liver Weight
  - Vomiting
  - Renal Toxicity
  - Prostate Inflammation

Trinitroglycerol

No RfD. EPA advisory values derived from a no effect level of 5E-3 mg/kg for vasodilation in humans.

- **Human**
  - Exposure Tolerance
  - Ischemic Heart Disease
  - Chest Pains
  - Death
- **Animal**
  - Methemoglobinemia
  - Liver Lesions
  - Behavioral Alterations

2,4,6-Trinitrotoluene

EPA RfD derived from a LOAEL of 5E-1 mg/kg/day based on dog liver effects.

- **Human**
  - Red Discoloration in Urine
  - Aplastic Anemia
  - Hepatitis
  - Death
- **Animal**
  - Hematopoiesis
  - Decreased Weight
  - Spleen Enlargement
  - Anemia
  - Increased Liver Weight
  - Myelofibrosis of Bone Marrow
  - Hepatomegaly
  - Altered Lipid Metabolism

Conclusions

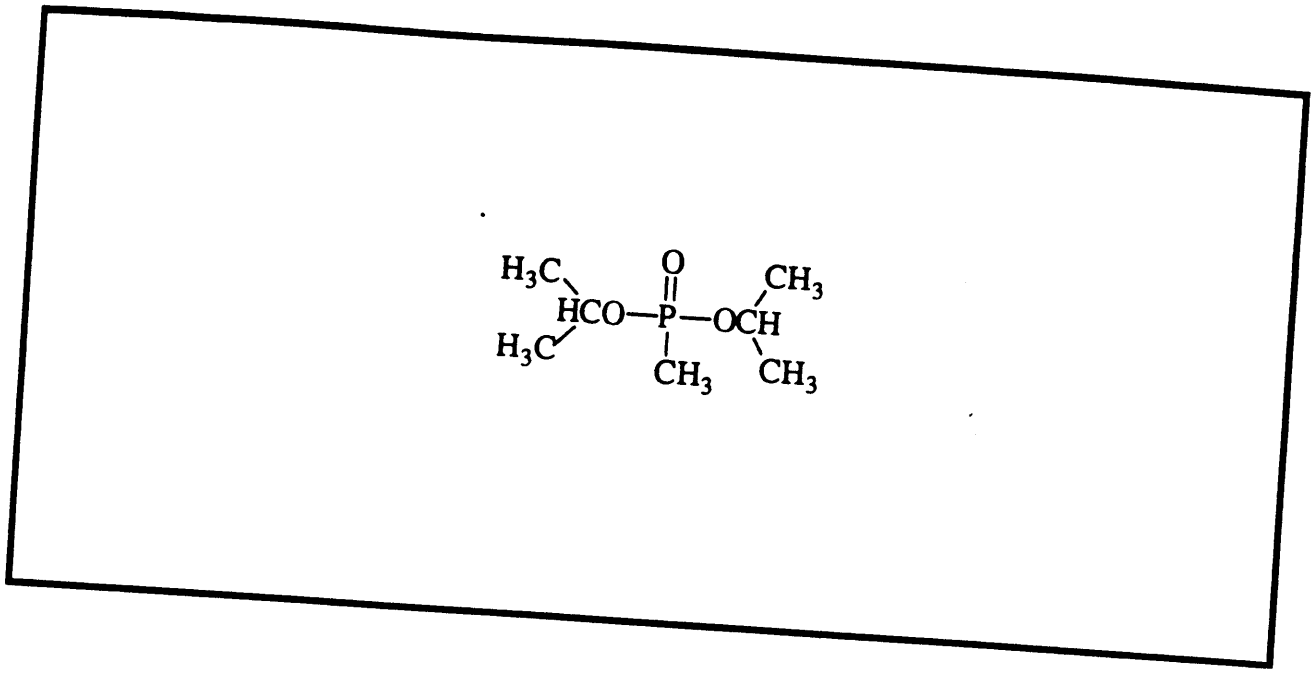
1. The variety of target organs affected by the nitrated munitions chemicals suggests multiple mechanisms of actions.

2. These chemicals vary from highly active to practically inert.

3. Methemoglobinemia is frequently caused by nitrated munitions chemicals, but the effect is not caused by all of them.

4. The U.S. Army and EPA have worked together effectively in risk assessment of nitrated munitions chemicals.

Diisopropylmethyl Phosphonate



- **EPA Reference Dose (RfD):** 0.08 mg/kg/day

- **EPA Cancer Classification:** Group C, possible human carcinogen.

- **Health Advisory Values:**

One-Day	8 mg/L
Ten-Day	8 mg/L
Longer-Term (child)	8 mg/L
Longer-Term (adult)	30 mg/L
Lifetime	0.6 mg/L

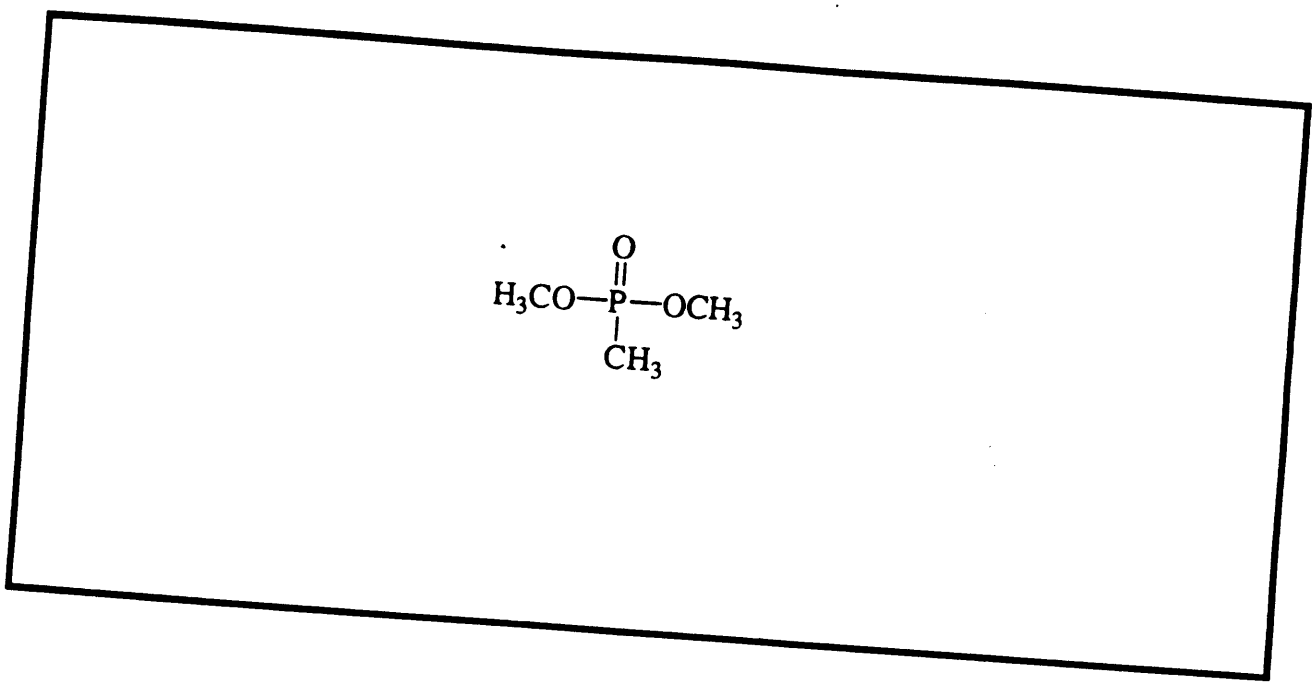
Diisopropyl methylphosphonate (DIMP) is a by-product produced during the manufacture of the nerve gas isopropyl methyl-phosphonofluoridate (GB or Sarin), where it occurs as 2%-3% of the crude nerve agent, and is neither a metabolite or degradation product of GB (Rosenblatt et al., 1975). There are no reported commercial or industrial uses reported for DIMP. It is known to have contaminated groundwater at and adjacent to GB production and storage sites (Robson, 1981). Studies of foods exposed to DIMP in the laboratory indicate a potential for the substance to bioconcentrate and pass through the food chain (O'Donovan and Woodward, 1977; Guenzi et al., 1979). There are no reported systemic effects of humans exposure to DIMP. There is, however, a report of the occurrence of skin irritation in people who contacted water in a disposal basin that contained DIMP (Thoburn and Gunter, 1981). The relationship of the skin irritation to DIMP is unclear because the basin contained a variety of pesticides and other organic substances.. In a modified Draize skin sensitization test of 215 adult volunteers, there was no evidence of allergic contact dermititis (Maibach, 1987).

All of the EPA HA values are derived from a feeding study where Beagle dogs were administered DIMP in drinking water for 90 days (Hart, 1980). Also considered acceptable for deriving HAs were 90-day feeding studies in rats and mice (Hart, 1976). The NOAELS for all three studies were 75, 150, and 315 mg/kg/day, respectively. A 3-generation study in rats did not result in any reproductive toxicity and indicated a NOAEL of 315 mg/kg/day (Hart, 1980). Because of the absence of data that distinguished between low effect and no effect levels, the most conservative NOAEL, 75 mg/kg/day in dogs, is used as an estimate for the HAs.

Hart (1980) did not detect mutagenicity from DIMP in a series of *Salmonella* assays. Tice (1990a-b; 1991a-g) showed that DIMP produced chromosomal abberation in Chinese hampster cells; however, it was negative in a battery of other genotoxicity studies involving microbial and mammalian cell assays in addition to *in vivo* testing in rats and mice.

There were no carcinogenicity studies found in the literature; therefore, DIMP is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant.

Dimethyl Methylphosphonate



- **EPA Reference Dose (RfD):** 2E-1 mg/kg/day

- **EPA Cancer Classification:** Group C, possible human carcinogen; potency factor (q_1^*) = 5 E-3 $(mg/kg/day)^{-1}$ by the LMS[1] model

- **Health Advisory Values:**

One-Day	2 mg/L
Ten-Day	2 mg/L
Longer-Term (child)	2 mg/L
Longer-Term (adult)	6 mg/L
Lifetime	0.1 mg/L

1/ Linearized Multistage

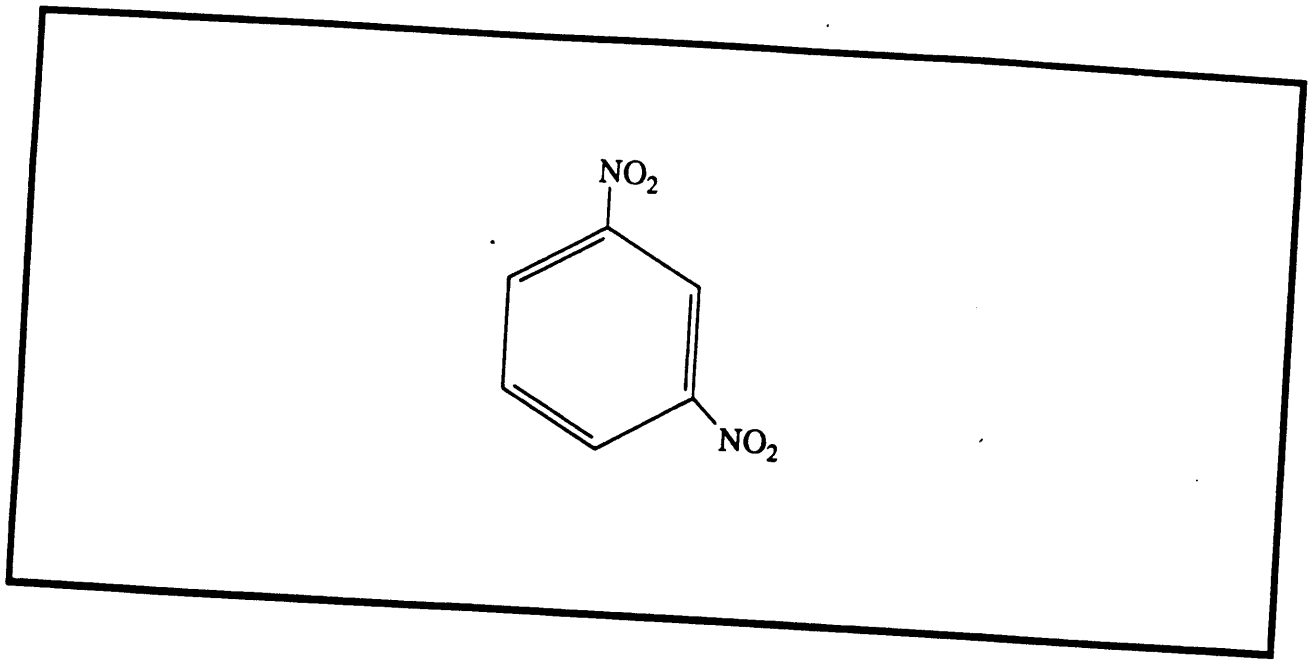
Dimethyl methylphosphonate (DMMP) is a colorless liquid used commercial in resins, latex, coatings, and flame retardants. The military uses it to simulate nerve agents for testing chemical agent detection equipment and techniques (Berkowitz et al., 1978). Synonyms include Dimethyl methane phosphonate and Fryol DMMP. Sources of potential human exposure are from occupational settings, military field uses, and effluents from production facilities that could contaminate water sources. Reported humans effects are limited to mild and severe irritation when DMMP was administered to the skin in a patch test (Ciba-Geigy, 1976).

