

Conventional Weapons Demilitarization: A Health and Environmental Effects Data Base Assessment Propellants and Their Co-Contaminants

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PREFACE

The U.S. Army Biomedical Research and Development Laboratory (USABRDL) has been charged with the responsibility of developing environmental criteria for military materials such as propellants, pyrotechnics, and explosives, as well as by-products associated with their demilitarization. USABRDL has funded Lawrence Livermore National Laboratory (LLNL) to prepare a health and environmental effects data-base assessment on technologies for demilitarizing conventional ordnance and the environmental by-products of those technologies. The study has been conducted in two phases. In Phase I, demilitarization technologies were examined, along with their solid, liquid, and gaseous effluents. The by-products were then ranked according to their potential health and environmental risks. In Phase II, data-base assessments were completed on the environmental chemistry, toxicology, and effects of the high-priority substances. This report contains data-base assessments on propellants and associated co-contaminants (i.e., ingredients in propellants and environmental degradation products) that are likely to be found at open-burning and open-detonation grounds. The assessments focus on those parameters that are needed to carry out analyses of the health and environmental risks of explosive residues. A companion report includes data-base assessments of explosives and their co-contaminants.

TABLE OF CONTENTS

Foreword	11
Preface	iii
Abstract	xi
1. Introduction	1-1
Propellants in the Demilitarization Inventory	1-2
Demilitarization Technologies and Environmental Residuals	1-2
Overview of Data-Base Assessments	1-2
2. Identification of the Primary Residuals Associated with the Open Burning and Open Detonation of Propellants	2-1
Trinitroglycerin	2-1
Production and Impurities	2-1
Photolysis Products	2-2
Biodegradation Products	2-2
Metabolism Products	2-2
Hydrolysis Products	2-2
Nitroguanidine	2-3
Production and Impurities	2-3
Biotransformation Products	2-4
Photolysis Products	2-4
Hydrolysis Products	2-4
Addition of Amines	2-4
Dibutyl Phthalate	2-5
Diethyl Phthalate	2-5
Diphenylamine	2-5
Ethyl Centralite	2-6
Overview of Propellants and Associated Co-Contaminants	2-8
3. Data-Base Assessment for Trinitroglycerin	3-1
Environmental Partitioning and Transport	3-1
Environmental Transformation Processes	3-1
Photolysis	3-1
Biotransformation	3-2
Hydrolysis	3-5

Toxic Effects on Animal and Humans	3-7
Toxicokinetics	3-7
Toxic Effects on Organs and Systems	3-9
Teratogenicity	3-11
Genotoxicity.	3-11
Carcinogenicity	3-12
Estimation of Intake Limits to Protection Public Health	3-13
Toxic Effects on Aquatic Species	3-13
4. Data-Base Assessment for Nitroguanidine	4-1
Environmental Partitioning and Transport	4-1
Environmental Transformation Processes	4-1
Photolysis	4-1
Biotransformation	4-5
Hydrolysis	4-8
Toxic Effects on Animals and Humans	4-8
Toxicokinetics	4-8
Toxic Effects on Organs and Systems	4-10
Teratogenicity	4-12
Genotoxicity	4-12
Carcinogenicity	4-13
Estimation of Intake Limits to Protect Public Health	4-13
Toxic Effects on Aquatic Species	4-14
5. Data-Base Assessment for Nitrosoguanidine	5-1
Environmental Partitioning and Transport	5-1
Environmental Transformation Processes	5-1
Photolysis	5-1
Biotransformation	5-2
Chemical Transformation	5-2
Toxic Effects on Animals and Humans	5-6
Estimation of Intake Limits to Protect Public Health	5-7
Toxic Effects on Aquatic Species	5-7

6. Data-Base for Dibutyl Phthalate.	6-1
Environmental Partitioning and Transport	6-1
Environmental Transformation Processes	6-2
Photolysis	6-2
Biotransformation	6-2
Reactions with Humic Substances	6-10
Hydrolysis	6-12
Toxic Effects on Animals and Humans	6-13
Toxicokinetics	6-13
Toxic Effects on Organs and Systems	6-15
Teratogenicity	6-17
Genotoxicity	6-18
Carcinogenicity	6-21
Estimation of Intake Levels to Protect Human Health	6-21
Toxic Effects to Aquatic Species	6-21
Toxic Effects to Plants	6-23
 7. Data-Base Assessment for Diethyl Phthalate	 7-1
Environmental Partitioning and Transport	7-1
Environmental Transformation Processes	7-1
Photolysis	7-2
Biotransformation	7-5
Reactions with Humic Substances	7-7
Hydrolysis	7-7
Toxic Effects on Animals and Humans	7-8
Toxicokinetics	7-8
Toxic Effects on Organs and Systems	7-9
Teratogenicity	7-10
Genotoxicity	7-11
Carcinogenicity	7-14
Estimation of Intake Limits to Protect Human Health	7-14
Toxic Effects to Aquatic Species	7-17

8. Data-Base Assessment for Diphenylamine	8-1
Environmental Partitioning and Transport	8-1
Environmental Transformation Processes	8-1
Photolysis	8-1
Biotransformation	8-3
Hydrolysis	8-7
Toxic Effects on Animals and Humans	8-7
Toxicokinetics	8-7
Toxic Effects on Organs and Systems	8-8
Genotoxicity	8-11
Carcinogenicity	8-13
Estimation of Intake Limits to Protect Human Health	8-14
Toxic Effects to Aquatic Species	8-15
 9. Data-Base Assessment for Ethyl Centralite	 9-1
Environmental Partitioning and Transport	9-1
Environmental Transformation Processes	9-1
Photolysis	9-1
Biotransformation	9-2
Binding to Humic Substances	9-5
Hydrolysis	9-6
Toxic Effects on Animals and Humans	9-7
Toxicokinetics	9-7
Toxic Effects on Organs and Systems	9-7
Genotoxicity	9-9
Carcinogenicity	9-9
Estimation of Intake Limits to Protect Human Health	9-9
Toxic Effects to Aquatic Species	9-10
 10. Health and Environmental Data Available on Propellants and Associated Co-contaminants	 10-1

Appendix A

Chemical/Physical Properties and Environmental Partition	
Coefficients: Calculations and Supporting Data	A-1
Vapor Pressure	A-1
Vapor-Pressure Equations	A-2
Vapor-Pressure Estimation with Limited Data	A-3
Vapor Pressures for Propellants and Co-contaminants	A-5
Estimation Methods for K_{OW}	A-6
Estimation of Log K_{OW} Values for Ethyl Centralite and NSGu	A-6
Water Solubility	A-9
Diffusion Coefficients of Chemicals in Air and Water	A-10
Coefficients for Equilibrium Distributions of Chemicals Between	
Soil/Water (K_d) and Soil-Organic-Carbon/Water (K_{OC})	A-11
Plant/Soil Partition Coefficient (K_{sp})	A-14
Bioconcentration Factors for Fish (K_{fw})	A-17
Beef-Fat/Diet Partition Coefficient (K_{fd})	A-19

Appendix B

Concentrations of Propellants in Environmental Media: Modeling,	
Detection Methods, and Measured Levels	B-1
Geotox Model	B-1
Detection Methods	B-5
Trinitroglycerin	B-5
Nitroguanidine	B-7
Dibutyl Phthalate	B-8
Diethyl Phthalate	B-9
Diphenylamine	B-9
Concentrations Reported in Environmental Media	B-9

References	R-1
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ABSTRACT

The demilitarization of propellants by open burning results in the deposition of residues on soils. Residues can consist of the main ingredients in propellant formulations, namely, nitrocellulose, nitroglycerin, and nitroguanidine. Co-contaminants, consisting of plasticizers and stabilizers present in propellant formulations as well as environmental degradation products of the propellants, represent additional soil contaminants. These substances include nitrosoguanidine, dibutylphthlate, diethylphthlate, diphenylamine, and ethyl centralite. To support studies of the health and environmental risks of such by-products, this report presents assessments of data available on parameters that affect the risks posed by propellants and their principal co-contaminants. Specifically, data-base assessments cover factors that influence the transport and fate of the contaminants in environmental media (e.g., soils, water, etc.) and subsequently, human exposures via different pathways (e.g., inhalation, ingestion, and skin absorption). Importantly, information on dose-response relationships for various toxic effects in humans and laboratory animals is evaluated so that acceptable daily intakes for noncarcinogenic substances and virtually safe dose rates for carcinogenic substances can be defined. Toxic effects on plant and aquatic species are also addressed.

1. INTRODUCTION

The demilitarization of propellants results in the release of various particulate and gaseous contaminants into the environment. The process of assessing the health and environmental risks of such contaminants begins with the identification of possible hazards; i.e., judging the potential detrimental health and environmental effects of a substance, based on available information. The next step, assuming that a potential hazard exists, is to estimate the concentrations that would occur in different media following release(s) into the environment. Concentrations are determined directly by measuring levels in soils, water, etc. and by estimation techniques; for example, models that simulate contaminant transport in air, water, and soils. An analysis is then conducted to define the human exposures that could result from the contaminant's occurrence in soils, water, etc. Based on the results of that analysis, a dose assessment is conducted to determine the absorbed doses from inhalation, ingestion, or through skin absorption.

To relate the doses to potential effects, dose-response relationships must be defined, if possible, for pertinent toxic effects. Risk assessments require data on the site-specific characteristics of the environmental media (e.g., soil, ground water, surface water, etc.) receiving the contaminants, the behavior of the contaminants in the various media, the transfer of the contaminants to man as well as target plant and animal species, and importantly, the toxicity of the substances. The specific parameters and supporting data required in chemical risk analyses depend largely on the methodologies and models used. Generally, such analyses utilize a mixture of measured and estimated parameters involving the properties of the contaminants, environmental media, and the plant and animal species potentially at risk. The basic objectives of this report are to assess the data available to quantify the health and environmental risks of propellants and their demilitarization by-products; to provide estimates of selected parameters required in risk analyses; and to identify relevant data gaps and key uncertainties.

PROPELLANTS IN THE DEMILITARIZATION INVENTORY

Propellants for small arms and large caliber weapons are generally divided into single-base, double-base, and triple-base formulations. Representative compositions of the three types of propellant formulations are depicted in Table 1-1. The primary components of the propellant mixtures are nitrocellulose (NC), nitroglycerin (glyceryl trinitrate (TNG)), and nitroguanidine (NGu). Minor ingredients of the propellants include dinitrotoluene, plasticizers (e.g., dibutyl phthalate (DBP) and diethyl phthalate (DEP)), oxidizers (e.g., barium nitrate and potassium nitrate), and stabilizers (i.e., diphenylamine (DPA) and ethyl centralite (EC)) (see Department of the Army, 1967). Our earlier analysis of the propellants scheduled for demilitarization (Layton et al., 1986) indicated that most of the propellants were in bulk form, with only a small portion derived from small arms ammunition.

DEMILITARIZATION TECHNOLOGIES AND ENVIRONMENTAL RESIDUALS

The technologies and procedures for demilitarizing propellants have typically involved combustion or detonation. Various kinds of furnaces have been used to incinerate propellants--especially in small arms ammunition--but rotary-kiln systems (notably the APE 1236 deactivation furnace) have become the most widely used incineration technology. The burning and detonation of propellants on the ground surface or in pits are probably the oldest methods of demilitarization, and they are used at many different facilities. As shown in Fig. 1-1, the open burning (OB) and open detonation (OD) of propellants result in atmospheric releases of gases and particles as well as residues in soils.

OVERVIEW OF DATA-BASE ASSESSMENTS

According to regulations proposed by the U.S. Environmental Protection Agency (U.S. EPA, 1987a) pursuant to the Resource Conservation and Recovery Act (RCRA), operators seeking permits for open-burning and open-detonation operations will have to perform analyses that show such operations will not adversely affect human health or the environment. Accordingly, a fundamental

Table 1-1. Representative compositions of major classes of propellant mixtures.

Chemical ingredient	Major propellant classes		
	SBP ^a	DBP ^b	TBPC ^c
	wt%		
NC (13.5 wt % N)	89	68	23
TNG		28	21
NGu			53
Dinitrotoluene	7		
DBP	3		
Barium nitrate		1	
Potassium nitrate		1	
Ethyl centralite ^d		2	2
DPA	1		
DEP		1	1
Total percent	100	100	100

^a Single-based propellant

^b Double-based propellant

^c Triple-based propellant

^d N,N'-diethylcarbanilide

goal of the data-base assessments contained in this report is to provide data on the parameters that are needed to carry out facility-specific risk analyses. The parameters and data assessed generally fall into two categories: (1) those that involve the estimation of contaminant exposures and absorbed doses and (2) those that involve estimation of potential effects. The exposure pathways that are of potential concern for OB/OD operations are shown in Fig. 1-2. In this schematic diagram, exposure pathways are linked to several environmental compartments where residual contamination can occur. Soil-based exposures consist of the inhalation of gases exhaled from surface soils, ingestion and dermal absorption of contaminated soils, and the

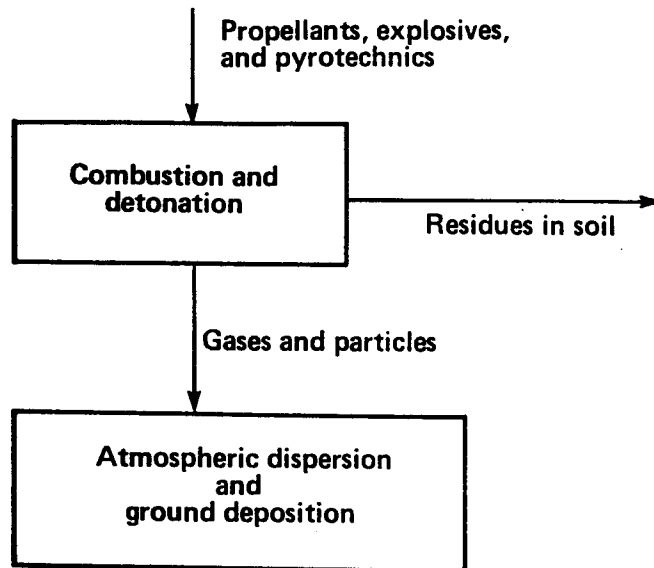


Figure 1-1. Diagram of the primary waste by-products from open burning and open detonation, see Layton et al., 1986.

ingestion of contaminated animals and crops. Water-based exposures occur via both ground and surface waters. Ground-water contamination can result from the migration of residual propellants from surface soils through the vadose zone to an unconfined aquifer. Subsequent exposures result from water consumption and the consumption of crops that have been irrigated with the contaminated ground water or perhaps even livestock that have consumed it. Surface-water contamination results from runoff from contaminated soils and/or discharges from contaminated ground water. Exposures can occur from direct consumption of water and aquatic species, animals, or crops that have accumulated a propellant or co-contaminant from surface water or sediments. Water-based exposures can also occur via dermal absorption and inhalation during showers.