EPA short term advisory values (1-day, 10-day, and longer-term) for a 10 kg child are based on increased resorptions in female rats that were impregnated by males that were administered DMMP via gavage for 90-days (Dunnick et al., 1984a). The HAs are derived from a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 250 mg/kg/day (179 mg/kg/day when adjusted from 5- to 7-day/week dosing). DMMP toxicicity to the male reproductive system is characterized by decreased sperm motility and count, male fertility index, and degenerative changes to the testes, epididymis, and prostate gland at doses of 250 to 2,000 mg/kg/day (NTP, 1987; Dunnick et al., 1984a; Chapin et al., 1984). Some kidney effects observed in DMMP-treated male rats are indicative of alpha-2u-microglobulin nephrotoxicity and are not considered relevant to humans (Baetcke et al., 1991).

DMMP was mutagenic in several assays to include: forward mutation assays, sister chromatid exchanges with Chinese hamster ovary (CHO) cells, and *Drosophila* sex-linked recessive lethal mutations (Tice, 1990b; NTP, 1987). It was positive in dominant-lethal assays with mice and rats (Dunnick et al., 1984a,b). However, DMMP showed limited evidence of clastogenicity in CHO cells, was not mutagenic in several strains of *Salmonella*, did not increase neoplastic transformations in BALB/c 3T3 cells, and did not induce reciprocal translocations in *Drosophila* (NTP, 1987; Sivak, 1983).

DMMP produced kidney transitional cell papillomas and carcinomas and mononuclear cell leukemia in male F344/N rats (NTP, 1987) and therefore, is classified as an EPA Group C (possible human) carcinogen (U.S. EPA, 1992a).

1,3-Dinitrobenzene



- **EPA Reference Dose (RfD):** 0.0004 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	0.04 mg/L
Ten-Day	0.04 mg/L
Longer-Term (child)	0.04 mg/L
Longer-Term (adult)	0.14 mg/L
Lifetime	0.001 mg/L

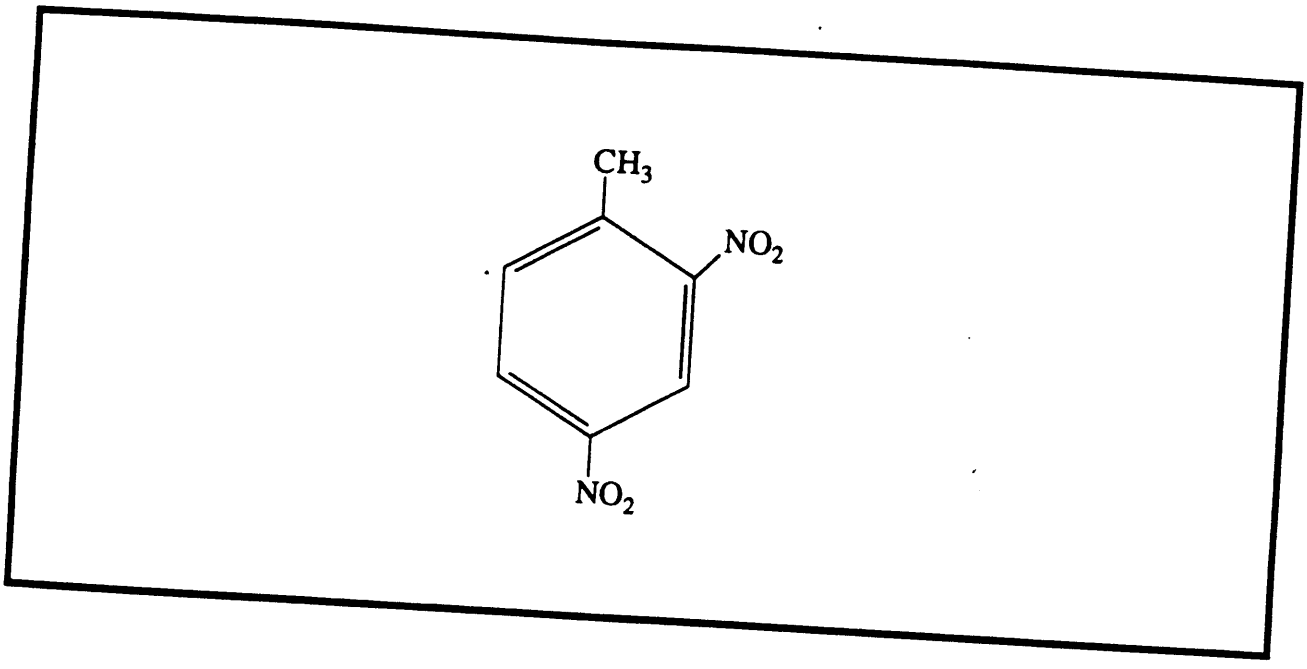
1,3-Dinitrobenzene (DNB) is: a by-product in the manufacture of trinitrotoluene; an intermediate in the production of phenylenediamine (a dye intermediate), is used in organic synthesis, and a camphor substitute in celluloid production (U.S. EPA, 1985a). Synonyms include *m*-dinitrobenzene, *m*-DNB, and 1,3-DNB. Sources of human exposure are occupational and environmental from production and manufacture wastewater effluents (U.S. EPA, 1985a; Okubo and Shigeta, 1982; Ishihara et al., 1976). Effects to reported in humans include cyanosis, methemoglobinemia, anemia, palpitations, dizziness, fatigue, and hemolytic jaundice (Gleason et al., 1969; Okubo and Shigeta, 1982; Ishihara et al., 1976).

EPA advisory values are derived from a study where Carsworth Farm rats were administered DNB in drinking water for 16 weeks (Cody et al., 1981). Effects on the spleen (hemosiderin deposition), testes (reduced weight and spermatogenesis) occurred at 1.14 mg/kg/day, the Lowest-Observed-Adverse-Effect-Level (LOAEL); there were no effects observed at 0.4 mg/kg/day, the No-Observed-Adverse-Effect-Level (NOAEL).

There are mixed results for mutagenicity in assays with *S. typhimurium*; however, the majority of the assays suggest that DNB is mutagenic with or without metabolic activation (Spanggord et al., 1982; McGregor et al., 1980; Kawai et al., 1987; Chiu et al., 1978; Garner and Nutman, 1977; Probst et al., 1981). In the presence or absence of metabolic activation, there was no DNB induced mitotic gene conversion in *S. cerevisiae* and no effect to DNA repair in *E. coli* (McGregor et al., 1980). Unscheduled DNA synthesis (UDS) was not increased in cultivated hepatocytes by DNB (Probst et al., 1981).

There were no carcinogenicity studies found in the literature; therefore, DNB is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1991a).

2,4-Dinitrotoluene



- **EPA Reference Dose (RfD):** 0.002 mg/kg/day

- **EPA Cancer Classification:** Group B2, probable human carcinogen; potency factor (q_1^*) = 6.8 E-1 (mg/kg/day)$^{-1}$ by the LMS[2] model

- **Health Advisory Values:**

One-Day	0.5 mg/L
Ten-Day	0.5 mg/L
Longer-Term (child)	0.3 mg/L
Longer-Term (adult)	1.0 mg/L
Lifetime	NA

2/ Linearized Multistage

Dinitrotoluene (DNT) is a white- to buff-colored solid and commonly occurs as a mixture that may consist of up to six isomers. Uses include military munitions, dye manufacture, and toluenediamine (polyurethane intermediate) synthesis (ATSDR, 1989; NIOSH, 1985; Small and Rosenblatt, 1974). Technical grade DNT (tg-DNT) is a mixture composed of approximately 76.5% 2,4-DNT, 18.8% 2,6-DNT, and 5% other DNT isomers.

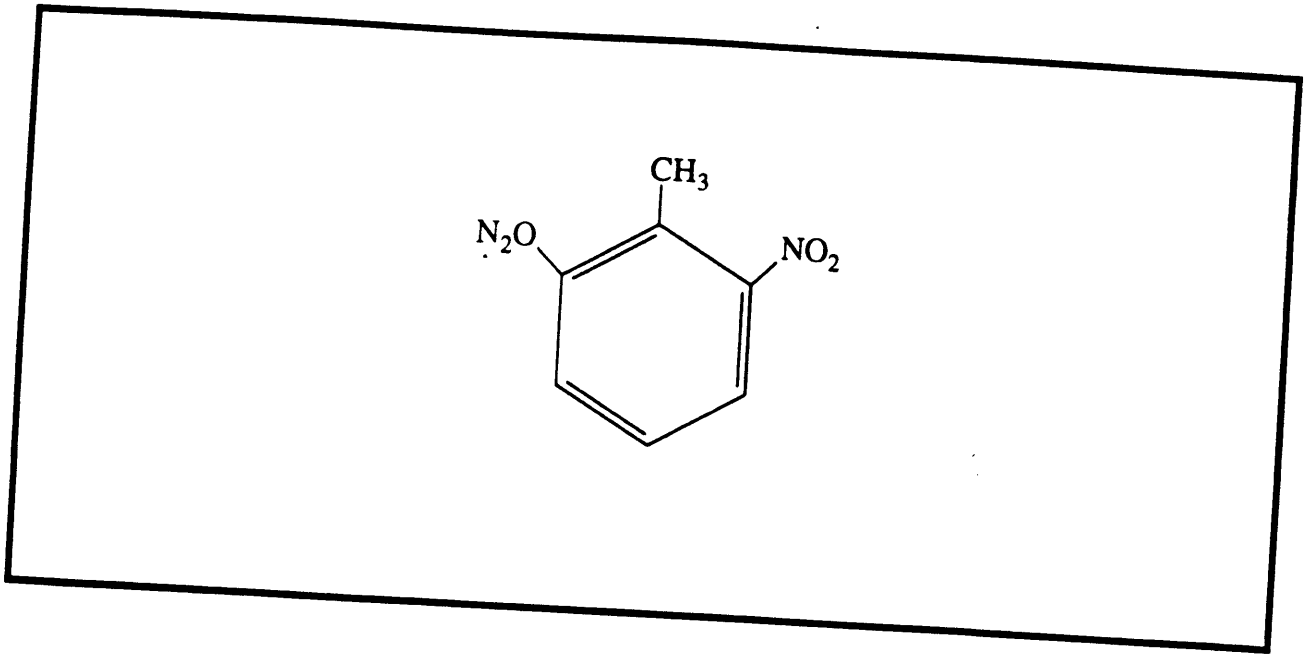
In humans, inhalation and dermal occupational exposures to 2,4- and tg-DNT suggest effects to the heart, circulatory, and central nervous systems (Etnier, 1987; U.S. EPA, 1980, 1986). Chronic exposure produces nausea, vertigo, methemoglobinemia, cyanosis, extremity pain or paresthesia, tremors, paralysis, chest pain, and unconsciousness. Rats, mice, and dogs, orally administered 2,4-DNT for 90-days to lifetime, developed severe reproductive effects in both sexes, and reduced viability and body weight in offspring (Hong et al., 1985; Lee et al., 1985; Ellis et al., 1985). It has not been shown to be a teratogen (Price et al., 1985).