Some of the parameters needed to conduct exposure and dose assessments include contaminant-specific properties such as aqueous solubility and vapor pressure, etc.; partition coefficients (e.g., soil/water, air/water);

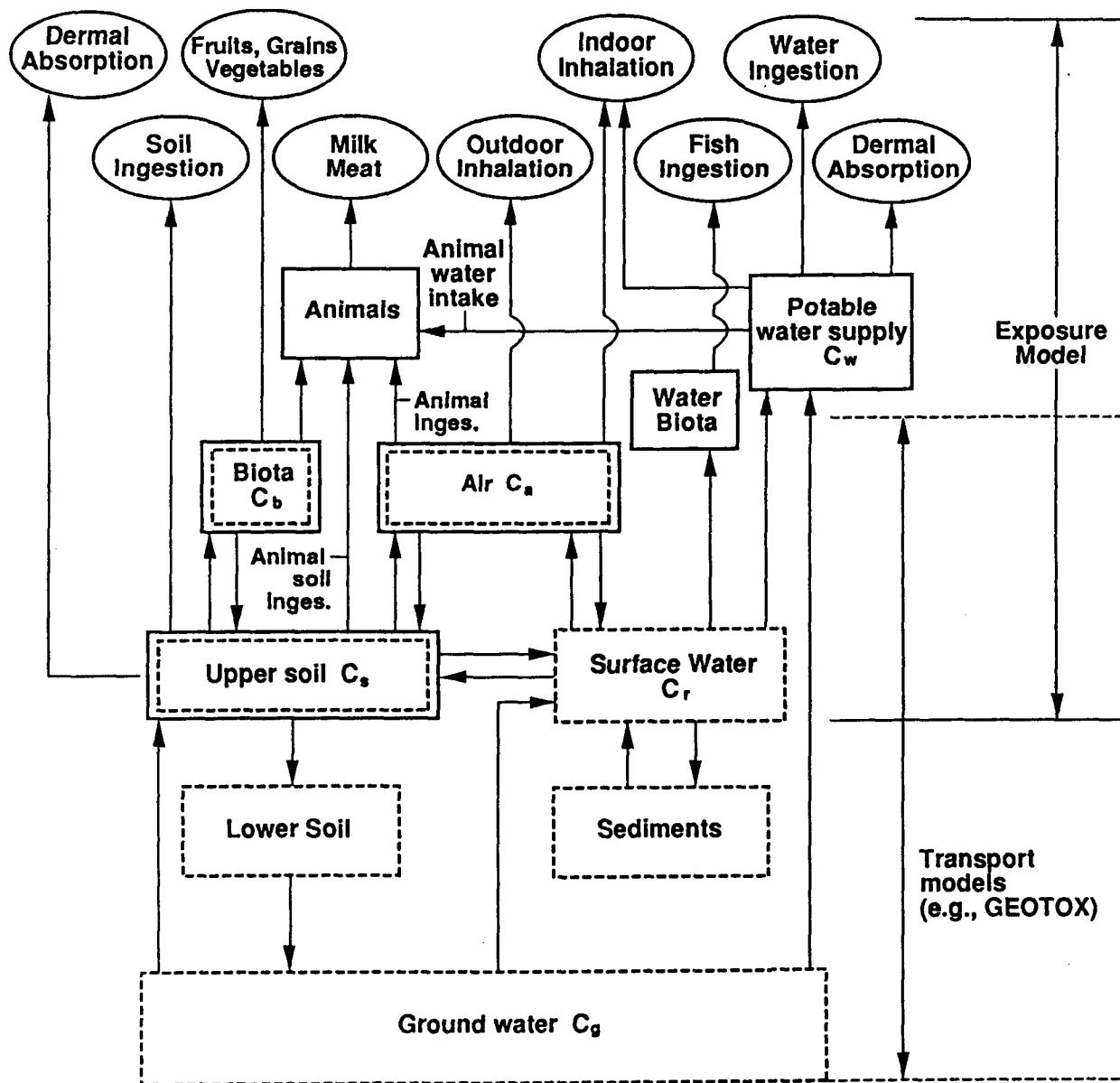


Figure 1-2. Overview of the relationships between contaminated environmental media and exposure pathways.

and degradation rates for various processes, including biodegradation, photolysis, and hydrolysis. Data are also needed on site-specific parameters describing pertinent characteristics of the environmental media transporting contaminants; the population at risk; and potential food-chain pathways.

The second key area that the data-base assessments address is the potential health effects of the propellant residues and associated co-contaminants. We examine the nature of toxic (i.e., carcinogenic and noncarcinogenic) effects produced in man and laboratory animals, together with the dose-response relationships for different toxic endpoints. In this regard, an important focus of our assessments is the derivation of safe intakes for noncarcinogenic contaminants and acceptable dose rates^a for carcinogenic substances, based on potency assessments of animal bioassay data. The final topics addressed are effects on aquatic species and plants. Although effects on aquatic species are of potential importance in some cases (e.g., direct discharges of ammunition production waste waters to a receiving stream), OB/OD operations do not normally pose a significant threat to aquatic systems because residues largely reside in the subsurface environment.

Consequently, our emphasis on aquatic effects is restricted primarily to overviews of the available literature related to toxic effects. In Table 1-2 we list the primary topics covered in the data-base assessments on individual contaminants.

The propellants and associated co-contaminants that are considered in the data-base assessments include TNG, NGu, and nitrosoguanidine (NSGu), DBP, DEP, DPA, and EC. (Dinitrotoluene is included in a companion assessment by Layton et al. (1987a) and is therefore not reviewed here.) Co-contaminants are either components of propellant mixtures or degradation products that are likely to be found along with the parent propellants in environmental media. Section 2 of the report reviews the primary co-contaminants. Subsequent sections contain data-base assessments on propellants and associated co-contaminants. Supporting appendices deal with chemical and physical properties (Appendix A) and modeling and measurements of propellants and co-contaminants in environmental media (Appendix B).

^a An acceptable dose rate is a chronic intake of a carcinogen that corresponds to a specific lifetime risk of cancer deemed acceptable by a risk manager. Based on the circumstances involved, such risk can range from 10^{-7} to 10^{-4} .

Table 1-2. Topics covered in the data-base assessments on individual substances.

Environmental Partitioning and Transport Properties

Chemical and physical properties

Partition coefficients

Environmental Transformation Processes

Photolysis

Hydrolysis

Biotransformation

Toxic Effects on Animals and Humans

Toxicokinetics

Toxic effects on organs and systems

Teratogenicity

Genotoxicity

Carcinogenicity

Estimation of intakes to protect human health

Toxic Effects on Aquatic Species

Acute toxicity

Subchronic and chronic toxicity

2. IDENTIFICATION OF THE PRIMARY RESIDUALS ASSOCIATED WITH THE OPEN BURNING AND OPEN DETONATION OF PROPELLANTS

The principal objective of this section is to identify the residual products associated with the demilitarization of propellants via open burning or open detonation. Co-contaminants of potential concern include impurities in the parent propellants and degradation products resulting from biotransformation, hydrolysis, etc. We did not evaluate NC as a contaminant of concern because it is essentially an inert substance. It is insoluble in water and toxicity studies with laboratory animals have shown that adverse effects occur only at very high dose rates (see Ryon (1986) for a review of studies dealing with NC).

TRINITROGLYCERIN

Although trinitroglycerin (TNG) was first made in 1846, it was not a practical explosive due to its great sensitivity to shock, especially in the liquid form. Instead, TNG has been used as a type of plasticizer in multi-base propellants formulations (Lindner, 1980). TNG is also used medicinally in the treatment of angina pectoris (Wu et al., 1981).

Production and Impurities

Trinitroglycerin has been produced by both batch and continuous processes. Both processes are based on the reaction of high-purity glycerol with a mix of nitric and sulfuric acids to form TNG. In the batch process, the TNG that is produced is washed with water, sodium carbonate solution, and then water again. In the continuous processes, the TNG produced is separated by centrifuge, and is then neutralized and washed with water (Urbanski, 1965a; Lindner, 1980; Department of the Army, 1967).

Trinitroglycerin does not corrode metals. Stockpiled TNG is stable over a period of years at room temperature and temperatures up to 50°C (Department of the Army, 1967). However, nitric acid or NO₂ and water and CO₂ have been found to accelerate decomposition of TNG; nitrogen, NO, CO and CO₂ do not (see Urbanski, 1965a). The difference in TNG stability therefore lies in the

residual nitric acid content and temperature. Urbanski (1965a) cites several examples of TNG showing no decomposition over many decades when temperatures were below 50°C and no residual acid was present.

Photolysis Products

Urbanski et al. (1939) (cited in Urbanski, 1965a) noted that the pH dropped progressively over several days after exposure of solid TNG to light in the visible region (320 to 410 nm). Presumably the acidity was due to the release of nitrogen oxides.

Biodegradation Products

Wendt et al. (1978) found that bacteria from a local sewage treatment plant produced dinitroglycerin from TNG in a basal salts medium with glucose. On the other hand, Spanggord et al. (1980b) could not isolate such products in their biodegradation experiments using TNG. They used bacteria from TNG-contaminated water and made their biotransformation measurements both in that water and in a basal salts medium. Nitrate was the only product measured in their experiments.

Metabolism Products

Metabolism of TNG in the livers of mammalian systems results in the formation of dinitroglycerins, which subsequently metabolize to mononitroglycerins, which then metabolize to glycerin itself (Baba et al., 1984).

Hydrolysis Products

Wu et al. (1981) studied the hydrolysis of TNG in 4 N HCl at 37°C and analyzed the product mixtures over a period of 60 h. The chromatograms (derived from high-performance liquid chromatography or HPLC) of the products showed that the acid hydrolysis of TNG produces di- and mononitroglycerins. At the completion of 60 h, there was very little TNG left. The two di- and two mononitroglycerins were produced in the stoichiometrically expected

amounts from random hydrolysis of the precursor nitrate esters. Capellos et al. (1984) analyzed the product mix from basic hydrolysis of TNG in distilled water. They found that a number of solids, ions, and volatiles were produced. Although they attempted to characterize the products, most were not identified. Calcium nitrate and calcium nitrate, ester nitrates, polyhydroxy (diol type) compounds, as well as a number of "solids" were separated. The solids were calcium salts, one of which was calcium oxalate.

NITROGUANIDINE

Nitroguanidine (NGu) has been used in propellants since 1900 and currently it is used primarily as a component in multi-base propellant mixtures. The addition of NGu to propellant mixtures results in lower burning temperatures, increased thrust, reduced flash, and increased storage stability (Small and Rosenblatt, 1974; Kenyon, 1982). NGu is much more soluble in water than TNT or RDX. It is fairly stable in water, but decomposes on exposure to sunlight. Microbial degradation will occur only with adapted organisms and with sufficient nutrients. Hydrolysis will not occur except in highly alkaline water.

Production and Impurities

Nitroguanidine can be produced by several processes. In one method, calcium carbonate is converted to calcium cyanamide, which with ammonium nitrate forms guanidine nitrate plus ammonia; finally, the guanidine nitrate plus sulfuric acid yields NGu. Wastewaters from this process contain NGu, cyanoguanidine, nitrosoguanidine (NSGu), ammeline, melamine, guanidine, urea, organic and ammonia-based nitrogen, Cl^- , NO_2^- , NO_3^- , and $\text{SO}_4^{=}$ (Burrows et al., 1984a). The military specification for NGu allows only 0.06 wt% acidity, 0.02 wt% chlorides and 0.2 wt% sulfate (Department of the Army, 1967).

Biotransformation Products

Kaplan et al. (1981, 1982) found that NGu was degraded microbially to the intermediate, NSGu. This compound rearranged, ultimately forming guanidine, cyanoguanidine, melamine, nitrogen, and water.

Photolysis Products

Sunlight photolysis of NGu produces a dominant product that has not yet been identified (Spanggord et al., 1985). Photolysis of NGu with ultraviolet (UV) light at 253.7 nm produced and then destroyed NSGu. For solutions irradiated with UV at this wavelength between pH 5 and 11, the final products found were guanidine, cyanoguanidine, cyanamide, urea, melamine, ammeline, and ammonia (Noss and Chyrek, 1984). However, Kaplan et al. (1981, 1982) found no evidence for the formation of either urea or guanidine when they irradiated NGu with "short-wave" UV light.

Hydrolysis Products

Under environmental conditions, NGu is stable in aqueous solution. Hydrolysis is very slow under pH 10. The principal product identified by Spanggord et al. (1985) is nitrourea.

Addition of Amines

Both NGu and its photolytic and microbial intermediate product, NSGu, react with aliphatic amines. Davis and Rosenquist (1937) reported that NSGu reacts readily in a water solution at room temperature with primary and secondary amines and rearranges to form cyanamide. In contrast, NGu reacts with primary amines substituting one amino group of NGu for an alkyl amine. These reactions suggest that NGu and NSGu may interact with proteins or humic materials having aliphatic amine groups.

DIBUTYL PHTHALATE

In conventional ordnance, dibutyl phthalate (DBP) is used primarily as a plasticizer in propellant formulations (Lindner, 1980). It is also a plasticizer for polymers used in many applications such as polyvinylchloride pipes, fabrics, and some housepaints (Virgin et al., 1981). DBP also occurs naturally in tobacco leaves, grapes and oxidized corn oil (Inman et al., 1984). After disposal or release into the environment, DBP will be degraded slowly by adapted microbes in soils and water systems. DBP will hydrolyze to the monoester and then to phthalic acid. Ultimately it will be biodegraded to carbon dioxide by microorganisms. Proposed intermediates and transformation mechanisms are discussed in Section 6.

DIETHYL PHTHALATE

Diethyl phthalate (DEP) is used as a plasticizer for numerous polymers and in propellants. In recent years, DEP from discarded materials has become more common in soils, sediments, and water. Biotransformation is the primary transformation process for DEP in the environment. Transformation products include the monoester, phthalic acid, and ultimately carbon dioxide.

DIPHENYLAMINE

Diphenylamine (DPA) is a non-explosive stabilizer and antioxidant for polymers, propellants, pesticides, rubbers, dyes and pharmaceuticals (Verschuere, 1983). Diphenylamine acts as a stabilizer in single- and double-based propellants by scavenging nitrous oxide (NO). Without a stabilizer, these propellants deteriorate rapidly; the free NO is oxidized to NO₂ with a simultaneous release of heat. This reaction catalyzes further degradation. The scavenging action of DPA results in a series of progressively more nitrated diphenylamines. Most of these amines are better stabilizers than DPA itself (Apatoff and Norwitz, 1973). When the DPA has been converted to dinitrodiphenylamine, the propellant is usually no longer stable. Care must be taken in using DPA as a stabilizer because, under

certain conditions, it attacks the NC that it is supposed to stabilize. Examples of these conditions are improper mixing or amine impurities. Centralites (i.e., N,N'-dialkyl-N,N'-diphenylureas) have replaced DPA in many applications because they cannot react with NC directly (Fedoroff et al., 1972). Berkowitz et al. (1978) listed four impurities found in crude DPA that may be responsible for abnormal toxicological properties seen in rats fed DPA. Two of these compounds are biphenyls with an amine group at either the ortho or para position of one ring, and two more are analogous, but the unsubstituted ring is saturated.

ETHYL CENTRALITE

Ethyl centralite (EC) is also known as Centralite 1, carbamate, N,N'-diethyl, N,N'-diphenylurea and N,N'-diethylcarbanilide. EC both dissolves and stabilizes NC. When the amount of EC is approximately 1 wt% of the proposed composition, it acts as a stabilizer. In concentrations of 3 to 10 wt%, it gelatinizes NC and sometimes reduces flash (Fedoroff and Sheffield, 1962). One composition still in use today is Ballisite 50/50, which consists of 49 to 49.5 wt% NC, 49 to 49.5 wt% TNG and 1 to 2 wt% EC (Urbanski, 1984). Besides its use as a "gelatinizer-stabilizer-flash reducer in smokeless gunpowders," it has been used as a plasticizer under the name of Mollit 1 in Germany after World War I and as an age-retarder in vulcanized rubber (Fedoroff and Sheffield, 1962).

The stabilization of propellants is achieved by neutralizing the acidity caused by the release of nitrogen oxides from the decomposition of NC, TNG (Ryder and Knowlton, 1983; Fedoroff and Sheffield, 1962), and ammonium nitrate (Urbanski, 1986b). These nitrogen oxides react with water to form nitrous and nitric acids. The nitrous acid hydrolyzes EC to N-ethylaniline, which reacts further with additional nitrous acid to form N-ethyl-N-ethylnitrosamine (Fig. 2-1). Any nitric acid formed in the decomposition of NC or TNG reacts with the phenyl groups of EC forming "mononitrocentralite" (Fedoroff and Sheffield, 1962).