The EPA One- and Ten-day HAs are based on decreased body weight and food consumption, and serum chemistry changes in male and female Sprague-Dawley rats, and testicular lesions in males fed 2,4-DNT for 14 days (LOAEL = 45 mg/kg/day) (McGowan et al., 1983). Dose-related decreases in body weight gain and food consumption in rats (LOAEL = 34 mg/kg/day) administered 2,4-DNT in the diet for 13 weeks (Lee et al, 1985), is the basis for the Longer-term HAs. The Drinking Water Equivalent Level (100 µg/L) and RfD (2E-3) are based on neurotoxicity, Heinz body formation, and biliary tract hyperplasia in dogs (NOAEL = 0.2 mg/kg/day) dosed orally with 2,4-DNT for 2 years (Ellis et al., 1985).

In *Salmonella* assays, 2,4-DNT is a weak mutagen; however, its metabolites are mutagenic (Couch et al., 1987). The DNTs are not genotoxic in mammalian cells *in vitro*, in mouse and rat dominant lethal tests, and in *Drosophila* systems (Abernethy and Couch, 1982; Styles and Cross, 1983; Rickert et al., 1984; Ellis et al., 1979; Soares and Lock, 1980).

DNT is classified B2 (probable human carcinogen) and thus a Lifetime HA is not recommended (U.S. EPA, 1992d). The cancer potency is associated with hepatocellular and mammary gland carcinogenic activity in rats after 2,4-DNT treatment (Ellis et al., 1979). 2,4-DNT also may be a promoter (Leonard et al., 1983, 1986).

2,6-Dinitrotoluene



- **EPA Reference Dose (RfD):** 0.001 mg/kg/day

- **EPA Cancer Classification:** Group B2, probable human carcinogen; potency factor (q_1^*) = 6.8 E-1 (mg/kg/day)$^{-1}$ by the LMS3 model

- **Health Advisory Values:**

One-Day	0.4 mg/L
Ten-Day	0.4 mg/L
Longer-Term (child)	0.4 mg/L
Longer-Term (adult)	1.0 mg/L
Lifetime	NA

3/ Linearized Multistage

Dinitrotoluene, (DNT) is a white- to buff-colored solid at room temperature and commonly occurs as a prominent component in mixtures that may consist of two or more of the six DNT isomers. It has been used in military munitions, dye manufacture, and the synthesis of toluenediamine (the organic intermediate used in the production of polyurethane). Technical grade DNT (tg-DNT) is a mixture composed of approximately 76.5% 2,4-DNT, 18.8% 2,6-DNT, and 5% other DNT isomers (2.4% 3,4-DNT, 1.5% 2,3-DNT, 0.7% 2,5-DNT, and 0.4% 3,5-DNT).

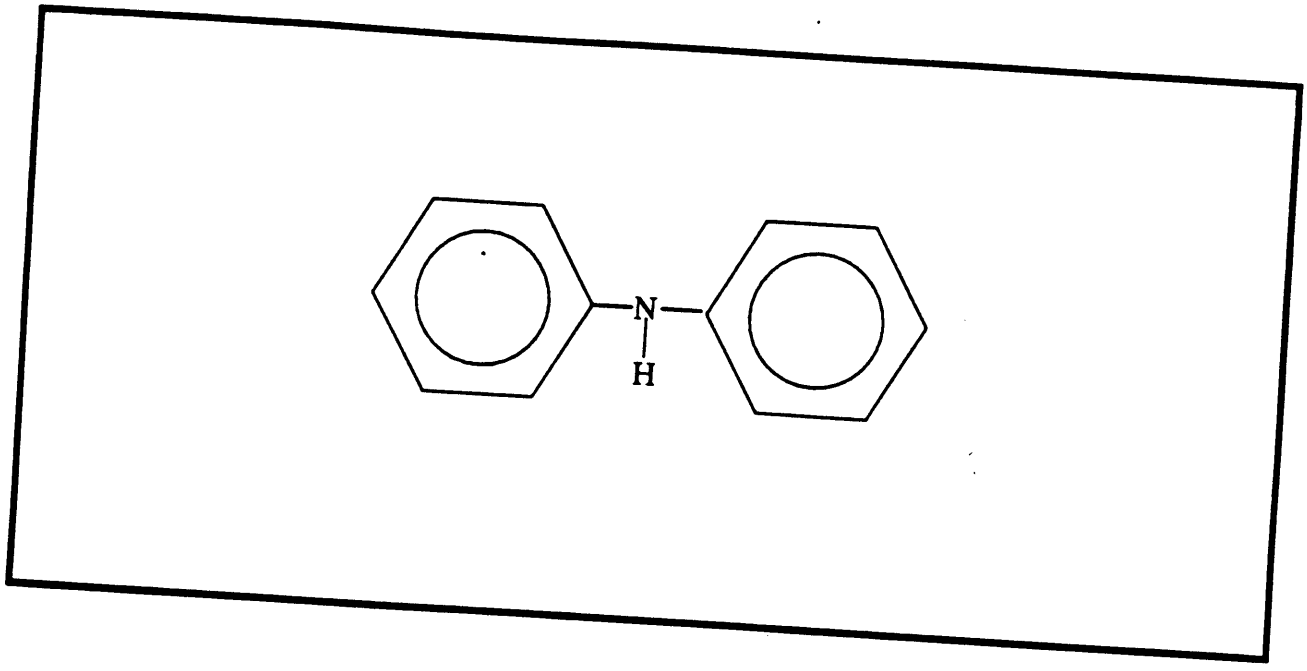
2,6-Dinitrotoluene has not been studied epidemiologically; therefore, it is uncertain as to whether it affects people in the same manner as tg- and 2,4-DNT(i.e., heart, circulatory system, and the central nervous system effects). Limited study of experimental animals (dogs, rats, mice) orally administered 2,6-DNT effected the central nervous system, blood, liver, and kidney, and caused death (Lee et al., 1976). No data on the reproductive or developmental effects of 2,6-DNT were found in the available literature.

All EPA HA values for 2,6-DNT are based on a 13-week study with dogs administered 2,6-DNT orally (Lee et al., 1976). The critical effects were neurotoxicity, Heinz bodies, bile duct hyperplasia, liver and kidney histopathology, and death. The HAs were derived from a NOAEL of 4 mg/kg/day. The 20 mg/kg/day dose level is a Frank-Effect Level (FEL) due to neurotoxicity and lethality.

The 2,6-DNT isomer is a weak mutagen in *Salmonella* test systems (Tokiwa et al., 1981; Spanggord et al., 1982; Couch et al., 1981). The DNTs are not genotoxic in mammalian cells *in vitro*, in mouse and rat dominant lethal tests, and in *Drosophila* systems (Abernethy and Couch, 1982; Styles and Cross, 1983; Rickert et al., 1984; Ellis et al., 1979; Soares and Lock, 1980).

DNT is classified B2 (probable human carcinogen) and thus a Lifetime HA is not recommended (U.S. EPA, 1992d). Leonard et al. (1987) demonstrated hepatocellular carcinoma in 85% to 100% of CDF male rats in a 12-month study. However, the cancer potency and risk estimate is associated with 2,4-DNT hepatocellular and mammary gland carcinogenic activity in rats (Ellis et al., 1979). There is some evidence which suggests that 2,6-DNT has both initiation and promotion activity and, therefore, may be a complete carcinogen (Leonard et al., 1983, 1986).

Diphenylamine



- **EPA Reference Dose (RfD):** 0.03 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	1.0 mg/L
Ten-Day	1.0 mg/L
Longer-Term (child)	0.3 mg/L
Longer-Term (adult)	0.9 mg/L
Lifetime	0.2 mg/L

N,N-Diphenylamine (diphenylamine, DPA, or N-phenylbenzeneamine), is a crystalline solid at room temperature. Its commercial and industrial uses include: stabilization of nitrocellulose explosives and celluloid in gun propellants; as a dip spray and impregnate of paper wraps to prevent scald on apples and other fruits; as an insecticide; therapeutically to treat helminthic infections in animals and humans; in the manufacture of dyes, polymers, greases, and oils; in rubber production; and as an analytical reagent (Budavari et al., 1989; Kirk-Othmer, 1978)

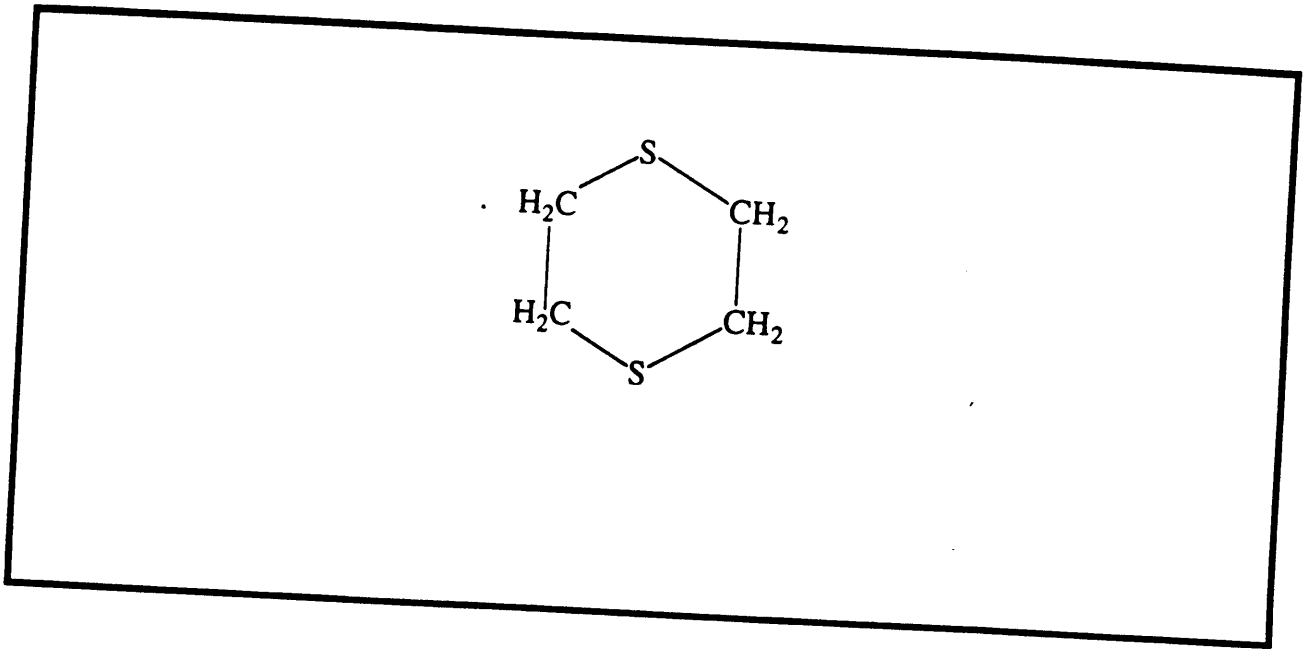
Except for some dermal studies in occupational workers, no epidemiological, clinical case histories, or experimental studies of potential human health effects to DPA exposure are available. Diphenylamine was not irritating to the skin of humans or rabbits (Slovak, 1980; Calnan, 1978; Epstein, 1967; Levenstein, 1976).

The EPA One- and Ten-day HAs are based on a 28-day feeding study in rats (LOAEL = 111 mg/kg/day) due to reduced liver, kidney, and spleen weights (Yoshida et al., 1989). The Longer-term HA is derived from a chronic (> 400 days) feeding study in dogs where there was growth retardation and adverse hematological effects with a NOAEL of 2.5 mg/kg/day (Thomas et al., 1967b). The Lifetime HA is calculated from a NOAEL of 2.5 mg/kg/day based upon a 2-year feeding study with dogs where there also was an absence of growth retardation and adverse hematological effects (Thomas et al., 1967b).

Diphenylamine was negative in the Ames reverse mutation assay and in *E. coli* with and without S9 activation (Ferretti et al., 1977; Florin et al., 1980; Probst et al., 1981). It also tested negative in isolated mouse lymphoma cells with S9 activation and did not cause unscheduled DNA synthesis in cultured rat hepatocytes (Probst et al., 1981; Amacher et al., 1980).

Several animal studies did not provide sufficient information to characterize diphenylamine's carcinogenic potential; therefore, it is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1992b). However, the chronic/lifetime bioassays in several mammalian species (U.S. EPA, 1985b; Thomas et al., 1976a,b; DiPaolo et al., 1973; Griswold et al., 1966) and the lack of mutagenicity provide more useful information to the risk assessor than a Group D classification chemical with no bioassay data.

1,4-Dithiane



- **EPA Reference Dose (RfD):** 0.01 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	0.4 mg/L
Ten-Day	0.4 mg/L
Longer-Term (child)	0.4 mg/L
Longer-Term (adult)	1.0 mg/L
Lifetime	0.08 mg/L

1,4-Dithiane (diethylene disulfide) exists as a volatile, white, monoclinic, crystalline solid at room temperature and may be formed during the storage of mustard gas (Berkowitz et al., 1978). Neither quantitative data on the toxicokinetics of 1,4-dithiane nor studies of potential human health effects were found in the literature.

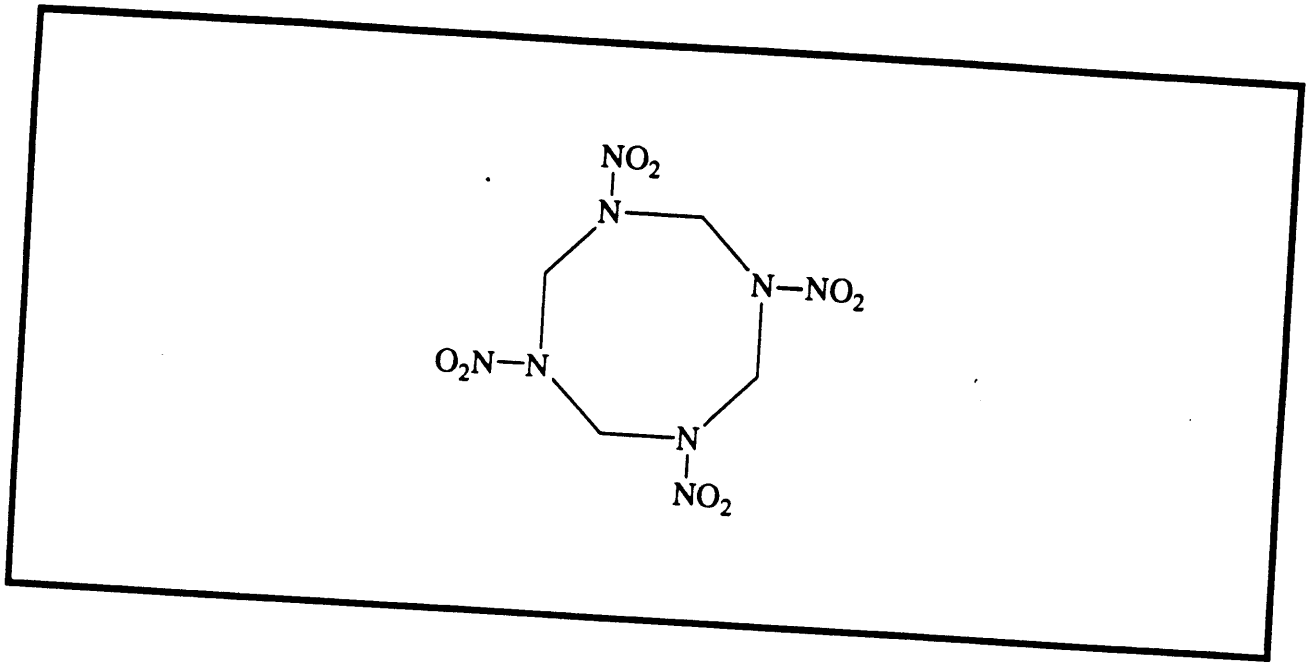
Experimental animal data are limited to studies with only one species (rat). CD rats did not exhibit mortality, overt toxicity, or treatment-related effects on water or food consumption in a 14-day range-finding gavage study (Schieferstein, 1987). Gross pathologic, histologic, clinical chemistry, hematologic, or ophthalmologic examinations were not performed, and a dose-response relationship was not established.

Morphologic lesions in the nose, female liver, and male kidney as well as changes in some absolute organ weights occurred in a subchronic gavage study of CD rats that were administered 1,4-dithiane for 90 days (Schieferstein, 1987; Schieferstein et al., 1988). No overt toxicity (including clinical and hematologic indicators), treatment-related mortality, and ophthalmologic changes were observed. Anisotropic crystals of an undetermined composition developed in the nasal olfactory mucosa of both sexes at all doses.

All EPA HAs are based upon the occurrence of nasal lesions in rats in the 90-day study and a LOAEL of 105 mg/kg/day. In the absence of adequate animal data to derive either a One-day or Ten-day value for a child, the Longer-term HA for a 10 kg child is applied as a conservative estimate for the shorter duration exposures.

1,4-Dithiane was not mutagenic in the *Salmonella* mutagenicity assay in the presence and absence of metabolic activation (Sano and Korte, 1985). There were no carcinogenicity studies found in the literature; therefore, 1,4-dithiane is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1992c).

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine



- **EPA Reference Dose (RfD):** 0.05 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	5 mg/L
Ten-Day	5 mg/L
Longer-Term (child)	5 mg/L
Longer-Term (adult)	20 mg/L
Lifetime	0.4 mg/L

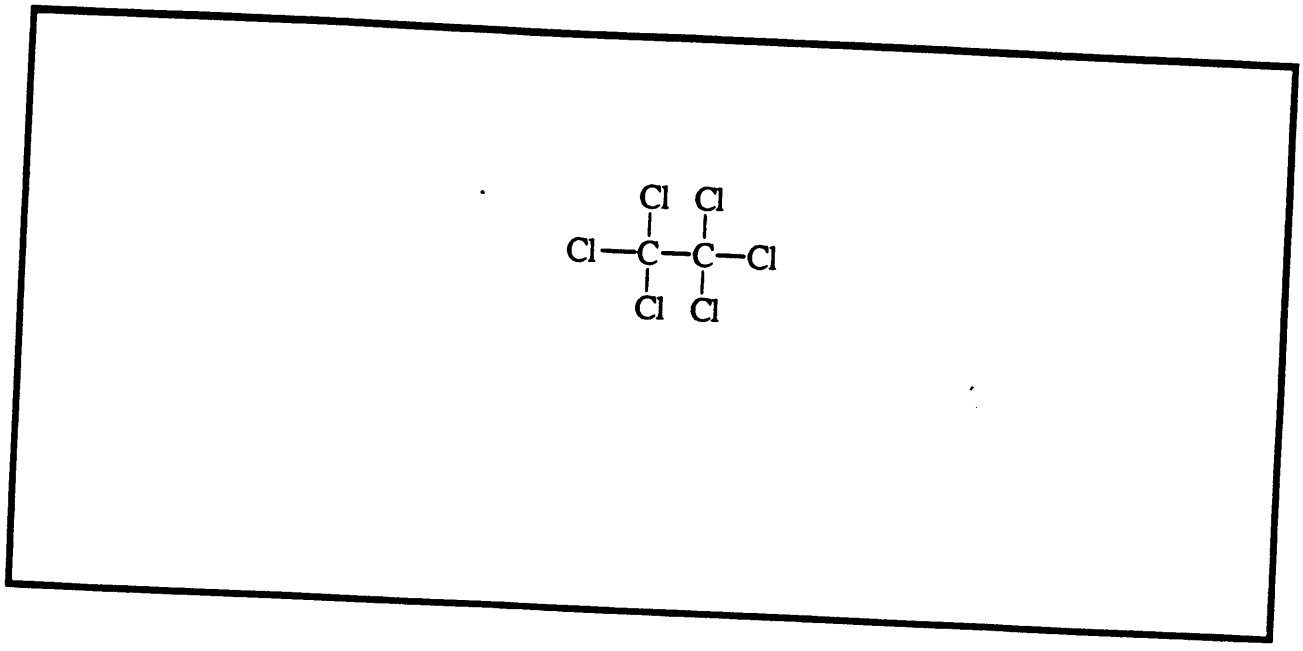
Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) is an explosive polynitramine that has been used to implode fissionable material in nuclear devices to achieve critical mass, and as a component in plastic-bonded explosives, solid-fuel rocket propellants and in military munitions (Sullivan et al., 1979b; Kitchens et al., 1979). Commonly referred to as HMX (for High Melting Explosive), other synonyms include Octogen, RRI, and cyclotetramethylenetetranitramine. Humans may be exposed to HMX occupationally by inhalation and dermal absorption when it is manufactured or incorporated into munitions at load, assembly, and pack (LAP) facilities. Potential environmental exposure could occur from drinking water sources contaminated by wastewater from HMX manufacturing and munitions LAP operations (Sullivan et al., 1979b). The only health effect reported in humans is skin irritation in volunteers exposed to solid HMX in a patch test (Ryon et al., 1984).

Chronic exposure values recommended by EPA are based upon a rat (F344 strain) 90-day feeding study by Everett et al. (1985). At doses of 115 mg/kg/day male rats developed liver lesions, characterized by enlarged centrilobular cells with pale nuclei. There were no effects at 50 mg/kg/day.

Genotoxicity studies are limited to mutagenicity assays with several strains of *S. typhimurium* and to a mitotic gene conversion assay with *S. cerevisiae* (Simmon et al., 1977; Stilwell et al., 1977; Whong et al., 1980). HMX was negative in all of the studies, but the results were considered inconclusive because of the low concentrations that were assayed or the lack of data reported (U.S. EPA, 1988b).

There were no carcinogenicity studies found in the literature; therefore, HMX is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1988b).

Hexachloroethane



- **EPA Reference Dose (RfD):** 0.001 mg/kg/day

- **EPA Cancer Classification:** Group C, possible human carcinogen; potency factor (q_1^*) = 1.4 E-2 $(mg/kg/day)^{-1}$ by the LMS[4] model

- **Health Advisory Values:**

One-Day	5 mg/L
Ten-Day	5 mg/L
Longer-Term (child)	100 mg/L
Longer-Term (adult)	450 mg/L
Lifetime	0.0007mg/L

4/ Linearized Multistage

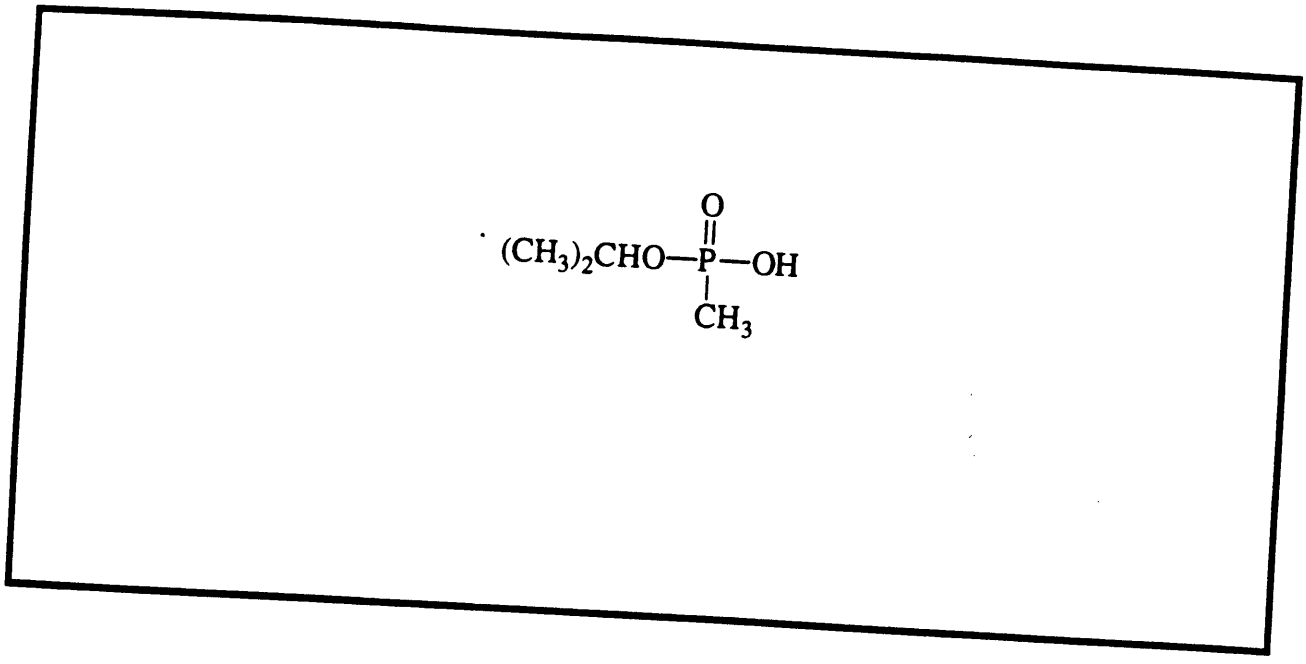
Hexachloroethane (HCE) is a chlorinated alkane and is a colorless to white crystalline material with a camphor-like odor. It is used by the military in the production of pyrotechnic devices and screening smokes (Davidson et al., 1988). Nonmilitary uses include fluorocarbon (used as dry-cleaner, aerosol, or refrigerant) precursor, lubricant, rubber and insecticidal formulation, moth repellant, fire extinguishing fluid, fermentation retardant, chemical precursor, rodentidide, veterinary medicine, and submarine paints (Sax, 1986). Reported effects of HCE to humans is limited to mild neurological effects and effects to the eye, e.g., irritation, tearing, inflammation, and photophobia (Grant, 1986).