Fedoroff and Sheffield (1962) reviewed many studies on the impurities present in EC itself and in impurities formed by the reaction of EC with the nitrogen oxide decomposition products of NC and TNG. According to them, newly

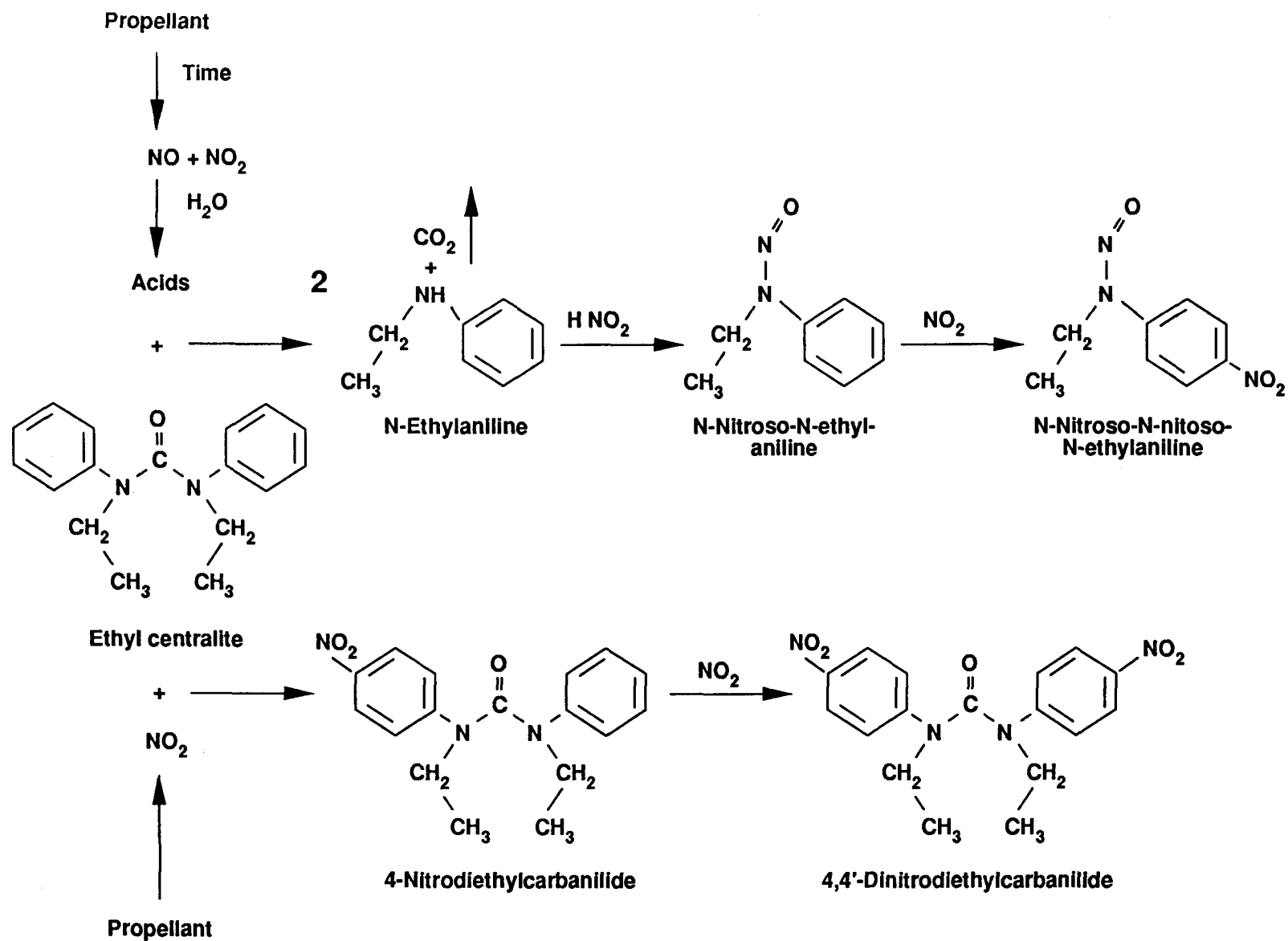


Figure 2-1. Some products formed by the stabilization of propellants by ethyl centralite (adapted from Fedoroff and Sheffield, 1962; Ryder and Knowlton, 1983).

manufactured EC should contain no more than 0.005 wt% chlorine and 0.04 wt% secondary amines. In addition, Fedoroff and Sheffield state that military specifications call for no more than 0.3 wt% ash, 0.2 wt% secondary or tertiary amines (ethylaniline and diethylaniline), and 0.1 wt% volatile matter.

Pauling et al. (1945) (as cited in Fedoroff and Sheffield, 1962) reported that two types of degradation products were formed from EC when propellants containing it were heated to 65 to 75°C for varying periods up to two years. One type of compound retained the urea structure: these compounds included 4-nitrodiethylcarbanilide, 4,4'-dinitrodiethylcarbanilide, and trace amounts of 2,4,4'-trinitroethylcarbanilide and 2-nitrodiethylcarbanilide. The other type of compound resulted from splitting the urea structure: compounds isolated were N-nitroso-N-ethylaniline, 4-nitro-N-nitroso-N-ethylaniline, and traces of 4-nitro-N-ethylaniline, 2-nitro-N-ethylaniline, 2,4-dinitro-N-ethylaniline, N-ethylcarbanilide, 4-nitroaniline, and 4-nitrophenol. Scavenging of nitrous oxide by EC produces carbon dioxide and N-ethylaniline. These products are formed by the hydrolysis of the urea linkage by the nitrous acid produced from the decomposition of NC and/or TNG. Further reaction of N-ethylaniline with nitrous acid produces ethylphenylnitrosamine (N-nitroso-N-ethylaniline), which is further converted to "nitronitrosamine" (probably 4-nitro-N-nitroso-N-ethylaniline) and nitro-N-ethylanilines. Propellants stabilized with EC will have various amounts of the reaction products noted above.

OVERVIEW OF PROPELLANTS AND ASSOCIATED CO-CONTAMINANTS

The primary energetic ingredients used in multibase propellant formulations are NC, TNG, and NGu. Minor ingredients of propellants (see Table 1-1) include stabilizers and plasticizers. Demilitarization of propellants through OB/OD operations will form combustion products as well as residual products that consist of the parent propellants, plus the stabilizers and plasticizers. Our Phase I report (Layton et al., 1986) on demilitarization operations did not identify any combustion products that would require further assessment at this time. Compared with the soil and water-concentration data on explosives such as TNT and RDX, concentration data

for the propellants in environmental media are sparse. We have therefore focused our data-base assessments on the major constituents of propellant mixes that are likely to be found in soil and water samples at locations where propellants have been handled or burned. The data-base assessments therefore focus on TNG, NGu and its primary degradation product, NSGu, the plasticizers DBP and DEP, and the stabilizers, DPA and EC.

3. DATA-BASE ASSESSMENT FOR TRINITROGLYCERIN

Nitroglycerin (denoted TNG, for trinitroglycerin) is a key ingredient in multibase propellant formulations. In those propellants it serves as a plasticizer for nitrocellulose (Lindner, 1980). TNG has also been used for many years as a vasodilator drug. Chronic cancer bioassays conducted by Ellis et al. (1978a) with rats and mice revealed carcinogenic responses in rats but not mice. Once released into the environment, TNG will be transformed by adapted bacteria; however, degradation by photolysis and hydrolysis will be slow.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

Chemical identifiers for TNG are found in Table 3-1, and pertinent physicochemical properties are shown in Table 3-2. Table 3-3 contains partition coefficients for plant/soil (K_{sp}), beef-fat/diet (K_{fd}), fish/water (K_{fw}), and soil organic carbon (SOC)/water (K_{oc}). For each partition coefficient we provide a value estimated from a regression equation (see Appendix A for details) as well as any measured values that are available from the literature. Measured partition coefficients were only available for K_{oc} and K_{fw} . Spanggord et al. (1980b) used a sterilized river sediment to measure the partitioning of TNG between sediment and water (denoted here as K_d) and SOC/water. The average K_d value for three sediment samples was 20 and the mean K_{oc} value was 593. For comparison, the calculated K_{oc} (see Table 3-3) was 100, based on the aqueous solubility of TNG. Bentley et al. (1978) completed TNG bioaccumulation studies with four species of fish (L. macrochirus, P. promelas, S. gairdneri, and I. punctatus). The K_{fw} value for L. macrochirus was approximately 15, and for the other species the K_{fw} value was about 8. For comparison, the predicted value of K_{fw} is 7.6.

ENVIRONMENTAL TRANSFORMATION PROCESSES

Photolysis

Nitroglycerin absorbs very little light in the visible spectral region (Spanggord et al., 1980b). However, Urbanski et al. (1939) (as cited in

Table 3-1. Chemical identifiers of nitroglycerin.

Empirical formula:	$C_3H_5N_3O_9$	Structural formula:
Molecular weight:	227.09	$\begin{array}{c} CH_2 - ONO_2 \\ \\ CH - ONO_2 \\ \\ CH_2 - ONO_2 \end{array}$
CAS reg. no.:	55-63-0	
RTECS no.:	QX2100000	

Urbanski, 1965a) reported that a 3-g sample of TNG slowly decomposed when irradiated with 320-410 nm of visible light for one hour at 15°C. The decomposition continued for 2 to 3 d. Spanggord et al. (1980b) investigated the photodecomposition of TNG in both natural and distilled water to determine whether indirect photolysis could contribute to the disappearance of TNG. Their measured photolysis rates and associated half-lives are shown in Table 3-4. The sample of Searsville Pond, California, water represented a natural eutrophic water, while the New River water sample represented TNG-contaminated water. The latter sample was taken down river from a TNG manufacturing facility at Radford, Virginia. All experiments were kept at 20°C for 34 d. There was an unexplained loss of 7 to 12% of the TNG in the dark controls of the Searsville Pond and New River water samples. The results shown in Table 3-4 have been corrected for this loss. The rate of loss of TNG in natural waters was twice that in distilled water, and thus Spanggord et al. concluded that humic materials enhance its photodecomposition. Their results indicate that the nominal half-life of TNG in water under winter lighting conditions is on the order of 2 to 4 months.

Biotransformation

Spanggord et al. (1980b) found that TNG at a concentration of 10 ppm in New River water was completely biotransformed in 13 d. The same results were obtained when river sediment or yeast was added. Using cultures of the biotransforming organisms, they found not only that TNG could be used by the

Table 3-2. Chemical and physical properties of TNG. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling Point	°C	218 (explodes)	Windholz et al., 1983
Freezing/melting point	°C	13.2	Lindner, 1980
Density	g/mL	1.59	Windholz et al., 1983
Vapor pressure	torr	2.5×10^{-4}	Jordan, 1954
Aqueous solubility	mol/L mg/L	7.9×10^{-3} 1800	Dean, 1985
Henry's law constant	(L-torr)/mol	0.032	Calculated as the ratio of vapor pressure to aqueous solubility
Diffusion coefficients:	Air Water	m^2/s m^2/s	Estimated ^a Estimated ^a
Log octanol/water partition coefficient (K_{ow})	log K_{ow}	1.62	Roberts et al., 1983

^a See Appendix A.

Table 3-3. Partition coefficients for use in estimating human exposures to TNG.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^a /(mg/kg soil)	2	Calculated ^b from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	1.5×10^{-3}	Calculated ^b from water solubility and log K_{ow}
Fish/water	K_{fw}	(mg/kg fish) ^a /(mg/kg water)	7.6	Calculated ^b from log K_{ow}
			8 to 15	Bentley et al. (1978) measured the K_{fw} partition coefficients for four fish species (see text)
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	158	Calculated ^b from solubility in water
			593	Average of three measured values (430, 540, and 810) reported by Spanggord et al. (1980b)

^a Wet-weights for plant and fish

^b See Appendix A

Table 3-4. Photolysis rates of 5.8 ppm TNG in water under winter sunlight (from Spanggord et al., 1980b).

Water	Rate constant ^a (s ⁻¹)	Half-life (d)
Distilled	6.9 x 10 ⁻⁸	116
New River	1.4 x 10 ⁻⁷	57
Searsville Pond	1.1 x 10 ⁻⁷	73

^a Rate constants are corrected for losses in the dark control. Half-lives are based on 24-h days having 10 h of sunlight. Natural waters were filtered through a 0.45- μ m filter.

bacteria as a sole carbon source but that an enriched culture of these organisms could grow on 120 ppm TNG in a basal salts medium. Spanggord et al. did not find any di- or mononitroglycerols in their HPLC analysis of the medium after culture with TNG. The only product isolated was nitrate. They suggest that these products, if formed, decomposed more rapidly than TNG. Wendt et al. (1978) used sewage sludge bacteria in a basal salts medium to study the biodegradation of TNG. They found that after a period of 5 d only 3.1% of the 70 ppm TNG had disappeared in a medium without glucose, but 53.6% had disappeared from the medium containing 1 g/L of glucose (there was, however, a 9.4% decrease in the TNG concentration in the control flask containing the sterilized equivalent).

Hydrolysis

No measurements of TNG hydrolysis have been made at temperatures and pH levels that are associated with natural waters. However, Spanggord et al. (1980a) prepared estimates of TNG half-lives from hydrolysis rates measured at elevated temperatures and pH's. For example, they estimated that hydrolysis half-lives of TNG at pH's 5 to 7 would be on the order of years, based on an extrapolation of a hydrolysis rate of $6 \times 10^{-8} \text{ s}^{-1}$, measured by Svetlov et al. (1976) at 80°C (the hydrolysis rate at 20°C and associated half-life was

calculated by assuming that the rate of hydrolysis was halved for each 10°C decrease in temperature -- a half-life of about 23 y is obtained by this method.) Spanggord et al. also estimated that hydrolysis under acidic conditions would be extremely slow, with a half-life over 50 y at pH 3 (derived from a hydrolysis rate measured by Rosseel et al. (1974) for TNG in 1 M HCl at 37°C). Finally, Capellos et al. (1979) measured a second-order rate constant for TNG under alkaline conditions as $2.15 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ at 25°C, and from this value Spanggord et al. estimated a half-life of 37 d at pH 9 (we estimated a half-life of 10 y at pH 7 and one year at pH 8 from the same rate constant). These estimates indicate that TNG hydrolysis is significant only at high pH's.

Acid hydrolysis forms dinitrate esters and monoesters. The dinitrate esters do not hydrolyze as quickly as TNG. Wu et al. (1981) suggested that the faster rate for TNG is due to the greater steric interaction of the trinitroesters in TNG than in the dinitroesters. Because the nitrate esters in TNG are bulky groups on three adjacent carbons, there is more steric interaction than in both dinitroglycerins where there are only two of these esters. This steric interaction is depicted in Fig. 3-1, which shows the conformations proposed by Winkler (1985) for TNG and 1,2-propanediol dinitrate. The stepwise hydrolysis of the nitro groups during the acid hydrolysis of TNG was not observed during the alkaline hydrolysis experiment conducted by Capellos et al. (1984). They concluded that the alkaline hydrolysis of TNG by $\text{Ca}(\text{OH})_2$ involves more than just the hydrolysis of the NO_2 groups of TNG because both NO_2^- and NO_3^- are formed during alkaline hydrolysis of alkyl nitrate esters. Capellos et al. suggested mechanisms including nucleophilic substitution and elimination. Hydroxyl attack can occur at either a carbon or a nitrogen atom in TNG, forming NO_3^- and an alcohol as substitution products. Loss of either the β - or α -hydrogen atoms followed by elimination of the $-\text{O}-\text{NO}_2$ or $-\text{NO}_2$ group, respectively, would produce NO_3^- and an olefin in the first case and NO_2^- and an aldehyde in the second.

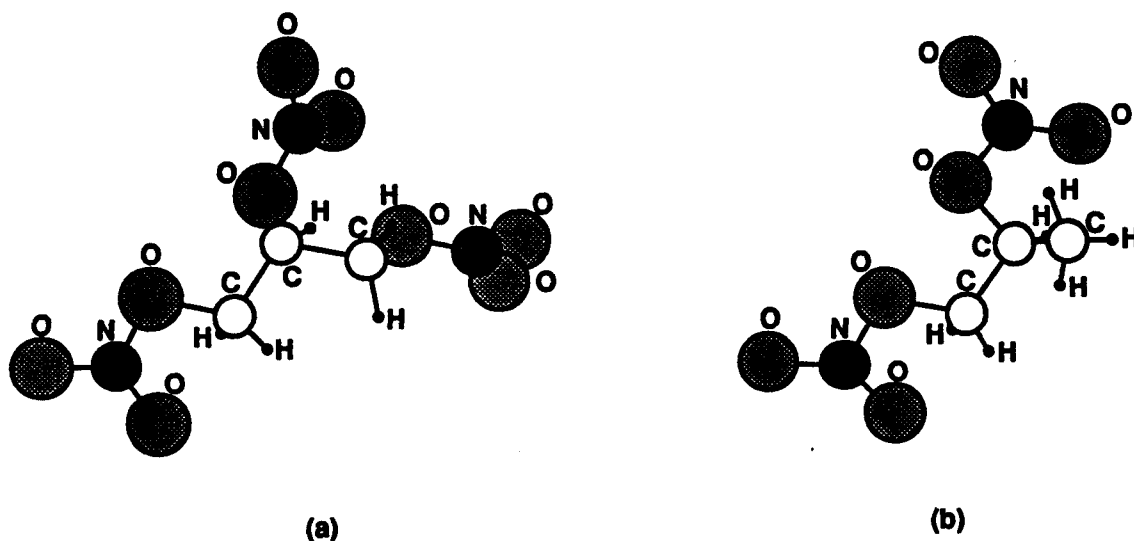


Figure 3-1. Conformation of a) TNG and b) 1,2-propanediol dinitrate (from Winkler, 1985).

TOXIC EFFECTS ON ANIMAL AND HUMANS

Toxicokinetics

Due in part to the widespread use of TNG as a vasodilator drug and as an important ingredient in propellant formulations, there have been a large number of animal and human studies conducted on different facets of the pharmacokinetic and toxicologic properties of TNG. Previous reviews of the toxicology of TNG have included those by Smith (1986), Khanna (1986), NIOSH (1978), and Shiotsuka (1979). In the subsections below we review the salient toxicologic characteristics of TNG, and conclude with a review of dose-response data available for estimating safe intakes.

Absorption. DiCarlo et al. (1968) detected radioactivity in the blood, heart, kidneys, liver, lungs, spleen, gastrointestinal tract, carcass, urine, feces, and in expired air (CO_2) of rats within 30 minutes of the administration of a single oral dose of 10 mg/kg ^{14}C -TNG. After 4 hours, 43% of the radiolable had been excreted or expired. Hodgson and Lee (1975) found that about 80 to 90% of an oral dose of ^{14}C -TNG was absorbed by rats during a 24-h period.

In humans, peak levels of TNG in blood have been measured within 5 minutes. Bogaert and Rosseel (1972), for example, reported that the absorption of 60 to 75% of a buccally administered dose of TNG took less than 4 minutes. Following the sublingual administration of 0.3 mg of TNG (Blumenthal et al., 1977) or 0.6 mg (Armstrong et al., 1979; Wei and Reid, 1979), peak concentrations of TNG in plasma were observed within 5 minutes. Armstrong et al. (1979) administered TNG sublingually to human volunteers and observed TNG in the blood in 0.5 minutes, a peak concentration of 2.3 ng/mL at 2 minutes, and the nearly complete disappearance from the blood at 20 minutes.

Distribution. TNG is rapidly and widely distributed in body organs after oral or intravenous administrations. The liver and muscle tissue appear to be the primary sites of accumulation. Within 30 minutes of the administration of single oral doses of radiolabeled TNG to rats, DiCarlo et al. (1968) measured radioactivity in the gastrointestinal tract, blood, heart, liver, lungs, kidneys, spleen, and carcasses. After 30 minutes 7.3 and 33% of the administered radiolabel remained in the livers and carcasses and decreased to 2.5 and 16.6%, respectively, four hours after exposure. In a similar experiment, Hodgson and Lee (1975) detected 4.6% of the initial radioactivity of orally administered ^{14}C -TNG in the liver of treated rats at 4 h, and 4.3% at 24 h. Muscle contained 9.3 and 2.8% of the radiolabel at 4 and 24 h, respectively. Small quantities (0.1 to 2.1%) of the administered radiolabel were observed in the blood, kidneys, brain, and lungs at 4 and 24 h. At 24 h after the oral administration of ^{14}C -TNG to several species, Lee et al. (1976) detected the highest levels of the radiolabel in the liver of mice, rats, and rabbits (4.3 to 6.8%) and in the skeletal muscle of dogs and monkeys (9.5 and 13.0%, respectively). The kidneys, spleen, lungs, and brain of all species contained smaller amounts of radioactivity.

Metabolism. In mammals, polynitric esters such as TNG are initially metabolized by hepatic organic nitrate reductases and glutathione (GSH) to glyceryl-1,2-dinitrate and glyceryl-1,3-dinitrate. These metabolites can react with glucuronic acid to form the corresponding glucuronide conjugates, or they can undergo subsequent denitration to glyceryl mononitrate and glycerol. Glycerol is metabolized to CO_2 ; some glyceryl mononitrate glucuronide is also formed. The various glucuronide conjugates are

eliminated in urine and bile (Wendt et al., 1978; McNiff et al., 1980; Noonan, 1983; Baba et al., 1984).

Although the site of TNG metabolism is not well defined, several studies have demonstrated that both hepatic and extrahepatic tissues are important. Lang et al. (1972) showed that the half-life of elimination of ^{14}C -TNG was approximately four times greater in eviscerated rats than in intact controls. Needleman and Harkey (1971) found that the rate of degradation of TNG in isolated perfused rat liver was similar to rates measured in vivo, while Needleman et al. (1972) showed that human liver biopsy samples contained a GSH-dependent nitrate reductase able to metabolize TNG to dinitrates and mononitrates. The same group (Needleman et al., 1971) reported that in vitro, homogenates of rat liver, brain, kidney, and skeletal muscle were able to metabolize glycerol to CO_2 , but were unable to metabolize TNG to CO_2 .

The results of Blei et al. (1984) and Fung et al. (1984a, 1984b) indicate that the liver may not play a major role in the elimination of TNG, but that extrahepatic tissues such as the blood vessels contribute to metabolism. For example, when Blei et al. (1984) injected TNG intravenously into rats that had portacaval shunts or who had undergone a sham operation, clearance of TNG was nearly identical among the two groups.

Both Armstrong et al. (1979) and McNiff et al. (1981) observed that the total body clearance of TNG in humans greatly exceeds liver plasma flow and cardiac output, indicating the importance of extra-hepatic metabolism. Blei et al. (1984) also observed that systemic plasma clearance exceeded hepatic blood flow in rats. Sokoloski et al. (1983) found that whole blood, blood cells, and plasma from humans can metabolize TNG in vitro. Similar observations were reported by DiCarlo and Melgar (1970) for rats.

Excretion. DiCarlo et al. (1968), Hodgson and Lee (1975), and Lee et al. (1975, 1976) have studied the excretion of radiolabeled TNG from animals. In general, most of the radiolabeled TNG administered to laboratory animals is excreted in urine and expired air.

Toxic Effects on Organs and Systems

In humans the only common symptom of TNG toxicity is headaches. In experimental animals, though, several different toxic endpoints have been

observed, including methemoglobinemia, testicular degeneration, and hepatocellular carcinomas. The most comprehensive sets of toxicity studies completed on TNG are those by Lee et al. (1976), dealing with subacute and subchronic administrations to dogs, rats, and mice, and by Ellis et al. (1978a), dealing with lifetime exposures to the same species. Key findings of those studies were summarized in Ellis et al. (1984). The subsections below provide an overview of the major effects observed.

Hematological effects. Dose-related increases in methemoglobin levels were observed in dogs receiving TNG at dose rates ranging from 25 to 200 mg/kg-d over a 5 d period (see Lee et al., 1976). In a 13 wk study with rats that received 2.5 wt% TNG in feed, Ellis et al. (1984) reported that the treated rats had significant ($p < 0.05$) increases in erythrocytes, reticulocytes, hematocrit, hemoglobin concentration, and alkaline phosphatase. In a chronic toxicity study, Ellis et al. (1984) reported that rats fed 1 wt% TNG in their diet developed methemoglobinemia after three months of dosing. Hemoglobin values had returned to normal by the end of the 24-month study period. Chronically-exposed mice also had hemotoxic effects from exposure to TNG, expressed as methemoglobinemia (males) and Heinz bodies (both sexes).

Hepatic effects. Rats that consumed TNG in the diet for 12 months (0.01, 0.1, 1.0, 1.0 wt%) had elevated serum enzyme levels, grossly enlarged livers, cholangiofibrosis, and a dose-related increase in the frequency of hepatic preneoplastic changes. Animals maintained on the same TNG-containing diet for 24 months had a similar spectrum of hepatic lesions. In the high-dose rats there was evidence of hepatic carcinomas and nodules. Mice fed TNG in their diet at the same levels for 12 or 24 months did not develop pathological changes of the liver (Ellis et al., 1984).

Reproductive effects. Lee et al. (1976) observed testicular degeneration, atrophy, and aspermatogenesis in rats consuming 1400 mg/kg-d of TNG over a period of 13 wk. Fifty percent of the male rats that received TNG in the diet for two years (1.0 wt%) developed interstitial cell tumors in one or both testes. A higher, unspecified incidence of aspermatogenesis among these animals (compared to controls) was attributed to the secondary effects of the tumors (Ellis et al., 1984). A three-generation reproductive effects

study was also completed by Ellis et al. (1978a) with rats. Infertility in the F₂ generation of rats was attributed to testicular effects (i.e., aspermatogenesis, increased interstitial tissues in testes, and testicular atrophy) in the F₂ males.

Teratogenicity

The three-generation study completed by Ellis et al. (1978a) did not produce conclusive data on the teratogenicity of TNG to rats. Diaphragmatic hernia was found in the soft tissue of fetuses from four of 10 litters in the high-dose group. Although its occurrence was not statistically significant, the authors considered this malformation a potential consequence of TNG exposures.

Genotoxicity

The genotoxicity of TNG has been evaluated in different bioassays, with inconclusive results. Simmon et al. (1977) obtained negative results when they evaluated the mutagenicity of TNG to several strains of Salmonella typhimurium. TNG was also inactive in short-term tests with Saccharomyces cerevisiae. Ellis et al. (1987b), however, found that TNG was weakly mutagenic in S. typhimurium strains TA 1535 and TA 1537, with or without metabolic activation. In other work, Lee et al. (1976) examined the cytogenetic effects on chromosomes from peripheral lymphocyte and kidney cultures derived from rats receiving TNG in their feed. Lee et al. did not observe any significant morphological aberrations in the chromosomes. Lee et al. also treated ovary cells from Chinese hamsters with TNG to determine whether TNG causes mutations in somatic cells. The cell cultures treated with TNG did not produce any mutants, even at levels that killed 65 and 99% of the cell populations. Ellis et al. (1978b) studied the genotoxic potential of TNG using assays to detect chromosomal aberrations in cell cultures (i.e., bone marrow and kidney cells from TNG-treated rats) and dominant lethal mutations in CD rats treated with TNG. Neither assay detected any mutagenic activity.

Carcinogenicity

Evidence on the carcinogenic potential of TNG comes mainly from a chronic bioassay conducted by Ellis et al. (1978a) that showed that TNG was carcinogenic to CD rats. There are no human data that indicate that occupational exposures to TNG poses an increased risk of cancer (see NIOSH, 1978 and Smith, 1986).

In the chronic studies conducted by Ellis et al. (1978a), groups of Charles River CD rats (38 males and 38 females) and CD-1 mice (58 males and 58 females) were given 0, 0.01, 0.1, or 1 wt% TNG in their feed for two years. The estimated dose-rates for male and female rats were 3.04 and 3.99 mg/kg-d, respectively, for the low dose groups, 31.5 and 38.1 mg/kg-d for the middle dose groups, and 363 and 434 mg/kg-d for the high-dose groups. The estimated dose-rates for male and female mice were 11.1 and 9.72 mg/kg-d, respectively, for the low dose groups, 114.6 and 96.4 mg/kg-d for the middle dose groups, and 1022 and 1058 mg/kg-d for the high-dose groups. After two years, no significant increases in the incidence of tumors were observed in mice. However, significant increases ($p < 0.05$) in the incidence of hepatocellular carcinoma were reported for both male and female rats in the high-dose groups compared to the control groups. A significant increase in the number of rats with testicular interstitial-cell tumors was observed as well. Ellis et al. also conducted a twelve month bioassay with groups of male and female dogs (six per group) given oral administrations of TNG at dose rates of 1, 5, or 25 mg/kg-d. No significant increases in malignant or benign tumors were found. Ellis et al. (1984) and Smith (1986) reviewed other bioassays conducted by Takayama (1975) with rats and by Suzuki et al. (1975) with C57BL/6JMS mice. In both of these bioassays TNG was administered to the animals via drinking water for more than a year. The only positive result was a statistically significant ($p=0.006$) increase in the incidence of unspecified pituitary tumors in high-dose female mice. However, Ellis et al. (1984) found pituitary tumors only in the low-dose group (0.01 wt% TNG in food) in the CD-1 mice used in their study.

Estimation of Intake Limits to Protect Public Health

The U.S. EPA (1987b) has adopted a weight-of-evidence approach to determine whether a substance represents a human carcinogen. Under the EPA guidelines TNG would be categorized as a Group C carcinogen (a possible human carcinogen) because the human data are inadequate, and there is only one animal species in which a statistically significant increase in malignant tumors has been detected. A quantitative estimate of the carcinogenic potency of TNG to humans can be estimated by statistically fitting the multistage model to the dose-response data for hepatocellular carcinomas in male rats reported by Ellis et al. (1978a). Smith (1986) and Khanna (1986) have independently prepared potency estimates of TNG using computer codes (i.e., GLOBAL82 or GLOBAL83) that provide a 95% percentile upper-bound estimate of potency. The average of their potency estimates (2.3×10^{-2} kg-d/mg by Smith and 1.7×10^{-2} kg-d/mg by Khanna) is 2×10^{-2} kg-d/mg. The potencies from which this average value is calculated were based on surface-area adjustments of the animal dose rates. Safe intake limits in mg/kg-d can be calculated by dividing a specified incremental lifetime cancer risk (e.g., 10^{-6}) by the potency. So, with a risk of 10^{-6} , the associated intake would be 5×10^{-5} mg/kg-d.

TOXIC EFFECTS ON AQUATIC SPECIES

The aquatic toxicity of TNG was studied by Bentley et al. (1978) using a series of acute and chronic tests (see Smith (1986) and Sullivan et al. (1979) for reviews of that work). In the 96-h flow-through acute tests conducted with channel catfish (Ictalurus punctatus), fathead minnow (Pimephales promelas), and bluegill (Lepomis macrochirus), the median lethal concentrations (LC50) ranged from 1.67 mg/L for bluegills to 3.0 mg/L for fathead minnows. Similar results were obtained for 96-h static tests (which were also conducted with rainbow trout, Salmo gairdneri), with mean LC50 values ranging from 2 to 3.2 mg/L. Bentley et al. (1978) also carried out acute tests with aquatic invertebrates (i.e., the amphipod Gammarus fasciatus; the midge Chironomus tentans; water flea Daphnia magna; and the isopod Asellus militaris). The 48-h EC50's (effective concentration for immobilization) from flow-through tests ranged from 20 mg/L (midge) to 32 mg/L (waterflea).

In the chronic toxicity tests, Bentley et al. (1978) exposed the eggs and fry of channel catfish and fathead minnows to TNG for 30 d. They found that the survival of fathead minnows was significantly reduced ($p = 0.05$) at concentrations as low as 0.06 mg/L. With channel catfish, survival was significantly affected at a nominal concentration of 0.31 mg/L. These studies were supplemented by a full life-cycle toxicity test with two generations of fathead minnows. The first generation of minnows were exposed for 266 d, while the second-generation fish were exposed for 30 d. Nominal TNG concentrations for both generations were 0.11, 0.22, 0.43, 0.84 and 1.75 mg/L. After 174 days, survival (percent alive) was significantly reduced ($p = 0.05$) at a concentration of 0.43 mg/L. After 266 days the wet weight of males was also significantly reduced at a concentration of 0.43 mg/L. The total length and mean wet weight of minnows from the second generation exposed for 30 d was significantly reduced at a nominal concentration of 0.22 mg/L. Survival of the fish was not significantly reduced at that concentration.

In another set of chronic studies, two generations of water fleas and midges were exposed to 1.5, 3.1, 6.2, 12.5 or 25.0 mg/L of TNG. At a TNG concentration of 12.5 mg/L the number of offspring produced was significantly reduced ($p = 0.05$). Survival was only affected at the highest concentration. The midge larvae and adult midges of the first-generation had significantly reduced survival at 12.5 mg/L, while in the second generation survival of larvae was significantly reduced at 3.1 mg/L.

Bentley et al. (1978) also examined the toxicity of TNG to four species of algae (Microcystis aeruginosa, Anabaena flos-aquae, Navicula pelliculosa and Selenastrum capricornutum). The toxicity of TNG to these algal species was assessed by 96-h EC50's for changes in chlorophyll a concentration, cell numbers (except A. flos-aquae), and optical density for A. flos-aquae. The most sensitive species was S. Capricornutum, which had a 96-h EC50 (reduction in the number of cells per mL) of 0.4 mg/L. The second most sensitive species for this endpoint was N. pelliculosa, with a 96-h EC50 of 3.3 mg/L.

4. DATA-BASE ASSESSMENT FOR NITROGUANIDINE

Nitroguanidine (NGu) is a widely used ingredient in triple-base propellants. The low flame temperature of NGu together with the nitrogen-rich content of its combustion gases help minimize muzzle blast and the wear of gun barrels. Lindner (1980) also notes that it apparently stabilizes nitrocellulose by reacting with nitrogen oxides. When released into the environment NGu should be fairly persistent, with photolytic degradation the primary transformation pathway. The available data from toxicity studies with laboratory animals indicate that NGu is not highly toxic.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

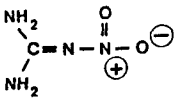
Chemical identifiers for NGu are found in Table 4-1 and pertinent physicochemical properties are shown in Table 4-2. The limited data available on the partitioning of NGu (see Table 4-3) indicate that it will not be strongly sorbed to soils and sediments and is unlikely to accumulate in aquatic organisms. Spanggord et al. (1985) studied the equilibrium partitioning of NGu in two different sediments with high clay and silt contents and organic carbon contents of 0.72 and 2.33 wt%. Their measurements indicated that the K_d for those sediments was less than 0.1. Our estimated $\log K_{oc}$ value is 0.6. The estimated value of K_{fw} is 0.088, which reflects its low octanol-water (K_{ow}) coefficient.

ENVIRONMENTAL TRANSFORMATION PROCESSES

Photolysis

In aqueous solutions NGu assumes two tautomeric forms, depending on the alkalinity of the solution. In neutral, acidic or slightly basic solutions, structure I in Fig. 4-1, which is characterized by a UV maximum of 264 nm, predominates (Kemula et al., 1970). Structure II in Fig. 4-1 (UV maximum of 246 nm) predominates as an aqueous solution becomes increasingly basic. Nitroguanidine in natural waters will therefore be present primarily as structure I, except in highly basic water (e.g., NGu-disposal lagoons). Structure I is more conjugated than structure II, making NGu more susceptible

Table 4-1. Chemical identifiers of NGu.