The EPA HAs are derived from experimental animal studies. The One- and Ten-day HAs are based on a NOAEL of 50 mg/kg/day derived from a 16-day oral dosing study where male rats exhibited a significant decrease in body weight gain and developed gross liver and kidney lesions (Gorzinski, 1980a). Longer-term and Lifetime HAs are based upon the develpment of kidney lesions in male rats (NOAEL of 1.3 mg/kg/day) that were administered HCE in the diet for 16 weeks (Gorzinski, 1980b).

Hexachloroethane was not mutagenic or genotoxic in *Salmonella* and *Saccharomyces* assay systems with and without metabolic activation (Nakumara et al., 1987; Weeks et al., 1979; Simon and Kauhanen, 1978).

Hexachloroethane was not carcinogenic when fed to Osborne-Mendel rats for 78 weeks (NCI, 1978). However, $B6C3F_1$ mice from the same study showed a significant increase in hepatocellular carcinoma. The mouse data yields a potency factor of 1.4×10^{-2} $(mg/kg/day)^{-1}$ by the LMS model (USEPA, 1991b). Hexachloroethane is classified as an EPA Group C (possible human carcinogen) contaminant.

Isopropyl Methylphosphonic Acid



- **EPA Reference Dose (RfD):** 0.1 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	30 mg/L
Ten-Day	30 mg/L
Longer-Term (child)	30 mg/L
Longer-Term (adult)	100 mg/L
Lifetime	0.7 mg/L

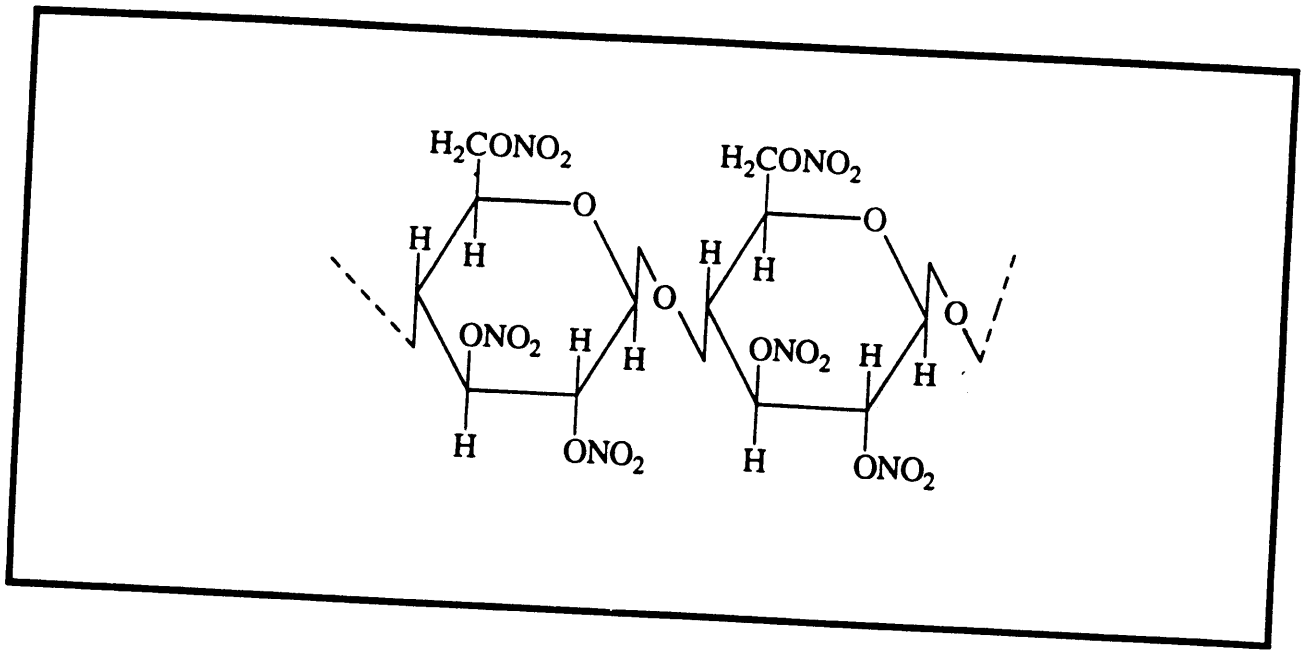
Isopropyl methyl phosphonic acid (IMPA) is a degradation product of the nerve gas isopropyl methylphosphonofluoridate (GB or Sarin) (Rosenblatt et al., 1975). It is nonvolatile and soluble in water. Some of the toxicokinetic and toxicological data that can be used in the evaluation of IMPA come from studies of Sarin and diisopropyl methyl-phosphonate (DIMP; a by-product produced during the manufacture of Sarin) (U.S. EPA, 1989). Since these compounds degrade to produce IMPA in living systems, the data are applicable to IMPA and are used to support the IMPA HAs.

There were no reports of IMPA effects to humans found in the available literature. In experimental studies with rabbits, there were no signs of toxicity or irritation when IMPA was applied to the eyes, but it was moderately irritating to the skin (Mecler, 1981). Dermal application of a 0.1% solution did not cause sensitization. Study of the chronic/longterm effects of IMPA are limited to a single 90-day study in rats (Mecler, 1981). Compound-related adverse effects did not develop in rats that were exposed to concentrations of up to 399 mg/kg/day of IMPA in drinking water. Data on the reproductive or developmental toxicity of IMPA were not found in the available literature.

All EPA HA values for IMPA were derived from the 90-day drinking water study of rats despite the lack of any effects in this study. The highest concentration tested (3,000 ppm; equivalent to a dose of 399.1 mg/kg/day for females and 278.5 mg/kg/day for males) was determined to be the no-observable-adverse-effect-level (NOAEL), based on observations of body weight, clinical signs, hematological parameters, terminal blood chemistry values, and histopathology.

Isopropyl methyl phosphonic acid was not mutagenic in assays with *S. typhimurium* (Mecler, 1981). There were no carcinogenicity studies found in the literature; therefore, IMPA is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1992e).

Nitrocellulose



- **EPA Reference Dose (RfD):** Not yet derived by EPA.

- **EPA Cancer Classification:** Not yet classified by EPA.

- **Health Advisory Values:**

One-Day	Non-Toxic[5]
Ten-Day	Non-Toxic
Longer-Term (child)	Non-Toxic
Longer-Term (adult)	Non-Toxic
Lifetime	Non-Toxic

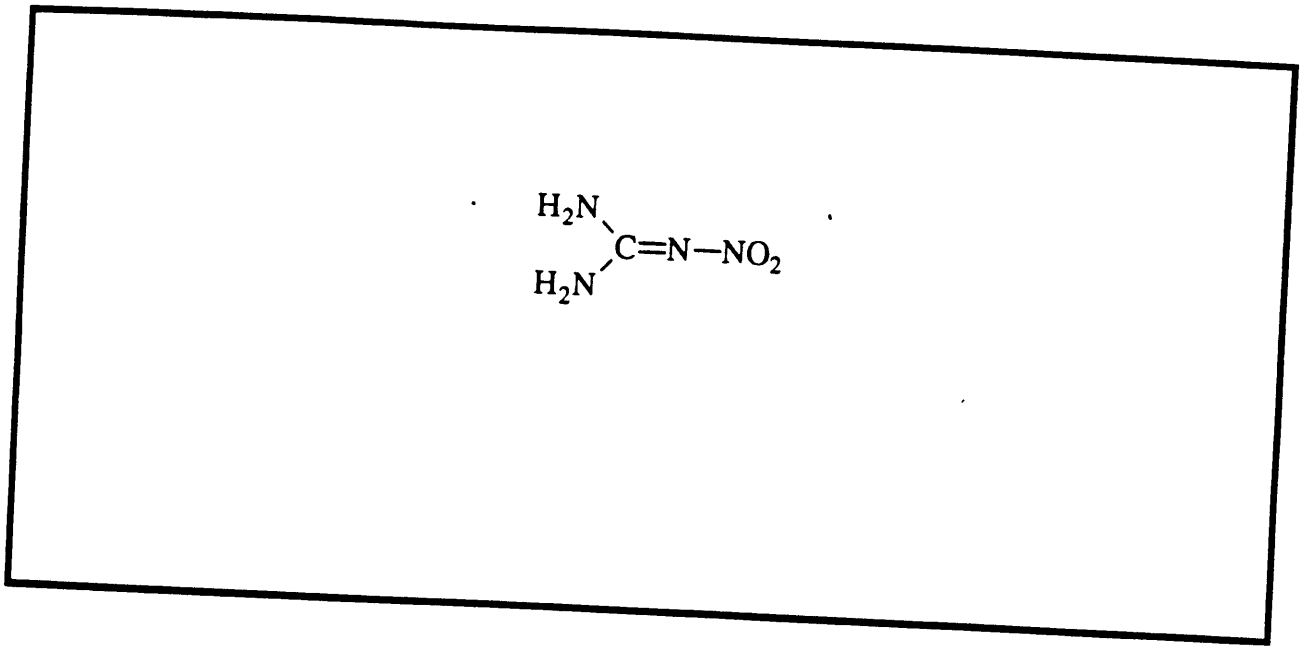
5/ Health Advisory values appear to be unnecessary because of the lack of toxicological indicators and apparent non-absorption and non-digestion of nitrocellulose fibers.

Nitrocellulose (NC), or cellulose trinitrate, consists of chains of glucosides linked to form nitrate esters (Sullivan et al., 1978). It is a principle ingredient of propellants, smokeless powders, rocket fuel, mortar increments, and some explosives (Rosenblatt et al., 1973). Theoretically, exposure is possible from potential drinking water sources that receive wastewater discharges from NC production sources. However, human toxicity from water and any other exposure has not been reported.

Exposure limits are not established by EPA for NC because it was non-toxic at all doses studied, in all species (dogs, rats, mice) tested, and failed to be digested and absorbed in all species (U.S. EPA, 1987b). Nitrocellulose was not toxic in mice and rats provided single acute doses up to 5,000 mg/kg (Lee et al., 1975). Similarly, it was not toxic in dogs, rats, and mice fed up NC in proportions up to 10% of the diet for 13-weeks (Ellis et al., 1976). Some deaths occurred in the high-dose mice from blockage in the lower gastrointestinal tract in the regions where water is removed from the chyme. Deaths by the same mechanism occurred in control mice fed non-nitrated 10% cotton-linters in the diet. Dogs, rats, and mice fed NC in the diet at doses up to 3874 mg/kg/day, 1422 mg/kg/day, and 6056 mg/kg/day, respectively, for up to 24 months did not exhibit any treatment related toxicity (Ellis et al., 1980).