Empirical Formula:	CH ₄ N ₄ O ₂	Structural formula:
Molecular weight:	104.07	
CAS reg. no.:	556-88-7	
RTECS no.:	MF4605000	

to photolysis because conjugation moves the light absorption maximum toward the visible region, increasing the amount of light absorption.

The photolysis of NGu in sunlight has been examined in two different studies. Spanggard et al. (1985) measured NGu photolysis rates at two concentrations (i.e., 3.2 and 0.4 mg/L) in distilled water, natural waters from Searsville Pond, California, and Kansas River, and in "synthetic natural water". They exposed samples to March sunlight in Menlo Park, California, and used an actinometer to compensate for daily differences in light intensity. Their results showed that the concentration of NGu and the type of water used had little or no influence on photolysis rates. They calculated half-lives ranging from 41 to 57 h for sunlight photolysis (Table 4-4). In addition, they calculated the half-lives expected at different times of the year using the NGu absorption spectrum and its quantum yield (5.3×10^{-3}). The predicted NGu photolysis half-lives in winter, spring, summer, and fall were 3.9, 2.0, 1.0 and 1.6 d, respectively. Dennis (1982) found that aqueous solutions of NGu degrade with a half-life of about 20 h in bright August sunlight in Frederick, Maryland.

Nitroguanidine absorbs strongly in the near ultraviolet (Spanggard et al., 1985) so photodecomposition rates will be much faster than those measured under natural sunlight. Noss and Chyrek (1984) found that photolysis of NGu in aqueous solutions was not accelerated by the presence of ozone or hydrogen peroxide (Noss and Chyrek, 1984). They also found little difference in UV photolysis rates at pH's between 5 and 11. NSGu was an intermediate at all pH's; however, at lower pH's it decomposed to guanidine and at higher pH's guanidine was not formed at all. Another pH-dependant phenomenon was the

Table 4-2. Chemical and physical properties of NGu. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling point	°C	--	
Freezing/Melting point	°C	245	Lindner (1980)
Density	g/mL	1.72	Lindner (1980)
Vapor pressure	torr	$\approx 5 \times 10^{-12}$	Estimated ^b
Aqueous solubility	mol/L	2.5×10^{-2a}	Measured by Spanggard et al., 1985
	mg/L	2600	
	mol/L	2.6×10^{-2}	Urbanski (1965b)
	mg/L	2660	
Henry's law constant	(L-torr)/mol	Not available	
Diffusion coefficients:	Air	1.0×10^{-5}	Estimated ^b
	water	8.9×10^{-10}	Estimated ^b
Log octanol/water partition coefficient (K_{ow})	log K_{ow}	-0.83	Measured by Spanggard et al., 1985

a Measured at 25 °C

b See Appendix A.

Table 4-3. Partition coefficients for use in estimating human exposures to NGu.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^a /(mg/kg soil)	14	Calculated ^b from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	4.0×10^{-4}	Calculated ^b from water solubility and log K_{ow}
Fish/water	K_{fw}	(mg/kg fish) ^a /(mg/kg water)	8.8×10^{-2}	Calculated ^b from log K_{ow}
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	0.59	Calculated ^b from solubility in water and melting point.

^a Wet-weights for plant and fish

^b See Appendix A

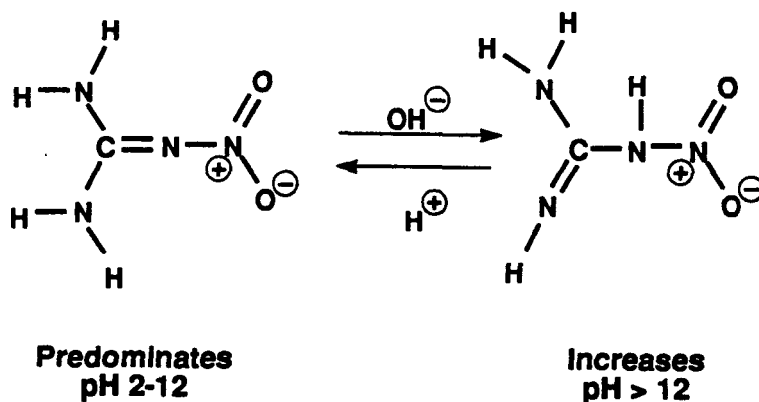


Figure 4-1. Tautomerism of NGu with pH (from Kemula et al., 1970).

recovery of the initial nitrogen present in NGu. At neutral or acidic pH, the recovery of nitrogen derived from NGu was 50%, with 40% identified as guanidine or nitrate, but at pH 11, the recovery of nitrogen was only 15 to 20%, but the percentage of guanidine increased. Clearly, the photolytic mechanism operating in highly alkaline solutions differed from that in neutral or mildly acidic ones. This implies that the form of NGu changes below pH 12, as was discussed above.

The products formed from photodecomposition of NGu were found by Kaplan et al. (1981, 1982), who studied the photodecomposition of the intermediate, NSGu, by short-range UV light. They identified cyanamide, but not urea or guanidine, as a photodecomposition product. Kaplan et al. (1982) noted that the same product, cyanamide, was formed from "chemical" (i.e., hydrolytic) transformation of NSGu, suggesting the possibility of similar degradation pathways.

Biotransformation

Nitroguanidine is very resistant to microbial transformation. In fact, biotransformation occurs only with adapted bacteria in nutrient-rich media. Spanggard et al. (1985) investigated the biotransformation of 5 mg/L NGu in a natural water (Searsville Pond) under both aerobic and anaerobic conditions, with and without added nutrients. No biotransformation was observed after

Table 4-4. Photolysis half-lives of NGu (from Spanggord et al., 1985).

Concentration mg/L	Water type	Half- life ^a (h)
3.2	Distilled	50
3.2	Kansas R.	41
3.2	Searsville Pond	47
3.2	Synthetic	43
0.4	Distilled	45
0.4	Kansas R.	57
0.4	Searsville Pond	57
0.4	Synthetic	52

^a Hours of sunlight each day were not specified.

63 d under either aerobic or anaerobic conditions without added nutrients. To enhance the biodegradation of NGu, they added sewage sludge organisms, 100 ppm glucose, and 20 ppm yeast extract to either a nutrient broth or a basal salts medium containing 15 ppm NGu. Under aerobic conditions, no decreases in the concentration of NGu were detected after 24 d. Under anaerobic conditions a 25% decrease in NGu concentration occurred in the nutrient broth, but no decrease was measured in the basal salts medium. A further experiment used NGu-contaminated water from the Sunflower Army Ammunition Plant (SAAP), DeSoto, Kansas. The two water samples utilized were from a disposal lagoon (Pond B) that had contained NGu and from a stream (Hansen Creek) at a point below a lagoon outfall. The results of these biodegradation studies (see Table 4-5) indicate that organisms can degrade NGu in aqueous solutions under aerobic conditions when nutrients are added. Results of the biodegradation experiments also show that aerobic biotransformation of NGu occurs faster than anaerobic transformation.

Studies by Kaplan et al. (1981, 1982) and Kaplan and Kaplan (1985) indicated that biotransformation took place only under anaerobic conditions. Kaplan et al. (1981, 1982) used sewage sludge organisms in a basal salts medium with and without added glucose and observed no biodegradation under aerobic conditions or without added nutrients. They also noted enhanced biotransformation rates under anaerobic conditions with added nutrients when the organisms were subcultured with NGu three successive times. In other

Table 4-5. Biodegradation of NGu in a lagoon water and Hansen Creek water (from Spangford et al., 1985).

Water type ^a	Condition	Nutrient Broth	Glucose + Yeast	Duration (d)	% Lost
Pond B	aerobic	15 ppm	200 ppm	6	95
Hansen Creek	aerobic	15 ppm	200 ppm	6	95
Pond B	aerobic	none	200 ppm	6	53
Hansen Creek	aerobic	none	200 ppm	6	29
Pond B	aerobic	none	none	?	0
Hansen Creek	aerobic	none	none	?	0
Pond B	anaerobic	15 ppm	200 ppm	6	50
Hansen Creek	anaerobic	15 ppm	200 ppm	6	50
Pond B	anaerobic	none	200 ppm	27	100
Hansen Creek	anaerobic	none	200 ppm	47	80
Pond B	anaerobic	none	none	?	0
Hansen Creek	anaerobic	none	none	?	0

^a Pond B and Hansen Creek have received waste waters from Sunflower Army Ammunition Plant.

work, Kaplan and Kaplan (1985) demonstrated that soil microbes will degrade NGu in the presence of added nutrients. They added 100 mL/d of an aqueous solution containing 150 mg/L of NGu to both microbially active and sterile soil columns. Within 8 days the NGu biotransformation was virtually complete when 2 g/L of glucose was added to the microbially active columns. No transformation of NGu was observed in the sterile control column effluent or in the effluent when the treatment solutions had no glucose.

The experiments described above indicate that NGu will undergo biotransformation in lagoons, soils, or streams only if sufficient organic nutrients are present. Furthermore, it appears that bacteria will adapt to degrade NGu under both aerobic and anaerobic conditions. The rate of degradation will depend on the amount of nutrients present, ranging from a half-life of a few days under nutrient-rich conditions, to an indefinitely long one in the absence of nutrients.

Kaplan et al. (1981,1982) studied the biodegradation mechanism of NGu and suggested that microbes degrade NGu to NSGu. Subsequent degradation results in

the formation of cyanamide, cyanoguanidine, melamine, and guanidine. They believed that biodegradation of NSGu would lead to further reduction, however, none of the postulated reduction products (i.e., urea, hydrazine or aminoguanidine) were detected in their culture medium. Instead, the products isolated and shown in Fig. 4-2 were produced from the chemical processes of decomposition, rearrangement, and combination.

Hydrolysis

Spanggord et al. (1985) studied the hydrolysis of NGu in neutral and basic aqueous solutions. They measured the hydrolysis rates of 1.3 mg/L of NGu in solutions with pH's of 9.56 to 12.99 at 25°C, and at 50°C they measured the hydrolysis rates at pH's of 6.97 to 11.35. From the time-varying changes in NGu concentrations, they estimated half-lives of greater than 8 y at pH 7 and greater than 200 d at pH 8.2. The hydrolysis products identified by chromatographic retention time and UV spectra were nitrourea and ammonia. Studies performed by Bissett and Levasseur (1976) showed that strong acids would enhance the hydrolysis of NGu. Weak acids, even at 100°C, resulted in no structural change of NGu after 24 h. Based on these results, it is safe to assume that hydrolysis will not be a significant transformation process for NGu in natural waters. Kenyon (1982) also concluded that NGu will hydrolyze very slowly in environmental waters.

TOXIC EFFECTS ON ANIMALS AND HUMANS

Toxicokinetics

Absorption. Ho et al. (1988) found that ^{14}C -NGu was rapidly and completely absorbed after the oral administration of both high (200 mg/kg) and low (20 mg/kg) doses to Sprague-Dawley rats. Morgan et al. (1986a) attributed the apparently easy passage from gut to bloodstream to the low molecular weight of NGu (i.e., 104.07 g/mole). Morgan et al. (1986b) found that almost all of the NGu applied to the skin of rabbits in a dermal irritation test remained on the skin surface. The limited dermal absorption of NGu could be due to the low K_{ow} of this compound.

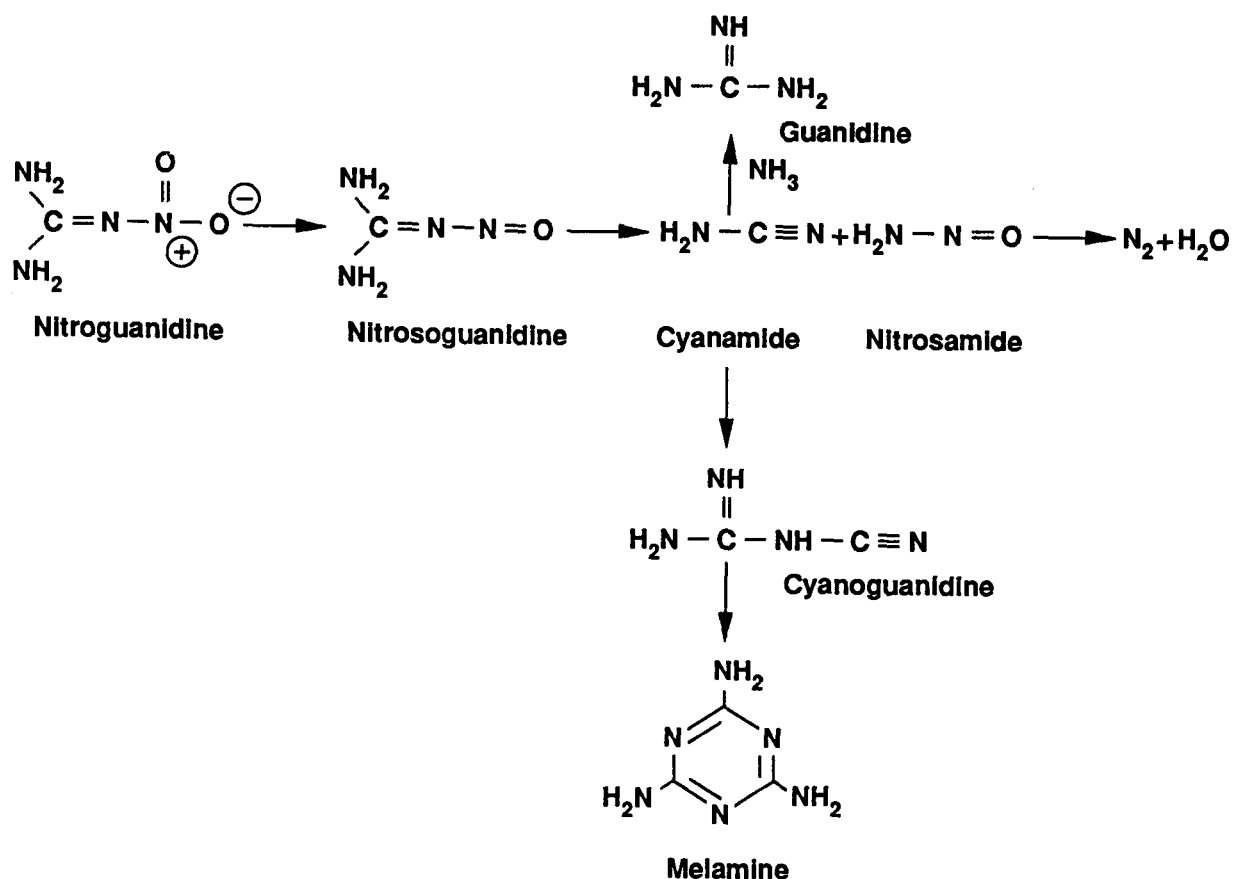


Figure 4-2. Biodegradation of NGu to NSGu followed by chemical reactions to various products (adapted from Kaplan et al. (1981, 1982)).

Distribution. One hour after the oral administration of ^{14}C -NGu to Sprague-Dawley rats, Ho et al. (1988) found that NGu was distributed to all of the major organs. After 48 h, however, less than 0.02% of the radiolabel remained in any of the major organs or tissues.

Metabolism. In their experiments with Sprague-Dawley rats, Ho et al. (1988) found that nearly all of the orally administered ^{14}C -NGu was eliminated in urine. Analysis of the urine by thin-layer chromatography showed that the R_f value of the predominant radioactive trace ($R_f = 0.43$) was identical to the

R_f value of the NGu standard, indicating that NGu is excreted essentially unchanged. The authors stated that under the aerobic conditions in vivo, it was unlikely that NGu would be metabolized in rats. Morgan et al. (1986a) also noted that NGu does not undergo metabolism in vitro in the presence of rat-liver supernatant.

Elimination. Nitroguanidine is excreted essentially unchanged in the urine of rats administered ¹⁴C-NGu. Following oral administration of either 20 or 200 mg/kg of ¹⁴C-NGu to rats, Ho et al. (1988) recovered 60 to 80% of the radiolabel in urine after 8 hours, with nearly 100% recovery after 48 hours. The small amounts of radioactivity found in the feces were attributed to contamination by urine. No ¹⁴C was present in expired CO₂.

Toxic Effects on Organs and Systems

Gastrointestinal effects. Following the oral administration of NGu to Sprague-Dawley rats at a dose of 5000 mg/kg, two of seven males, and two of six females died (Hiatt et al., 1985). Six of the thirteen rats tested displayed signs of toxicity related to the gastrointestinal tract including diarrhea, staining of the perianal region, or both.