Nitrocellulose was not mutagenic in several strains of *S. typhimurium* with or without metabolic activation, and genotoxicity was not demonstrated in bone marrow cells, kidney cells, and lymphocytes from rats fed NC for 13-weeks or 2-years (Ellis et al., 1976). Treatment related carcinogenicity was not observed in dogs, rats, or mice fed NC in the diet for 12 or 24 months (Ellis et al., 1980). Nitrocellulose does not have an EPA cancer classification.

Nitroguanidine



- **EPA Reference Dose (RfD):** 0.1 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	11 mg/L
Ten-Day	11 mg/L
Longer-Term (child)	11 mg/L
Longer-Term (adult)	37 mg/L
Lifetime	0.74 mg/L

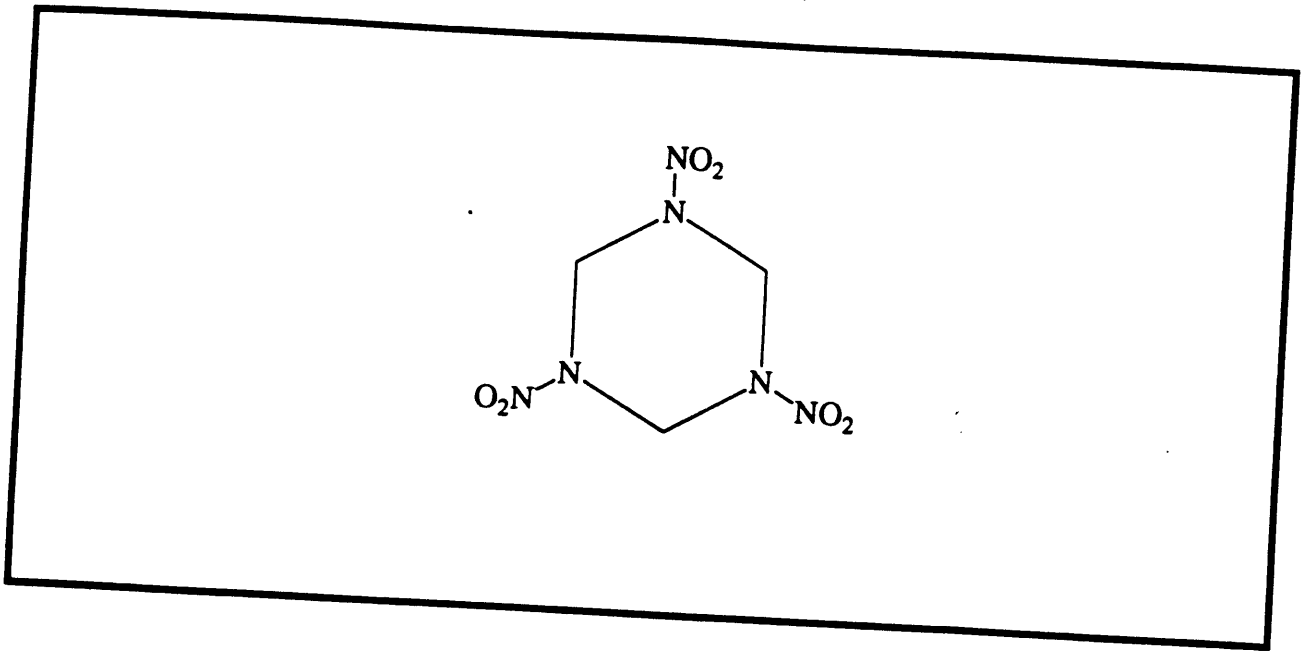
Nitroguanidine (NQ) is a nitramino compound that is used in triple-base propellant mixtures to produce flashless, less erosive formulations (Kenyon, 1982; Encyclopedia of Explosive and Related Items, 1974). Synonyms include alpha-nitroguanidine, beta-nitroguanidine, NG, NGu, and picrite. The abbreviation NQ is used in lieu of NG to prevent confusion with the explosive nitroglycerol. Humans may be exposed to NQ occupationally when it is manufactured or incorporated into munitions at load, assembly, and pack (LAP) facilities. Environmental exposure could occur from drinking water sources contaminated by wastewater from NQ manufacturing and munitions LAP operations (Kaplan et al., 1982). No studies on the health effects of NQ in humans have been reported.

Exposure limits recommended by EPA for longer-term and lifetime advisories were derived from effects in Sprague-Dawley rats fed NQ in the diet for 90 days (Morgan et al., 1988). Decreased body weight and increased brain-to-body weight ratios in female rats, and increased water consumption in male and female rats occurred in animals dosed at 1000 mg/kg/day, the LOAEL. There were no treatment related effects in rats receiving doses of 316 mg/kg/day, the NOAEL. Uncertainty introduced by equivocal evidence of developmental toxicity in rabbits was accounted for in the recommended exposure limits (Coppes et al., 1988).

Nitroguanidine was not genotoxic in microbial assays with *S. typhimurium*, *S. cerevisiae* and *Escherichia coli* with and without metabolic activation ((Ishidate and Odashima, 1977; Kaplan, 1982; Sebastian and Korte, 1988; McGregor et al., 1980; Kenyon, 1982; Brusick and Matheson, 1978). It was not mutagenic in assays with mouse lymphoma cells and Chinese Hamster Ovary cells with and without metabolic activation (Harbell and Korte, 1987; Harbell et al., 1988). Mutagenicity was not demonstrated in a sexed-linked recessive lethal mutation assay with *Drosophila melanogaster* (Gupta et al., 1988). Brusick and Matheson (1978) did not detect a clastogenic response in dominant lethal assays with mice and rats. Ishidate and Odashima (1977) reported that NQ was a clastogen for Chinese Hamster fibroblast (lung) cells; their conclusions may be compromised by deficiencies in methodology (U.S. EPA, 1990a).

Carcinogenicity studies were not found in the literature; therefore, NQ is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1990a).

Hexahydro-1,3,5-trinitro-1,3,5-triazine



- **EPA Reference Dose (RfD):** 0.003 mg/kg/day

- **EPA Cancer Classification:** Group C, possible human carcinogen; potency factor (q_1^*) = 1.1E-1 $(mg/kg/day)^{-1}$ by the LMS[6] model

- **Health Advisory Values:**

One-Day	0.1 mg/L
Ten-Day	0.1 mg/L
Longer-Term (child)	0.1 mg/L
Longer-Term (adult)	0.4 mg/L
Lifetime	0.002 mg/L

6/ Linearized Multistage

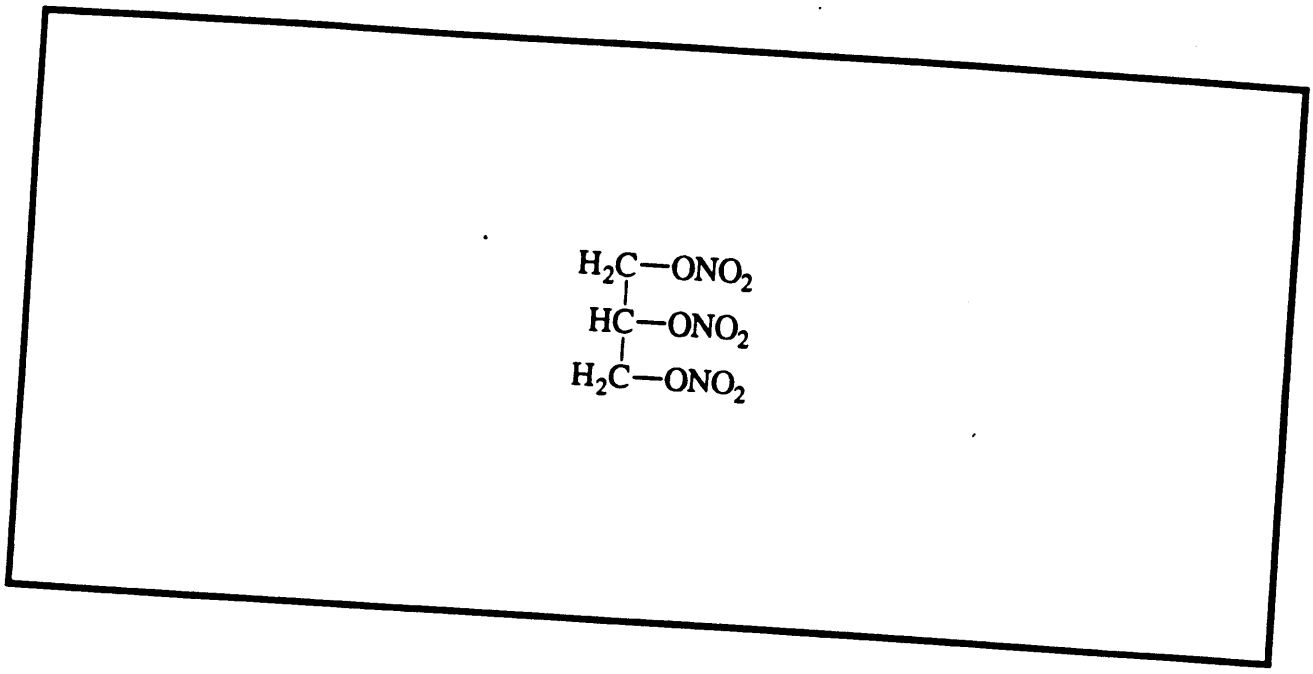
Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) is a polynitramine that has been used as a high-impact explosive in munitions and as a rat poison (ACGIH, 1986; Windholz, 1983). Commonly referred to as RDX (a British code name for Research Department Explosive or Royal Demolition Explosive), other synonyms include cyclonite, T_4, and cyclotrimethylene-trinitramine. Occupational exposures to RDX occur by inhalation and dermal absorption as it is manufactured and at load, assembly, and pack (LAP) facilities (Kaplan et al., 1965; ACGIH, 1986). Environmental exposure can occur from drinking water sources contaminated by wastewater from RDX manufacturing and LAP operations (Sullivan et al., 1979b). Ingestion and inhalation exposures to RDX have been reported (Ketel and Hughs, 1972; Hollander and Colbach, 1969; Stone et al., 1969; Knepshield and Stone, 1972; Merrill, 1968; Woody et al., 1985, 1986). The later was by soldiers who burned composition C-4 (91% RDX) to heat food in the field. Health effects include convulsions, unconsciousness, mental confusion, headache, fever, dizziness, nausea, vomiting, neuromuscular irritability, gastrointestinal symptoms, hematuria, and oliguria.

EPA longer-term (up to 7-years) exposure values for RDX are based upon neurological effects observed in cynomolgus monkeys that were fed the chemical for 90 days (Martin and Hart, 1974). Convulsions occurred in those fed 10 mg/kg/day, the LOAEL. There were no effects in monkeys that received 1 mg/kg/day, the NOAEL. Lifetime exposure values were derived from effects in rats fed RDX for 24 months (Levine et al., 1983a). Suppurative prostate inflammation occurred in males at 1.5 mg/kg/day, the LOAEL; there were no effects at 0.3 mg/kg/day, the NOAEL.

RDX was not mutagenic in *S. typhimurium* and in *S. cerevisiae* with and without metabolic activation (Cholakis et al., 1980; Whong et al., 1980; Simmon et al., 1977). It was negative in a dominant lethal assay with F344 rats and an UDS assay with human diploid fibroblasts (Cholakis et al., 1980; Dilley et al., 1978).

RDX was not carcinogenic when fed to Sprague-Dawley and F344 rats for 2 years (Levine et al., 1983a; Hart, 1977). Lish et al. (1984) did find that female $B6C3F_1$ mice developed hepatocellular carcinomas and adenomas when fed RDX. The mouse data yields a potency factor of 1.1×10^{-1} $(mg/kg/day)^{-1}$ by the LMS model (U.S. EPA, 1988a). RDX is classified as an EPA Group C (possible human carcinogen) contaminant.

Trinitroglycerol



- **EPA Reference Dose (RfD):** Not yet derived by EPA.