Hematological effects. Morgan et al. (1986a) reported that the dietary administration of NGu for 14 d (100, 316, or 1000 mg/kg) to male rats had no statistically significant adverse effect on the total number of eosinophils, segmented neutrophils, or monocytes. Hemoglobin concentration was also unaffected. Female rats treated by the same protocol had lower hemoglobin values than controls; however, these differences were not statistically significant. The total number of eosinophils, segmented neutrophils, and monocytes, as well as the percentage of eosinophils and monocytes were significantly lower in low-dose females ($p = 0.05$) compared to untreated animals. Because these parameters were within published normal limits, the authors did not consider their findings to be indicative of NGu-induced toxicity (Morgan et al., 1986a).

Ocular effects. Hiatt et al. (1986a) evaluated the potential of NGu to produce primary eye irritation in male New Zealand White rabbits. One-tenth milliliter (0.025 g) of NGu was dropped inside the lower eyelids of the treated animals. Examinations for ocular reactions were performed at 1, 4, 24, 48, and 72 hours. Slight conjunctival vasodilation (indicative of mild inflammation) was observed in the eyes of 5 of the 6 treated rabbits. This response was not sufficiently severe to be considered a positive (adverse) reaction. Because of the presence of an undissolved compound that remained in the eye, Hiatt et al. concluded that the inflammation was due to physical irritation (abrasion) rather than to any inherent pharmacologic activity of NGu.

Dermal effects. The primary dermal irritation potential of NGu was evaluated in New Zealand White rabbits (Morgan et al., 1986b). Following the removal of patches that had held 0.5 g in contact with the skin for 4 hours, examinations at 1, 24, 48, and 72 hours revealed no erythema or edema. Consequently, NGu was classified as a non-irritating chemical.

Hiatt et al. (1985) presented negative results from dermal toxicity and sensitization tests. No evidence of systemic toxicity was observed following the application of NGu at 2.0 g/kg for 24 hours to the shaved backs of rabbits. None of the guinea pigs treated with three weekly applications of NGu developed any dermal reactions.

Renal effects. Serum electrolyte levels (Ca^{2+} , K^{+}) decreased in male rats in response to dietary administration of NGu (14 d, 100 and 1000 mg/kg). In female rats, NGu in the diet at 100, 316, or 1000 mg/kg (14 d) caused both increases and decreases in serum K^{+} , Mg^{2+} , and uric acid levels. When these values were compared to controls by analysis of variance, the differences were significant ($p = 0.05$). However, when these data were analyzed by Dunnett's test, the differences were not statistically significant (Morgan et al., 1986a). In the same study, water consumption increased with dose in rats of both sexes during the first week of treatment. Although this trend was maintained during the second week of the study, animals in all groups drank less than during the first week. In view of the rapid urinary elimination of

NGu, the alteration in serum electrolyte levels and increased water consumption following treatment, the authors speculated that NGu may be an osmotic diuretic similar to urea.

Teratogenicity

Nitroguanidine was administered by gavage at dose levels of 0, 100, 316, and 1000 mg/kg-d to pregnant Sprague-Dawley rats on days 6 through 15 of gestation (Coppes et al., 1986). Signs of maternal toxicity (such as dehydration, red urine, and hunched posture) were observed in 100% of the high-dose group. There were no toxic effects observed in the dams that received the lower doses. A dose-related increase in the number of fetuses with tracheal stenosis (1 of 107 fetuses in the 316 mg/kg-d group and 3 of 102 fetuses in the 1000 mg/kg-d group) was observed (level of statistical significance was not reported). A significantly increased incidence ($p < 0.05$) of retarded ossification of the sternbrae and caudal vertebrae was observed among fetuses in the 1000 mg/kg-d group. Coppes et al. (1986) suggested that effects observed at the high-dose level could be attributed to maternal toxicity rather than to a direct effect of NGu on the fetuses.

Genotoxicity

Nitroguanidine has given consistently negative results in the Ames reverse mutation assay with Salmonella typhimurium. These results have been reported in strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 in the presence and absence of S9 (Brusick and Matheson, 1978; McGregor, 1980; Kaplan et al., 1982; Harbell et al., 1987). Nitroguanidine was also inactive in short-term assays with Saccharomyces cerevisiae (McGregor, 1980).

Brusick and Matheson (1978) evaluated the genetic toxicity of NGu in a series of short-term assays. They found that oral administration of NGu (0.2, 0.67, 2.0 g/kg) did not induce dominant lethal mutations in rats. Nitroguanidine tested over a range of concentrations did not produce unscheduled DNA synthesis in cultured human cells (0.1 to 5.0 mg/mL) or forward mutations in mouse lymphoma cells (1.25 to 5.0 mg/mL). Harbell et al. (1987) confirmed that NGu is not mutagenic to mouse lymphoma cells at the TK locus.

A concentration of 384.4 mg/mL NGu produced chromosome aberrations in 26% of Chinese Hamster cells (Ishidate and Odashima, 1977). Aberrations included chromatid gaps, chromatid or chromosomal breaks, and translocations. At lower concentrations of NGu (3.9 mg/mL with metabolic activation; 2.0 mg/mL without), Harbell et al. (1987) reported that NGu produced no significant increases in sister chromatid exchanges (SCE) in Chinese hamster ovary cells. Due to some toxicity, though, the total yield of metaphases was inadequate for SCE scoring at the highest NGu concentration tested (4.0 mg/mL without activation).

Carcinogenicity

No carcinogenicity bioassays or epidemiological studies are available on NGu. However, the evidence from the genotoxicity studies does not indicate that NGu is genotoxic. Nitroguanidine gave negative responses in mutagenicity tests in bacteria (Brusick and Matheson, 1978; McGregor, 1980; Kaplan et al., 1982; Harbell et al., 1987). It also failed to show mutagenic activity or to elicit DNA damage in mammalian cells (Brusick and Matheson, 1978; Harbell et al., 1987). However, NGu gave a positive response in chromosome aberration tests designed to screen for chemicals with carcinogenic activity (Ishidate and Odashima, 1977). The authors of that study emphasized that chromosomal damage is not typically a mutagenic event since cell death usually follows.

Estimation of Intake Limits to Protect Public Health

Morgan et al. (1986a) reported that the administration of NGu at 1000 mg/kg-d for 14 days to rats produced no toxic effect. However, Coppes et al. (1986) reported that the administration of NGu at the same dose rate for 11 days to pregnant rats resulted in decreased food consumption, dehydration, weight loss, red urine, red material on the nose and whiskers, and hunched posture in the dams. Coppes et al. suggested that the signs of toxicity observed in that study might reflect a physical problem with the administration of large doses of test compound rather than a toxic response. The apparent discrepancy in effects at the same dose may also be due to the immunocompromised state of the pregnant animals or to the varying degrees of sensitivity in the examinations. If we consider the toxic effects observed in

the pregnant rats a valid response to NGu, then the next lower dose (316 mg/kg-d), at which these maternal toxic effects are absent, might serve as a subchronic NOEL. Using safety factors of 10 to account for the subchronic nature of exposure and 100 to account for inter- and intra-species differences, the resulting intake limit to protect human health would be 0.32 mg/kg-d (i.e., 316/1000). The potential significance of the one case of tracheal stenosis in a fetus from the 316 mg/kg-d group may warrant choosing the lower dose level (100 mg/kg-d) as a subchronic NOEL (refer to Coppes et al., 1986). Using the same conversion factors noted above, the corresponding intake limit is 0.10 mg/kg-d. These intake limits should be considered as provisional values because they are based on short-term toxicity studies.

TOXIC EFFECTS ON AQUATIC SPECIES

Van der Schalie (1985) studied the toxicity of NGu on fish (i.e., fathead minnows, bluegills, channel catfish, and rainbow trout), invertebrates (water fleas, midge larva, aquatic worm, and amphipods), and an aquatic algae. The acute toxicity tests (96-h exposures) with the fish species showed that even at concentrations of NGu at its solubility limit in the well water used for the test solutions, there was only limited mortality. In fact, no 96-h LC50 values could be determined for the test species because of the lack of mortality at the highest concentrations of NGu (i.e., up to 2714 mg/L). The 48-h acute tests with the invertebrate species showed that the amphipod, Hyallela azteca, was the most sensitive to NGu, however, only at the maximum NGu concentration (2730 mg/L and 46.7% mortality). An early life stage test (42 d duration) was also conducted with rainbow trout with NGu concentrations ranging from 1.5 to 1703 mg/L. Endpoints analyzed included hatching success, time-to-hatch, time-to-swim-up, fry survival, overall survival, fry deformities, fry length, and fry weight. The only statistically significant ($p < 0.05$) effects between controls and treated fish were of the percent fry deformities, fry length, and fry weight. These effects were observed at the highest NGu concentration and at a lower concentration (418 mg/L) where fry length was significantly different from controls. However, the author considered this an artifact because other effects were not observed at that concentration and at the next highest treatment concentration (857 mg/L). The

algal species tested, Salenastrum capricornutum, had a 120-h EC50 of about 2000 mg/L for two growth measures: dry weight and relative chlorophyll a of the standing crop of algae. In a follow-on experiment, van der Schalie also studied the toxicity of an aqueous solution of photolyzed NGu and found that the 120-h EC50 for those two measures of toxicity were reduced to 32.3 mg/L (dry weight) and 34.3 mg/L (relative chlorophyll a). The 96-h LC50 for fathead minnows using the photolyzed NGu was 34.5 mg/L and 48-h EC50 values for water flea were 24.6 mg/L (unaged solution) and 35.0 mg/L (solution aged 3 d).

5. DATA-BASE ASSESSMENT FOR NITROSOGUANIDINE

Nitrosoguanidine (NSGu) is a microbial degradation product of NGu that has been detected in waste waters associated with the production of NGu. We found no reports of measurements of NSGu in soils or ground waters at open-burning or open-detonation sites. The information available on NSGu transformation processes indicates that it is subject to photolytic degradation and chemical rearrangement. Little is known about the toxicity of this compound.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

The chemical identifiers, chemical and physical properties, and partition coefficients for NSGu are presented in Tables 5-1, 5-2, and 5-3, respectively. No measurements have been made of its vapor pressure, diffusion constants in air and water, or octanol-water partition coefficient. Based on its solubility in water and estimated octanol-water partition coefficient, we do not expect that there is much potential for bioaccumulation in fish or meat (see Table 5-3). However, the low molecular weight of this compound indicates that there is some potential for plant uptake (see Appendix A). Indeed, the estimated K_{sp} of 20 is the highest of the propellant-related compounds considered.

ENVIRONMENTAL TRANSFORMATION PROCESSES

Photolysis

Kaplan et al. (1981, 1982) studied the photodecomposition of NGu and NSGu in distilled water exposed to UV light. They found that NSGu photolytically decomposed at twice the rate of NGu. If this relationship is applicable for sunlight as well, then we would expect that the half-life of NSGu would be between 0.5 to 2 d, based on the half-lives estimated for NGu by Spanggord et al. (1985). Noss and Chyrek (1984) used UV light to examine the photolytic degradation of NSGu in aqueous solutions at pH's of 5 and 11. They found that essentially all the nitrogen in NSGu was recovered in the form of guanidine, nitrate, or nitrite at pH 5. At pH 11 only 25% of the initial nitrogen from

Table 5-1. Chemical identifiers of NSGu.

Empirical formula:	CH ₄ N ₄ O	Structural formula:
Molecular weight:	88.09	$\begin{array}{c} \text{H}_2\text{N} \\ \text{H}_2\text{N} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{C} = \text{N} - \text{NO}$
CAS reg. no.:	674-81-7	
RTECS no.:	MF4725000	

NSGu was recovered in these forms. These results are similar to those found with NGu except that more of the nitrogen was recovered after UV treatment of NSGu than from the UV treatment of NGu.

Biotransformation

Kaplan et al. (1981, 1982) examined the biotransformation of NSGu under anaerobic conditions and were unable to find sewage sludge organisms that could transform NSGu. They attempted to isolate potential microbial reduction products such as aminoguanidine, urea, hydrazine, ammeline, ammelide and cyanuric acid, but found none.

Chemical Transformation

In their studies on the biotransformation of NGu, Kaplan et al. (1981, 1982) noted that the NSGu formed did not undergo further biotransformation, but instead decomposed "chemically." The same products isolated from both the attempted biotransformation of NSGu and the sterile controls were cyanamide, cyanoguanidine, and melamine. We postulate that these products result from chemical rearrangement as shown in Fig. 5-1, not reduction or oxidation processes.

Kaplan and Kaplan (1985) also found that NSGu disappeared "chemically" in biodegradation experiments with NGu. They conducted an experiment in which aqueous solutions of NGu containing nutrients were added to columns packed with garden soil and supplemented with sewage-sludge bacteria. With 2 g/L of

Table 5-2. Chemical and physical properties of NSGu. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling point	°C	--	
Freezing/Melting point	°C	161 (explodes)	Richter, 1961
Density	g/mL	Not available	
Vapor pressure	torr	Not available	
Aqueous solubility	mol/L mg/L	2.0×10^{-2} 1760	Richter, 1961
Henry's law constant	(L-torr)/mol	Not available	
Diffusion coefficients:	Air	1.0×10^{-5}	Estimated ^a
	water	9.3×10^{-10}	Estimated ^a
Log octanol/water partition coefficient (K_{ow})	log K_{ow}	less than -0.83 ^a	

^a See Appendix A.

Table 5-3. Partition coefficients for use in estimating human exposures to NSGu.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^a /(mg/kg soil)	20	Calculated ^b from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	0.00083	Calculated ^b from aqueous solubility
Fish/water	K_{fw}	(mg/kg fish) ^a /(mg/kg water)		Not available
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	3.7	Calculated ^b from solubility in water and melting point.

^a Wet-weights for plant and fish

^b See Appendix A

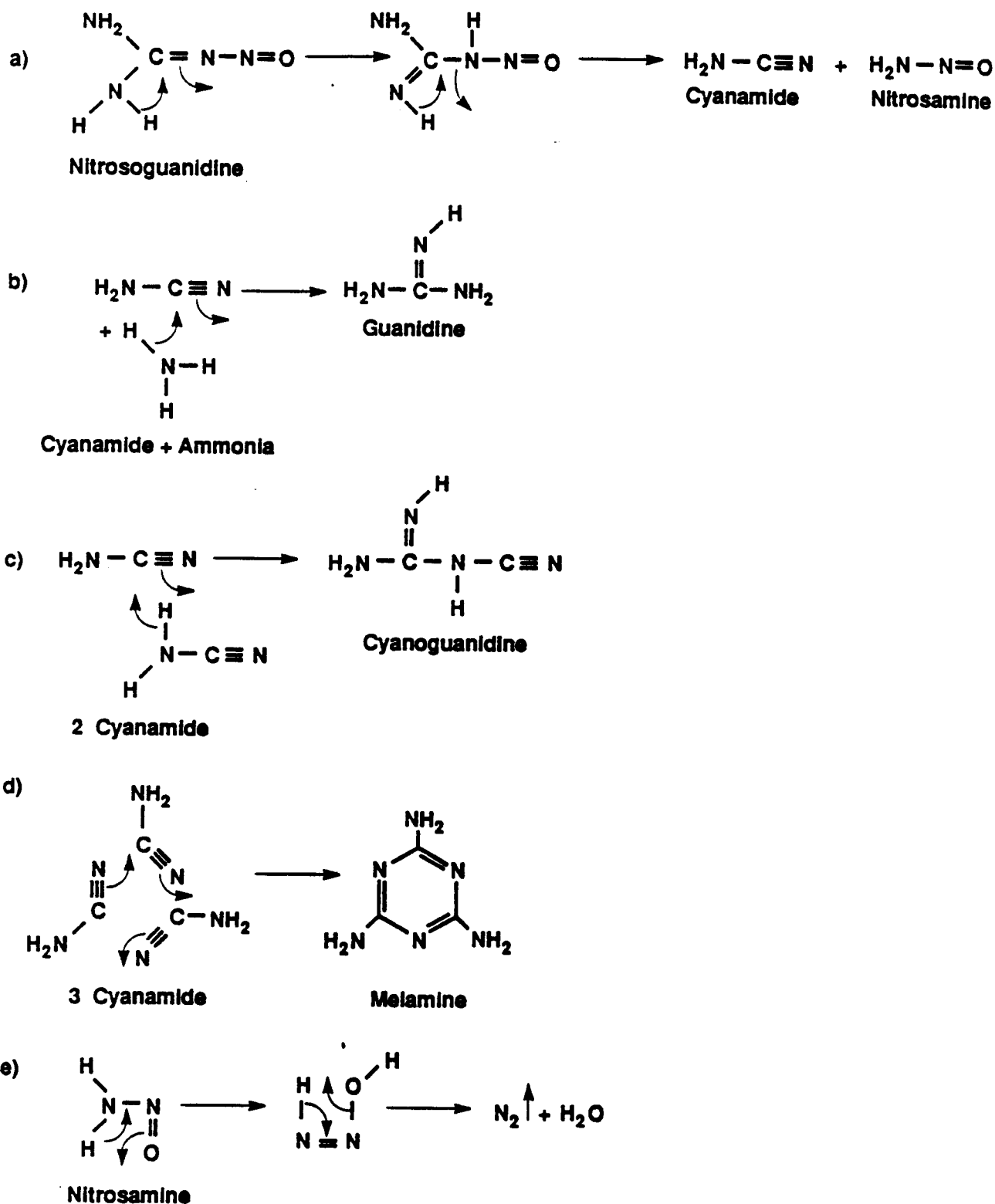


Figure 5-1. Possible rearrangement mechanisms for NSGu. (Representations show the source of atoms or electrons only. Reactions may involve more steps or more molecules.) a) Cleavage of NSGu to cyanamide and nitrosamide. b) Addition of ammonia to cyanamide and nitrosamide. c) Dimerization of cyanamide. d) Trimerization of cyanamide. e) Decomposition of nitrosamide.

glucose, NGu was completely biodegraded within the 7 days required for NGu to pass through the sterile columns. They found "no significant concentrations" of NSGu in the effluents of the microbially active columns. The absence of NGu and NSGu in the these effluents showed that the NSGu chemical decomposition also occurred within the 7 days required for breakthrough.