- **EPA Cancer Classification:** Not yet classified by EPA.

- **Health Advisory Values:**

One-Day	0.005 mg/L
Ten-Day	0.005 mg/L
Longer-Term (child)	0.005 mg/L
Longer-Term (adult)	0.005 mg/L
Lifetime	0.005 mg/L

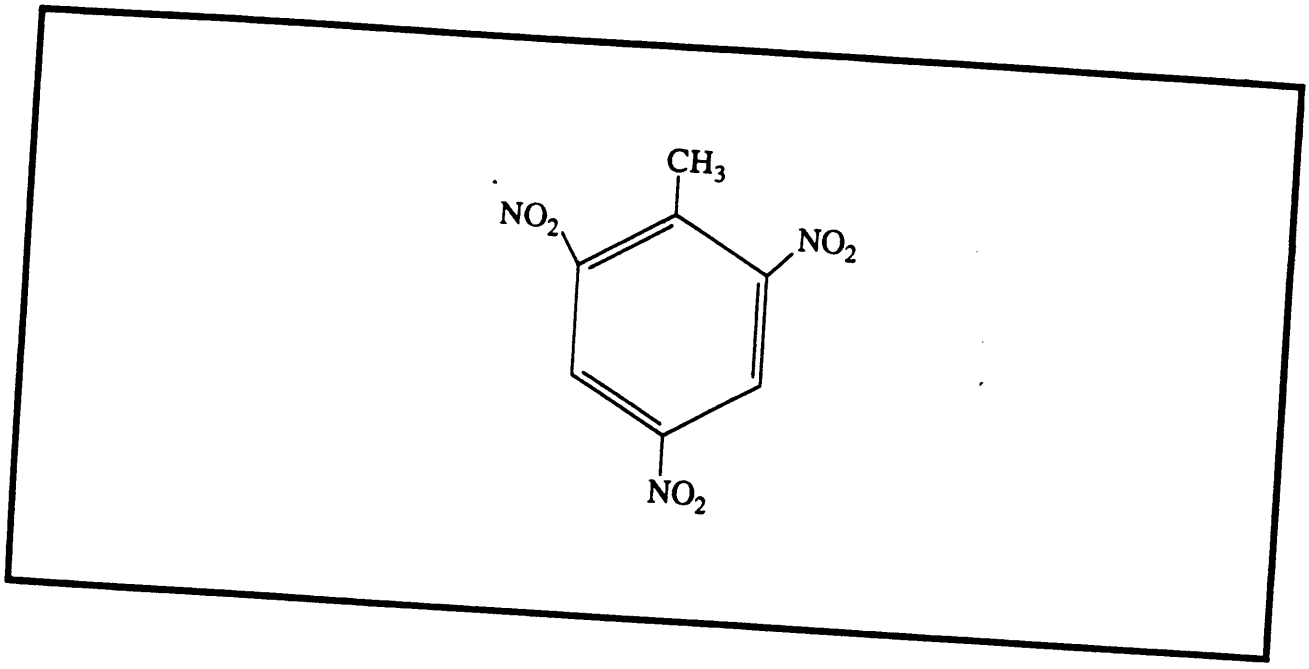
Trinitroglycerol (TNG), also known as glyceryl nitrate and nitroglycerin, is an aliphatic nitrate ester, and has been used as an explosive since 1864 (Sullivan et al., 1979a). Humans may be exposed to TNG clinically (as a vasodilator), occupationally, or as an environmental contaminant (Rosenblatt et al., 1973; Shiotsuka, 1979). The major health effects in acutely exposed people are: relaxation of smooth muscle, vasodilatation, hypotension, dizziness, fainting, headache, vasodilatation, hypotension, dizziness, fainting, headache, and rapid pulse rate. Chronic exposure has been associated with chest pain, ischemic heart disease, and the development of tolerance. Death has occurred subsequent to both acute (from respiratory paralysis) and chronic (from myocardial infarction) exposures.

The exposure limit adopted by EPA for TNG in drinking water is 0.005 mg/L (5 µg/L) for all durations of exposure and for both adults and children (U.S. EPA, 1987a). This limit is based upon the sublingual administration of TNG in the treatment of acute angina in humans. The therapeutic dose range is usually 0.15 to 0.60 mg which may cause a marked hypotensive effect and result in transient episodes of dizziness, weakness, and other manifestations of cerebral ischemia (Needleman and Johnson, 1980). Assuming the average weight of an adult is 70 kg, the usual dose ranges from 0.002 to 0.009 mg/kg which has an arithmetic mean of 0.005 mg/kg.

Trinitroglycerol had either absent or weak mutagenic activity in assays with bacteria *(S. typhimurium)* and yeast (*Saccharomyces cerevisiae*) with and without metabolic activation (Ellis et al., 1978b; Simmon et al., 1977). It was not genotoxic or mutagenic in *in vitro* mammalian test systems to include rat bone marrow and kidney cell cultures, lymphocytes from dogs and rats, and Chinese Hamster Ovary (CHO) cells (Lee et al., 1976; Ellis et al., 1978b). A dominant lethal assay with rats also was negative (Ellis et al., 1978b).

Trinitroglycerol was not carcinogenic in 2-year bioassays with dogs and mice; however, hepatocellular carcinoma was detected in male and female Charles River CD rats (Ellis et al., 1978a). Based on the rat hepatocellular carcinomas a potency factor of 1.66×10^{-2} $(mg/kg/day)^{-1}$ was derived by the linearized multistage (LMS) model (U.S. EPA, 1987a). Trinitroglycerol does not have an EPA cancer classification.

2,4,6-Trinitrotoluene (TNT)



- **EPA Reference Dose (RfD):** 0.0005 mg/kg/day

- **EPA Cancer Classification:** Group C, possible human carcinogen; potency factor (q_1^*) = 1.1E-1 $(mg/kg/day)^{-1}$ by the LMS[7] model

- **Health Advisory Values:**

One-Day	0.02 mg/L
Ten-Day	0.02 mg/L
Longer-Term (child)	0.02 mg/L
Longer-Term (adult)	0.02 mg/L
Lifetime	0.002 mg/L

7/ Linearized Multistage

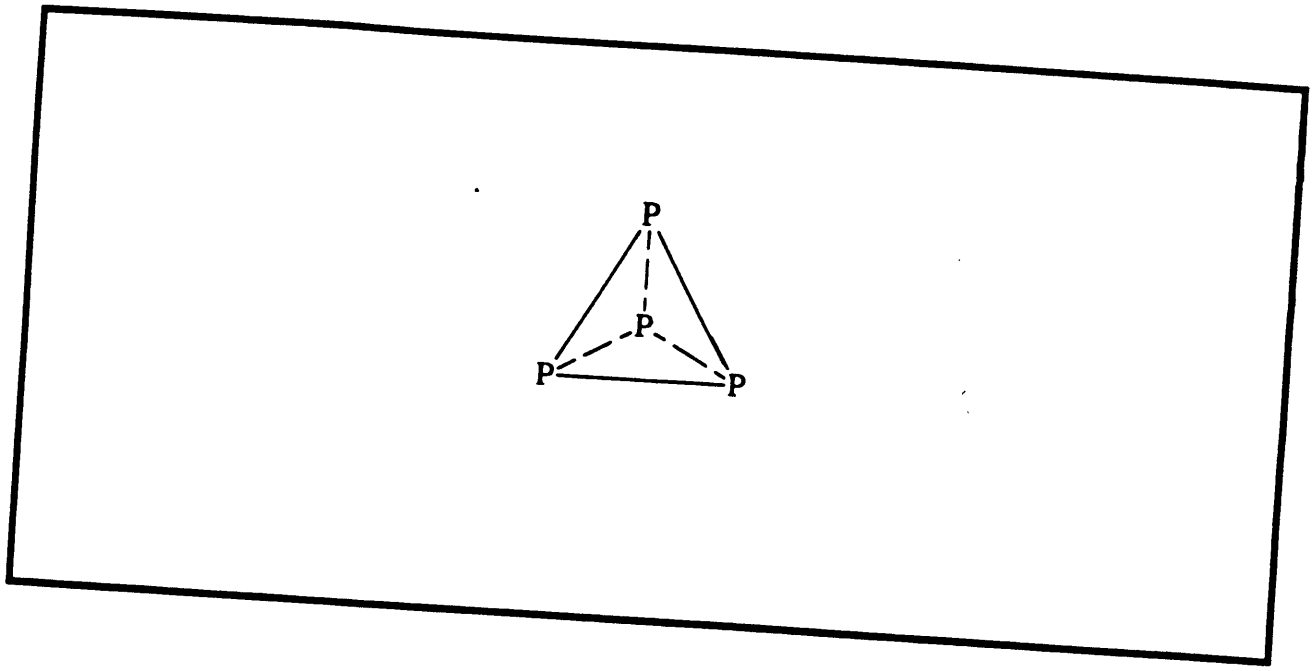
2,4,6-Trinitrotoluene (TNT), also known as alpha-trinitrotoluol and alpha-TNT, has had wide application in shells, bombs, grenades, demolition explosives, and propellant compositions (Castorina, 1980; Department of the Army, 1967). Deaths and toxicity in humans have been primarily occupational via dermal and inhalation exposure routes. There are a variety of health effects associated with TNT exposure, but toxic hepatitis (jaundice) and aplastic anemia are the principle causes of death (Zakhari and Villaume, 1978). Other TNT effects include respiratory and skin irritation, gastrointestinal disorders, cataract formation, menstrual disorders, neurological disorders, nephrotoxicity, and hematological effects.

EPA advisory values are derived from a study where dogs were fed TNT in the diet for 26 weeks (Levine et al., 1983b). Hepatocytomeglia occurred at the lowest dose studied (LOAEL), 0.05 mg/kg/day, and was considered the critical effect because of demonstrated liver pathology at higher dose levels.

Trinitrotoluene was found to be mutagenic in several strains of *S. typhimurium* with and without metabolic activation (Ellis et al., 1978b; Dilley et al., 1978). It was negative in all mammalian genotoxicity assays which included an *in vivo* assay of bone marrow cell from treated rats, an *in vitro* Unscheduled DNA synthesis (UDS) assay with human diploid fibroblasts, a mouse bone marrow micronucleus assay, and an *in vivo/in vitro* UDS with rat hepatocytes (Dilley et al., 1978; Ashby et al., 1985).

Two year bioassays for carcinogenicity were conducted with Fischer 344 rats and hybrid $B6C3F_1$ mice (Furedi et al., 1984a-f), Female rats were positive for urinary bladder papillomas. There were no statistically significant treatment related cancers in male rats or in male and female mice. The female rat data was used to calculate a potency factor of 3×10^{-2} $(mg/kg/day)^{-1}$ by the LMS model (U.S. EPA, 1987c). Trinitrotoluene is classified as an EPA Group C (possible human carcinogen) contaminant.

White Phosphorus



- **EPA Reference Dose (RfD):** 0.00002 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	None[8]
Ten-Day	None
Longer-Term (child)	None
Longer-Term (adult)	None
Lifetime	0.0001mg/L

8/ Health Advisory values are not recommended because of extreme toxicity

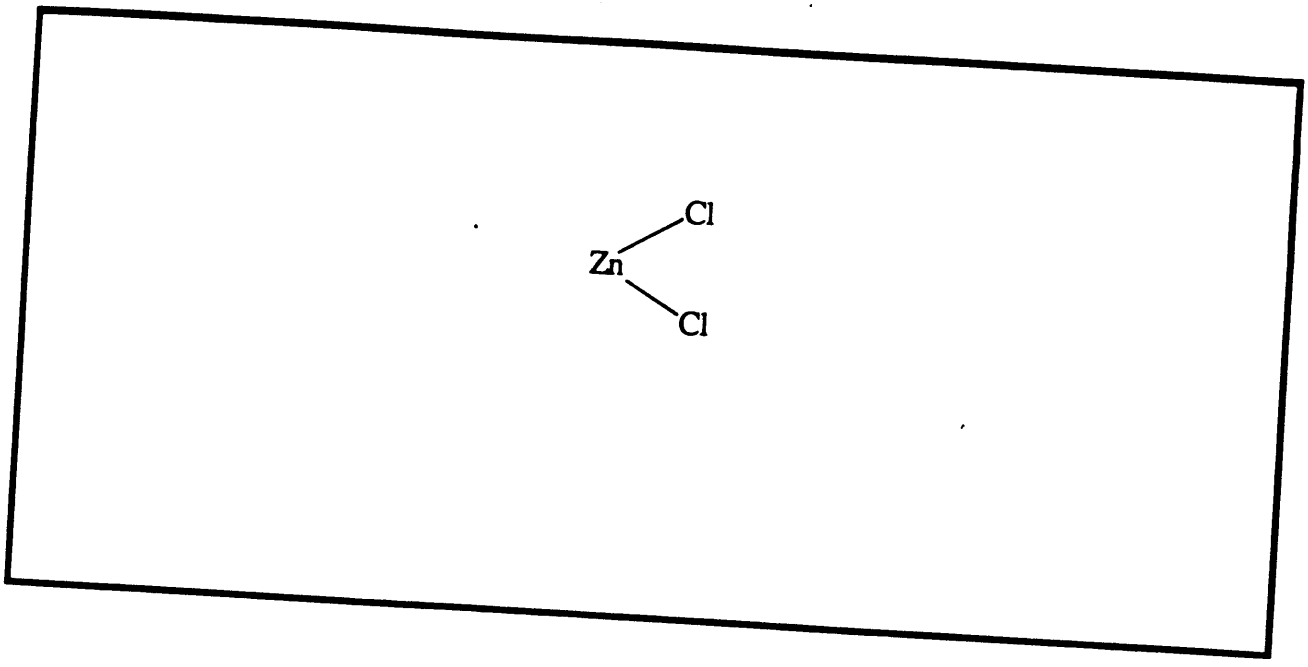
White phosphorus (WP) is a transparent waxy solid that is an allotropic form of the element phosphorus. Military and commercial uses of WP include: as a incendiary device and as a screening smoke; once used in matches, fireworks, and rat poisons (these uses, however, were discontinued due to its toxicity); and current uses include analytical chemistry, the manufacture of phosphorus compounds, and as an additive to semiconductors and electroluminescent coatings (Brown et al., 1981; Hawley, 1981).

In humans, chronic exposure to white phosphorus is associated with its necrotic effect on bone and the occurrence of "phossy jaw" (necrosis of the jaw usually related to inhalation exposure or direct contact) (Hughes et al., 1962). Fatalities have been reported to occur from ingestion of 1 mg/kg in adult and 3 mg total in a child. Acute exposure is reported to affect the heart, central nervous system, blood, and serum chemistry (U.S. EPA, 1990b). In experimental animal (rats, rabbits, and guinea pigs) studies with exposure durations that ranged from 90 days to lifetime, oral administration of WP resulted in weight loss, and adverse effects to the liver and bone.

The EPA RfD and Lifetime HA were derived from a reproductive toxicity study of female rats (Condray, 1985). A NOAEL of 0.015 mg/kg/day was based on an increase in offspring mortality due to parturition difficulty in WP treated females. One-day, ten-day, and longer-term HAs are not recommended for WP because of extreme toxicity following oral ingestion in humans and animals, and the lack of additional data (U.S. EPA, 1990b).

White phosphorus was not mutagenic in assays with *S. typhimurium* (Ellis et al, 1978b). There were no carcinogenicity studies found in the literature; therefore, WP is classified as an EPA Group D (not classifiable as to human carcinogenicity) contaminant (U.S. EPA, 1990b).

Zinc and Zinc Chloride



- **EPA Reference Dose (RfD):** 0.3 mg/kg/day

- **EPA Cancer Classification:** Group D, not classifiable as to human carcinogenicity.

- **Health Advisory Values:**

One-Day	5.0 mg/L
Ten-Day	5.0 mg/L
Longer-Term (child)	3.0 mg/L
Longer-Term (adult)	10 mg/L
Lifetime	2.0 mg/L

Zinc (Zn) occurs naturally earth's crust as a bluish-white metal in its pure form. It can exist as a divalent inorganic compound such as zinc chloride ($ZnCl_2$), zinc sulfate, and zinc oxide. In the environment, Zn compounds hydrolyze when dissolved in water. $ZnCl_2$ may be introduced into the environment through its use as a military screening smoke (Cullumbine, 1957).

Zn is an essential trace element that is a constituent of several enzymes involved in key biological processes. Its deficiency causes appetite loss, retarded growth, skin and immunological abnormalities, retarded wound healing, and developmental effects (NRC, 1989). In humans, oral acute effects from up to 1,000 mg/kg of Zn, are vomiting, diarrhea, lethargy, and mouth, throat, and stomach irritation (Potter, 1981; Chobian, 1981). Oral exposure to ≥ 50 mg/day Zn for 6–12 weeks reduced serum erythrocyte superoxide dismutase [E-SOD] and ceruloplasmin (biomarkers of copper status), and high density lipoprotein (HDL) (Yadrick et al., 1989; Samman and Roberts, 1988; Black et al., 1988; Fischer et al., 1984).

Rats given 100 mg/kg/day $ZnCl_2$ orally with a low pantothenic acid diet for six weeks developed a deficiency syndrome (Gross et al., 1941). Other animal subchronic oral effects from Zn include renal damage, reproductive dysfunction, and fetotoxicity (Llobet et al., 1988; Seidenberg and Becker, 1987; Seidenberg et al., 1986).

The EPA HAs for Zn (and $ZnCl_2$) consider the minimal amount needed for essential physiological needs (5.5 mg/day) and that which produces minimal adverse effects. The One- and Ten-day HAs are based upon the Recommended Daily Allowance (NRC, 1989) for a 9-kg infant (0.56 mg/kg/day). The Longer-term and Lifetime HAs are derived from a 10-week human study where E-SOD concentrations were depressed after 10-week exposure to 1.0 mg/kg/day of Zn (Yadrick et al., 1989).

$ZnCl_2$ was not mutagenic in a variety of bacterial and *in vitro* mammalian cell systems (McGregor, 1980; Casto et al., 1979; DeKnudt and Deminatti, 1978). It also did not cause chromosomal aberrations when administered to the animals in an *in vivo* assay. $ZnCl_2$ and other Zn compounds are classified as EPA Group D (not classifiable as to human carcinogenicity) contaminants (U.S. EPA, 1992f).

TABLE 1. NTIS[a] Accession Numbers for Munitions Drinking Water Health Advisories and Other Munitions Documents

Chemical	NTIS Accession Number
p-Chlorophenyl methyl sulfide, -sulfoxide, -sulfone (PCPMS, PCPMSO, PCPMSO2)	PB93-116986
Diethylene glycol dinitrate (DEGDN)	PB93-117000
Diisopropyl Methylphosphonate (DIMP)	PB90-273517
Dimethyl methylphosphonate (DMMP)	PB93-117018
1,3-Dinitrobenzene (DNB)	PB91-159640
2,4- and 2,6-Dinitrotoluene (2,4-/2,6-DNT)	PB92-189315
Diphenylamine (DPA)	PB93-116978
1,4-Dithiane	PB93-117026
Hexachloroethane (HCE)	PB91-159657
Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)	PB90-273533
Isopropyl methylphosphonic acid (IMPA)	PB92-232149
Nitrocellulose (NC)	PB90-273541
Nitroguanidine (NQ)	PB90-273509
Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)	PB90-273525
Tetranitromethane (TNM)	PB93-116994
Trinitroglycerol (TNG)	PB90-273558
Trinitrotoluene (TNT)	PB90-273566
White Phosphorus (WP)	PB91-161026
Zinc chloride	PB93-13660
Drinking water toxicity profiles	PB93-122406

a/ National Technical Information Service (NTIS),U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161.

Summary

Since the initiation of the cooperative program between the Army and the EPA, drinking water HAs have been published for sixteen munitions. They include advisories for several nitrated munitions such as trinitroglycerol; nitrocellulose; hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX); octahydro-1,3,5,7- tetranitro-1,3,5,7-tetrazocine (HMX); 2,4,6-trinitrotoluene (TNT); 2,4-/2,6-dinitrotoluene (2,4-/2,6-DNT; nitroguanidine; and 1,3-dinitrobenzene. Most advisory values for these nitrated compounds are based on observations from animal studies. The exception is trinitroglycerol, which is based on pharmacological effects in humans. All of the advisory values are calculated from a NOAEL or a

LOAEL for systemic effects which include body and organ weight changes and/or organ histopathology. Cancer studies have been reported for only the DNTs, TNT, RDX, and trinitroglycerol. The DNTs are classified by the EPA as probable (Group B2) human carcinogens. Both TNT and RDX are clasified as possible (Group C) human carcinogens because of the equivocal nature of the data when assessed according to a weight-of-evidence scheme. The cancer risk potential for TNG has not been established by the EPA.

Additionally, drinking water HAs have been published for several unnitrated munitions chemicals to include diisopropyl methylphosphonate; dimethyl methylphosphonate; isopropylmethyl phosphonic acid; diphenylamine; 1,4-dithiane; hexachloroethane; white phosphorus; and zinc chloride. The critical toxic endpoints differ within this group of chemicals and only the dinitrotoluenes. Dimethyl methylphosphonate and hexachloroethane both are possible (Group C) carcinogens. The zinc/zinc chloride advisory values are based on human toxicological effects)in consideration of minimum nutritional requirements) and is the only HA in this group that is derived from human studies.

All of the munitions health advisories and other munitions health effects publications are available to the public and may be obtained from the National Technical Information Service (NTIS), Alexandria, VA (accession numbers are listed in Table 1). A summary of EPA drinking water values for the munitions chemicals are displayed in Table 2.

TABLE 2. Summary of Drinking Water Advisory Values for Munitions Chemicals

Munitions	RfD[1] (mg/kg/day)	DWEL	Health Advisories (mg/L)					EPA[2] Cancer Classification	Cancer Potency Factor (mg/kg/day)-1
			1-Day	10-Day	Longer-Term Child	Longer-Term Adult	Lifetime		
Diisopropylmethyl Phosphonate	0.08	3	8	8	8	30	0.6	D	NA[3]
Dimethyl Methylphosphonate	0.2	7	2	2	2	6	0.1	C	0.005
1,3-Dinitrobenzene	0.0001	0.005	0.04	0.04	0.04	0.14	0.001	D	NA
2,4-Dinitrotoluene	0.002	0.1	0.5	0.5	0.3	1	NA	B2	0.68
2,6-Dinitrotoluene	0.001	0.04	0.4	0.4	0.4	1	NA	B2	0.68
Diphenylamine	0.03	1	1	1	0.3	0.9	0.2	D	NA
1,4-Dithiane	0.01	0.4	0.4	0.4	0.4	1	0.08	D	NA
HMX[4]	0.05	2	5	5	5	20	0.4	D	NA
Hexachloroethane	0.001	0.04	5	5	0.13	0.45	0.0007	C	0.014
Isopropyl Methylphosphonic Acid	0.1	4	30	30	30	100	0.7	D	NA
Nitrocellulose	NC[5]	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	NC	NA
Nitroguanidine	0.1	4	11	11	11	37	0.74	D	NA
RDX	0.003	0.1	0.1	0.1	0.1	0.4	0.002	C	0.11
Trinitroglycerol	NC	0.005	0.005	0.005	0.005	0.005	0.005	NC	NA
2,4,6-Trinitrotoluene	0.0005	0.02	0.02	0.02	0.02	0.02	0.002	D	NA
White Phosphorus	0.00002	0.0005	None[6]	None	None	None	None	D	NA
Zinc (Zinc Chloride)	0.3	10	5	5	3	10	2	D	NA

1/ RfD, Reference Dose (rounded to one significant figure)
2/ United States Environmental Protection Agency Cancer Classification: A - human carcinogen; B - probable human carcinogen (limited evidence in epidemiological studies [B1] and/or sufficient evidence from animal studies [B2]), ; C - possible human carcinogen; D - not classifiable as to human carcinogenicity; E - not a human carcinogen
3/ NA, Not Applicable
4/ HMX, Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine
5/ NC, Not classified by EPA
6/ Health advisories are not recommended because of extreme toxicity

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