Davis and Rosenquist (1937) isolated other compounds from aqueous solutions of NSGu under more rigorous conditions than would be expected in the environment. They evaporated a solution of ammonia water and NSGu to dryness on a steam bath and isolated melamine, ammeline, ammelide, urea, and guanidine. They also concluded that cyanamide and nitrosamide are intermediate "dearrangement" products from aqueous solutions of NSGu because when these solutions were boiled, decomposition of nitrosamide would account for the nitrogen evolution, and dimerization of the cyanamide would account for the formation of "dicyandiamide" (cyanoguanidine). Nitrosoguanidine rearrangement did not occur rapidly in distilled water solutions at lower temperatures.

They also found that NSGu in the presence of aliphatic amines rearranges "vigorously" to form cyanamide at room temperature in aqueous solutions. The cyanamide combined with the amines to form alkylated guanidines (by analogy, reactions with alipatic amines in humic materials with NSGu may result in the humic materials incorporating guanidine). Davis and Rosenquist found that the reactions with aromatic amines were considerably slower; after 3 days at room temperature, 77% of the NSGu was recovered unchanged in aqueous solution with excess aniline chloride.

TOXIC EFFECTS ON ANIMALS AND HUMANS

Most of the references to nitrosoguanidine in the literature actually are concerned with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), commonly shortened to "nitrosoguanidine". MNNG is frequently used as a positive control in the Ames test for mutagenicity. In addition, it is used as a diagnostic for particular reversions caused by base-pair substitutions. The use of the term nitrosoguanidine for MNNG has so permeated the literature that it is often not possible to determine which substance is addressed. For example, a study by Epstein et al. (1972) that evaluated the mutagenic potential of a series of chemicals by the "Dominant Lethal" assay in the mouse was listed in the

Registry of Toxic Effects of Chemical Substances (Lewis and Sweet, 1984) as the source of a relatively low lethal dose for NSGu (CAS registry number 674-81-7). That the "nitrosoguanidine" tested was categorized before the test as a carcinogen makes one skeptical about its true identity.

Given this background, our assessment of the literature on the toxicity of NSGu revealed only two studies, discussed below, dealing with its genotoxicity. No data were available on its toxicokinetics, systemic effects, teratogenicity, or carcinogenicity. Harbell et al. (1987) reported that NSGu was not mutagenic in the Ames assay, with or without activation. Kaplan et al. (1982) also found NSGu to be negative in the Ames test for mutagenicity. Harbell et al. (1987) found NSGu to be moderately mutagenic in a series of mammalian cell systems. Nitrosoguanidine showed marked toxicity in the mouse lymphoma assay at concentrations greater than 1.2 mg/mL. Toxicity greatly increased with metabolic activation. In this assay, significant ($p < 0.05$) mutagenic activity was observed both with and without activation. Nitrosoguanidine also produced a significant ($p < 0.0001$) rise in the sister chromatid exchange rate.

Estimation of Intake Limits to Protect Public Health

Without additional toxicity testing with laboratory animals it is not possible to determine an acceptable intake limit for the protection of human health.

TOXIC EFFECTS ON AQUATIC SPECIES

No studies have been completed on the toxicity of NSGu to aquatic species.

6. DATA-BASE ASSESSMENT FOR DIBUTYL PHTHALATE

Dibutyl phthalate (DBP) has been used as a plasticizer in propellant formulations, and consequently it represents a potential contaminant after the open-burning and -detonation operations involving propellants. It is also a widely used plasticizer in plastics, and consequently it has been detected in environmental media in the U.S. and elsewhere in the world where plastics have been discarded (see Perwak et al., 1981). It is conceivable, therefore, that at some OB/OD sites measured levels of DBP in soils and water may not necessarily be associated with the destruction of propellants. DBP released into the environment will be biodegraded slowly by adapted microbes. Transformation by photolysis and hydrolysis is expected to be minor.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

Chemical identifiers for DBP are presented in Table 6-1, while pertinent physicochemical parameters are in Table 6-2, and partition coefficients are in Table 6-3.

The partitioning and migration of DBP in soils has been studied by Russell and McDuffie (1986). In one set of experiments they measured the equilibrium partitioning of DBP between soil and water in sealed flasks that were shaken gently for 24 h at approximately 25°C. The soil used was a local Broome County soil composite containing 1.59 wt% organic carbon. The K_d value for this soil type was 22 and the associated K_{oc} value was 1386. The K_{oc} derived from their soil column experiments was 1800. The equation of Briggs (1981) that correlates water solubility with K_{om} (see Appendix A) gave a value of 2512 for K_{oc} .

Mayer and Sanders (1973) reported a bioaccumulation factor of 400 for water fleas exposed to 0.08 µg/L DBP for 14 d and a bioaccumulation factor of 1400 for scud (Gammarus pseudolimnaeus) exposed to 0.1 µg/L of DBP for 14 d. By comparison, the K_{fw} value for fish calculated from K_{ow} is 2422, which is somewhat higher than the values calculated for the invertebrate species.

Table 6-1. Chemical identifiers of DBP.

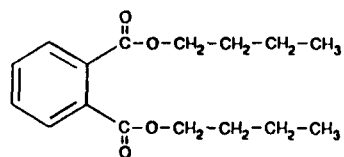
Empirical formula: C₁₆H₂₂O₄

Molecular weight: 278.35

CAS reg. no.: 84-74-2

RTECS no.: TI0875000

Structural formula:



ENVIRONMENTAL TRANSFORMATION PROCESSES

Photolysis

Dibutyl phthalate does not degrade upon exposure to light in the visible region (above 290 nm) (Mansour et al., 1985). This is to be expected because the UV absorption spectrum has a maximum absorption at 198.5 nm ($\log \epsilon = 4.54$) and smaller maxima at 229.5, 275.5, and 281 nm. At wavelengths greater than 281 nm, the light absorption drops rapidly with increasing wavelength, approaching an extinction coefficient of near zero above 300 nm (Leyder and Boulanger, 1983).

Biotransformation

Microorganisms degrade DBP to various metabolites. Some microorganisms, for example, Norcardia sp., Arthrobacter sp., Pseudomonas sp. (Englehardt and Wallnöfer, 1978) and Micrococcus sp. (Taylor et al., 1981) are capable of using DBP as a sole carbon source and thereby degrading it. Other bacteria hydrolyze DBP to the monoester or degrade various metabolites of DBP, but do not degrade the aromatic ring. Biotransformation occurs under both anaerobic and aerobic conditions in soil as well as water. In some cases there is a lag time before microbes are able to degrade DBP (Walker et al., 1984).

The biotransformation of DBP begins with hydrolysis to the monoester, then hydrolysis to phthalic acid, which is then oxidized. Englehardt and Wallnöfer (1978) isolated monobutyl phthalate (MBP) by extraction of liquid

Table 6-2. Chemical and physical properties of DBP. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling point	°C	340	Windholz et al., 1983
Freezing/melting point	°C	-35	Windholz et al., 1983
Density	g/mL	1.043	Windholz et al., 1983
Vapor pressure	torr	7.3×10^{-5a}	Howard et al., 1985
Aqueous solubility	mol/L	3.63×10^{-5}	Leyder and Boulanger, 1983
	mg/L	10.1	
	mol/L	4.02×10^{-5a}	Howard et al., 1985
	mg/L	11.2	
Henry's law constant	(L-torr)/mol	1.8	Calculated as the ratio of vapor pressure to aqueous solubility ^c
Diffusion coefficients: Air Water	m ² /s	4.5×10^{-6}	Estimated ^b
	m ² /s	4.3×10^{-10}	Estimated ^b
Log octanol/water partition coefficient(K _{OW})	log K _{OW}	4.79	Measured, Howard et al., 1985

a Measured at 25°C.

b See Appendix A.

c Based on the aqueous solubility and vapor pressure measured at 25°C.

Table 6-3. Partition coefficients for use in estimating contaminant movement in environmental media and human exposures to DBP.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^b /(mg/kg soil)	1	Calculated ^a from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	4.9×10^{-2}	Calculated ^a from water solubility and log K_{ow}
Fish/water	K_{fw}	(mg/kg fish) ^b /(mg/kg water)	2420	Calculated ^a from log K_{ow}
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	2512	Calculated ^a from water solubility
			1386	Calculated from a measured K_d value of 22 and a soil organic carbon content of 1.59 wt%, from Russell and McDuffie, 1986

^a See Appendix A.

^b Wet-weights for plant and fish.

cultures (mineral base + yeast extract) of DBP and soil bacteria (Norcardia sp.) They were unable to separate phthalic acid or its biodegradation production protocatechuic acid under aerobic conditions. When they incubated monobutyl phthalate with the same bacteria under anaerobic conditions, phthalic acid was produced along with traces of protocatechuic acid. Additional information on the degradation mechanism of DBP was provided by Eaton and Ribbons (1982), who studied the metabolism of DBP by a Micrococcus sp. and proposed the transformation mechanism shown in Fig. 6-1. After ester hydrolysis, phthalic acid oxidation produces a diol adjacent to the carboxyl groups. The next step is decarboxylation of the central carboxyl group. The resulting compound, protocatechuic acid (called "protocatechuate" by them, see Fig. 6-1), can be further oxidized through ring cleavage at two locations. Ring cleavage can occur between or adjacent to the hydroxyl groups and thereby produce β -ketoadipic acid in the first case and produce pyruvic and oxaloacetic acids in the second case. To confirm their proposed metabolic degradation scheme, Eaton and Ribbons also studied the metabolic decomposition of the proposed intermediates--phthalic acid, 3,4-dihydroxyphthalic acid, protocatechuic acid, and 4-carboxy-2-hydroxymuconic semialdehyde. In addition, they noted that their Micrococcus strain did not metabolize the butanol resulting from the initial phthalate hydrolysis.

Johnson et al. (1984) studied the biodegradation of phthalate esters in freshwater sediments and water from Little Dixie Lake in Columbia, Missouri. After 14 d of incubation in an aerobic sediment at 22°C, 84.5% of the DBP had degraded to the mono ester, as measured by $^{14}\text{CO}_2$ evolution from ^{14}C -labeled carbonyl groups. They also studied the effects of concentration, temperature, pre-exposure, and nutrients on biodegradation of DBP and other phthalates. Degradation rates were nearly the same for 0.082 to 8.2 mg/L concentrations of DBP, and it degraded at rates "directly proportional to temperature" between 4 and 21°C (see Table 6-4). Nutrients only affected degradation rates if they were added after the addition of DBP. They measured no increased degradation rates when the microbial population had been exposed to DBP for 14 d and then was inoculated with ^{14}C -DBP and the $^{14}\text{CO}_2$ evolution measured. However, Little Dixie Lake is an impoundment in an agricultural watershed, so the microorganisms may already have been exposed to DBP.

Walker et al. (1984) measured DBP degradation rates in six sediments and associated waters from several sites along the Gulf coast of Florida and

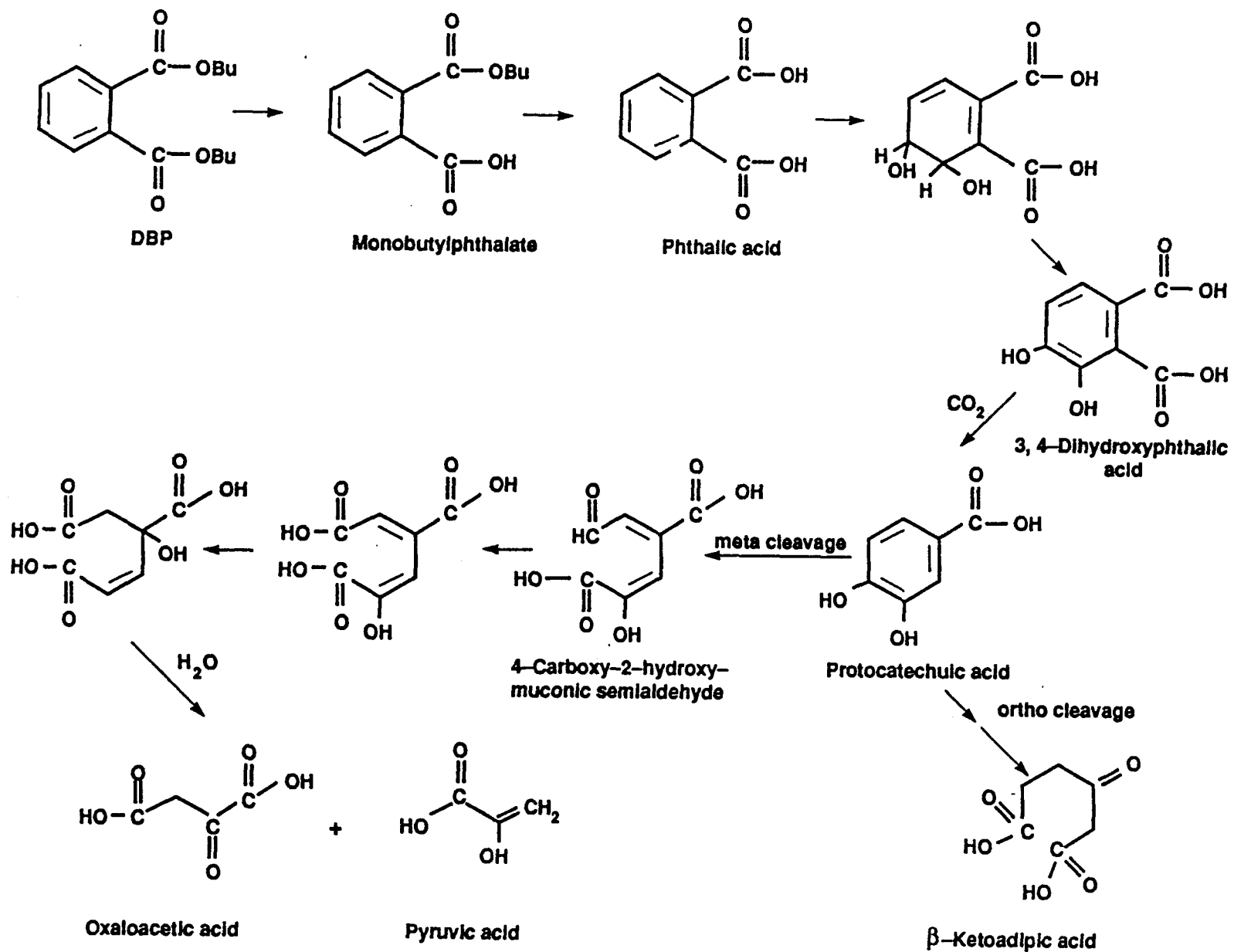


Figure 6-1. Mechanism of microbial degradation and products proposed by Eaton and Ribbons, 1982; and Englehardt and Wallnöfer, 1978.

Table 6-4. Microbial transformation rates for DBP.

Media	Temp. (°C)	pH	Conditions	Results	Lag-time (d)	Half-life ^a (d)	Reference
Ultimate degradation---generation of CO ₂							
FW ^b sediment	22	7.6	aerobic	84.5% lost in 14 d	---	5.2	Johnson et al., 1984
FW sediment	22	7.6	aerobic?	64.1% lost in 7 d	---	4.7	Johnson et al., 1984
"	"	"	"	63.2% lost in 7 d	---	4.8	Johnson et al., 1984
"	"	"	"	64.6% lost in 7 d	---	4.6	Johnson et al., 1984
Silica sand	23	7.6	aerobic	less than 1% lost 200 d	---	---	Inman et al., 1984
Muck and sand	23	7.4	aerobic	20.1-58.8% lost 11-18 d	20	7.3 (17)	Inman et al., 1984
Natural sand	23	6.2	aerobic	2.6-77.9% lost 53-80 d	50	12.6 (72)	Inman et al., 1984
Silt/loam	23	5.9	aerobic	8.7-89.4% lost 53-80 d	50	8.6 (68)	Inman et al., 1984
Chalmers loam	23	6.0	anaerobic	12.3-68.6% lost 18-53 d	11	24 (44)	Inman et al., 1984
Chalmers loam	23	5.2	aerobic	1.9-39.3% lost in 14 d	18	20 (36)	Inman et al., 1984
Chalmers loam	23	6.0	aerobic	32.4-84.7% lost in 27 d	32	12.5 (63)	Inman et al., 1984
Chalmers loam	23	7.2	aerobic	16.5-63.3% lost in 5 d	3	4.2 (9)	Inman et al., 1984
Chalmers loam	30	6.0	aerobic	9.8-77.7% lost in 21 d	18	10.4 (44)	Inman et al., 1984
Chalmers loam	4	6.0	aerobic	less than 2% lost 200 d	---	---	Inman et al., 1984
Chalmers loam	23	6.0	aerobic	36.4-97.2% lost in 27 d	35	6 (60)	Inman et al., 1984
Primary degradation---hydrolysis to monoester							
SW ^b sediment	25	7.8	aerobic	$k^c = 0.04556 \text{ h}^{-1}$	---	0.63(1.0)	Walker et al., 1984
FW sediment	25	7.0	aerobic	$k = 0.01259 \text{ h}^{-1}$	---	2.3 (3.6)	Walker et al., 1984
SW sediment	25	8.0	aerobic	Lack of data	---	(1.6)	Walker et al., 1984
SW sediment	25	8.0	aerobic	$k = 0.01841 \text{ h}^{-1}$	---	1.6 (2.6)	Walker et al., 1984
SW sediment	25	7.7	aerobic	$k = 0.01529 \text{ h}^{-1}$	---	1.9 (2.0)	Walker et al., 1984
SW sediment	25	8.0	aerobic	$k = 0.01243 \text{ h}^{-1}$	---	2.3 (1.9)	Walker et al., 1984
FW sediment	25	7.1	aerobic	$k = 0.01017 \text{ h}^{-1}$	---	2.8 (3.6)	Walker et al., 1984
FW sediment	25	6.8	aerobic	$k = 0.00855 \text{ h}^{-1}$	---	3.4 (4.8)	Walker et al., 1984
Salt water	25	7.8	aerobic	$k = 0.00293 \text{ h}^{-1}$	---	9.8(13.1)	Walker et al., 1984
Fresh water	25	7.0	aerobic	$k = 0.01003 \text{ h}^{-1}$	---	2.9 (6.8)	Walker et al., 1984

Table 6-4. (continued)

Media	Temp. (°C)	pH	Conditions	Results	Lag-time (d)	Half-life ^a (d)	Reference
Primary degradation---hydrolysis to monoester							
Salt water	25	8.0	aerobic	$k = 0.01599 \text{ h}^{-1}$	---	1.8 (6.2)	Walker et al., 1984
Salt water	25	7.7	aerobic	$k = 0.02133 \text{ h}^{-1}$	---	1.4 (2.4)	Walker et al., 1984
Salt water	25	8.0	aerobic	$k = 0.04092 \text{ h}^{-1}$	---	0.71(5.2)	Walker et al., 1984
Fresh water	25	7.1	aerobic	$k = 0.02362 \text{ h}^{-1}$	---	1.2 (7.3)	Walker et al., 1984
Fresh water	25	6.8	aerobic	$k = 0.02291 \text{ h}^{-1}$	---	1.3 (7.0)	Walker et al., 1984
Garden soil	30	8.2	aerobic	472 to 110 mg/kg in 5 d	---		Shanker et al., 1985
Garden soil	30	8.2	anaerobic	470 to 239 mg/kg in 20 d	---		Shanker et al., 1985
6-9 Broome Co. soil	25		aerobic	70% to 19% 7 - 24 h	---	0.38 (0.42)	Russell et al., 1985
Leachate + soil	25		aerobic	98% to 30% 7 - 24 h	---	0.41 (0.58)	Russell et al., 1985
Sterile soil	25		aerobic	100% to 40% 0 - 48 h	---	1.5 (1.5)	Russell et al., 1985

^a Half-lives were calculated from values taken when concentration changes were greatest with respect to time. Values in parentheses are time from addition of DBP to disappearance of one-half of the initial concentration.

^b FW = freshwater, SW = saltwater.

^c Rate constant for biodegradation.

Louisiana. Although they found loss of DBP from their sterile controls, it was much slower than that associated with their microbially active waters and sediments. They ascribed the loss of DBP from controls to binding to humic materials. Experiments were done in darkened shakers; and half-lives of DBP in sediments ranged from 1 to 4.8 d. The half-lives of DBP in water alone ranged from 2.7 to 13.1 d, with the majority of values between 5 and 7 d. They also determined rate constants for the more rapid disappearance of DBP after completion of a lag period during which microorganisms underwent adaptation. The associated half-lives (see Table 6-4) ranged from 0.63 to 3.4 d in sediments and 0.71 to 9.8 d in natural waters. In three sterile sediments they measured disappearance rates for DBP and calculated half-lives of 5.6 to 17 d. They suggested that the either the DBP loss was the result of microbial enzymes remaining active after formalin sterilization or that DBP was binding to the sediment. The remainder of the sterile sediments and all of the sterile water samples showed no significant loss of DBP. They noted that degradation of DBP in some sediments proceeded immediately, while in others, there was a lag time before degradation started. They also found no relationship between lag time and organic carbon content, temperature, salinity, pH, or sediment composition. Taylor et al. (1981) also found that DBP was readily degraded by microorganisms from sediments within the Mississippi Delta area as well as by some Florida marine microorganisms.

Biodegradation of DBP in soils is similar to that observed in sediment and water. Shanker et al. (1985) measured DBP disappearance in tubes of garden soil under both aerobic and anaerobic conditions at 30°C in the laboratory. They defined aerobic conditions as soil saturated to 60% of its water holding capacity and anaerobic conditions as soil in a stoppered flask and flooded with sterile water. Under aerobic conditions, DBP disappeared rapidly (half-life of 2.4 d); under anaerobic conditions, however, it disappeared very slowly (half-life of about 20 d). The biotransformation mechanisms appear to be different for the aerobic and anaerobic conditions. A degradation product, phthalic acid, accumulated very little under aerobic conditions, but accumulated to a greater extent under anaerobic ones.

Additional factors influencing DBP biotransformation were investigated by Inman et al. (1984) in their soil biodegradation studies of DBP. They found that decomposition was enhanced by increasing pH, the addition of organic matter, and raising the temperature from 23 to 30°C. They found that phthalic

acid was rapidly decomposed, but DBP and its monoester required a lag time of 6 to 53 d when added to their test soils (Chalmers silt loam, Everglades peaty muck and sand, Fincastle silt loam, Plainfield sand, and acid-washed silica sand). Soil pH affected only the initial rate of DBP loss--DBP decomposed more rapidly at pH 7.4 than at pH 6.0, but after 80 d of incubation, degradation rates were the same at all initial pH levels. Addition of ammonia and calcium carbonate did not affect DBP decomposition rates. Less than 3% decomposition took place in either the sterile control of "Chalmers" soil or in the silica sand. They were measuring $^{14}\text{CO}_2$ evolution from labeled carbonyl groups--not the disappearance of DBP--so they could not detect losses of DBP due to binding with the soil. The half-lives for DBP loss (based on the amounts of $^{14}\text{CO}_2$ produced) ranged from 4.2 d for aerobic "Chalmers" soil at pH 7.2 and 23°C to 21 d at pH 6.0 under anaerobic conditions.

Sugatt et al. (1984) used shake-flask experiments to study the biodegradation of DBP by microorganisms from soils and sewage sludge. After 28 d, 57% of the initial DBP had been converted to CO_2 . Shelton et al. (1984) examined the anaerobic degradation of DBP in sewage sludge and in a 10% sludge - mineral salts medium combination. They measured primary degradation by extraction and ultimate degradation by methane and carbon dioxide generation. They defined ultimate degradation as mineralization of all carbon atoms in the molecule. They found that methane production increased as the DBP concentration decreased in the 10% sludge mixture. About 90% of the DBP degradation occurred within 7 d in the sludge itself and within 40 d in the 10% sludge. The work of Shelton et al. showed that there are organisms capable of converting the aromatic ring to methane anaerobically in addition to those that convert the ring to carbon dioxide aerobically (Johnson et al., 1984).

Reactions with Humic Substances

Humic materials have been found to complex with, adsorb to, or react with xenobiotic materials. Although the nature of the interaction between humic acids and DBP is not completely understood, it appears to be a reversible surface adsorption. Martin et al. (1981) studied the components of soil humic acids by oxidation with potassium persulfate to produce low-molecular-weight acids. DBP was among the products isolated, although only in a small quantity.

Because their procedure involved the conversion of the acids formed to methyl esters, a dibutyl ester (i.e., DBP) could not have been chemically part of the humic acid. The DBP could have been adsorbed or otherwise complexed to the humic acids. Schnitzer and Kahn (1972) reported that 950 g of fulvic acid can "complex" 278 g of DBP, thereby making the DBP more water soluble. They noted that the infrared spectrum of a phthalate is not modified by addition to fulvic acid; therefore, they concluded that the phthalate does not chemically react with the fulvic acid. They suggested that the phthalates are adsorbed on the surface of the fulvic acid. Finally, Carlberg and Martinsen (1982) studied the binding of DBP to humic substances in filter-sterilized waters. They found that storage at 4°C decreased the recoverable DBP to less than 10% in two weeks. Thereafter, the rate of decrease in extractable DBP was much slower, and after 60 days DBP was nonextractable.

The experiments discussed in the previous section on biotransformation lend additional support to the concept of complex formation by DBP and humic acid components, followed by later release. For example, dibutyl phthalate disappeared from "sterile" aqueous solutions containing soils, sediments, or humic materials (Walker et al., 1984). The disappearance rate from these solutions was slower than that with active microbial populations, but was nonetheless significant. This phenomenon was observed when the disappearance of DBP was determined by analysis for DBP and not CO₂. Using this technique, Russell et al. (1985) measured the disappearance of DBP in local (Broome County) soils and soils that had been sprayed with sewage leachate. They sterilized their controls by adding 0.1% formaldehyde. From the loss rates of DBP from the microbially-active soils, we calculated half-lives of about 10 h (0.38 d). The corresponding half-life for DBP disappearance from the controls was 36 h (1.5 d). However, DBP completely disappeared from the microbially-active soils in about 70 h, whereas in the controls 29% of the starting material was still extractible after 120 h. Using the same type of analysis, Walker et al. (1984) found that DBP disappeared from some sterile sediments, but not in sterile water from samples taken along the Gulf Coast of Florida and Louisiana (they sterilized the samples by adding 37% formaldehyde/L). Four of the eight sterile sediment samples lost one-half the starting material in 5.6 to 17 d. These half-lives were 2 to 17 times longer than the corresponding ones for their microbially-active counterparts.

On the other hand, when disappearance of DBP was measured by analysis of the breakdown products of DBP itself, Inman et al. (1984) found no degradation/disappearance of DBP from a sterile control, because adsorption does not result in gas evolution. After 200 d, less than 2.5% of the ^{14}C -labeled CO_2 had evolved from the sterilized control soil (they did not state their method of sterilization). However, $100 \pm 11\%$ of the added ^{14}C was recovered as CO_2 from the flasks containing the active cultures under aerobic conditions by that time. In other work, Shelton et al. (1984) showed that the DBP degradation rate changed with time. The DBP loss rate became much slower after 1 week, with DBP totally degraded after 3 weeks.

Total degradation of DBP was shown by Johnson et al. (1984) when degradation was measured by CO_2 evolution. They reported that more than 90% of the potential amount of CO_2 had been produced after 2 weeks incubation at 28°C of DBP in freshwater sediment. At lower temperatures, DBP degradation, although incomplete after two weeks, was still progressing. Similar results for the degradation of DBP under anaerobic conditions in water amended with 10% sewage sludge were observed by Shelton et al. (1984). They measured the production of methane from DBP and found that it increased at a steady rate until 80% of the amount calculated for the mineralization of the butyl alcohol as well as of the aromatic ring was evolved by 30 d.

These experiments indicate that DBP will complex with or adsorb to humic substances. The reaction between DBP and humic materials proceeds more rapidly at warmer temperatures, but always more slowly than microbial degradation in the experiments noted above. Quantitative and near quantitative production of CO_2 by microorganisms from DBP showed that the sorption of DBP is reversible and that DBP is still susceptible to microbial degradation. Therefore, because DBP solubility and transport will be increased by adsorption to humic materials, its rate of loss will be enhanced by the presence of such materials because sorbed DBP is readily available for microbial degradation.

Hydrolysis

Wolfe et al. (1980b) studied the hydrolysis of phthalate esters in water at high pH. Their hydrolysis rate constant for DBP was second order in base concentration, that is, $0.01/\text{M}_{\text{OH}}\text{-s}$. By substituting the hydroxide ion

concentrations at pH's of 7 and 8 in the second-order rate constant, we obtained half lives of 22 and 2.2 y, respectively. No studies reported the products formed when hydrolysis occurs at higher pH; however, Wolfe et al. studied dimethyl phthalate in detail. They found that it hydrolyzes first to the monoester and then slowly to phthalic acid. The hydrolysis of DBP should produce analogous products.

TOXIC EFFECTS ON ANIMALS AND HUMANS

Previous reviews on the toxicology of DBP and other phthalate esters have been completed by the Cosmetic, Toiletry, and Fragrance Association (CTFA, 1985), the U.S. EPA (1980a), Thomas and Thomas (1984), and Perwak et al. (1981). The literature on DBP contains no definitive data on human health effects. Studies with laboratory animals have demonstrated effects on liver and testes. In addition, DBP was found to be teratogenic to rats and mice. Mutagenicity studies have largely been negative, both with and without metabolic activation. Chronic toxicity studies have shown that DBP is noncarcinogenic. In the subsections below we review the key studies on the toxicity of DBP.

Toxicokinetics

Absorption. Studies with rats indicate that radiolabeled DBP is readily absorbed from the gastrointestinal tract. In a study by Tanaka et al. (1978) more than 90% of the radioactivity of ^{14}C -DBP administered orally (60 mg/kg) to male Wistar rats was recovered in urine within 48 h of administration. Similar results were obtained in an earlier study by Williams and Blanchfield (1975), who orally administered ^{14}C -DBP to male Wistar rats (doses of 2.31 and 0.27 g/kg) and recovered 82.5 and 91.5% of the radioactivity in urine within 48 h.

Distribution and bioaccumulation. DBP has been found in the kidneys, adipose tissue, blood, and umbilical cords of humans (see CTFA, 1985). Animal studies have shown that DBP is rapidly cleared from the body, and no organs or tissues have any significant tendency for accumulation. Tanaka et al. (1978) measured the residual radioactivity in the carcasses of Wistar rats 24 h after

oral administration of ^{14}C -DBP (60 mg/kg) and found that the intestines, adipose tissues, liver, kidney, blood, and muscle had the most activity.

Williams and Blanchfield (1975) investigated the distribution of radioactivity in rats that had received oral doses of DBP- ^{14}C (0.27 and 2.31 g/kg). Measurements were made at 4, 8, 24, and 48 h after administration. Twenty-four hours after the oral ingestion of 0.27 g/kg of DBP, radioactivity was found mainly in the kidney, liver, and adipose tissue. At 48 h, only trace amounts of radioactivity remained in tissues and organs, even at the higher dose (2.13 g/kg).

Metabolism. In vitro studies (Tanaka et al., 1978; Kaneshima et al., 1978; Lake et al., 1976; Rowland et al., 1977) on the metabolism of DBP have demonstrated that it is hydrolyzed to monoester products in tissues and organs such as liver, kidneys, and small intestines. Kaneshima et al. (1978), for example, incubated rat liver and kidney homogenates with 0.4 mg/mL of DBP at 37°C. After a 2 h incubation with rat liver homogenates, DBP disappeared almost completely. Although the action of rat kidney homogenates was slower, it also degraded nearly 90% of the DBP after 5 h of incubation. Lake et al. (1976) incubated ^{14}C -DBP with rat, ferret, and baboon hepatic and intestinal-mucosal cell homogenates. DBP was hydrolyzed by all preparations, and more than 90% of the total metabolites formed were monobutyl phthalate (MBP). In a later study by Lake et al. (1977), human intestinal preparations were also shown to catalyze the monohydrolysis of DBP. Rowland et al. (1977) incubated 1 mg/mL of DBP with the contents of rat stomach, small intestines, cecum, and human feces. The rate of in vitro hydrolysis of DBP was greatest in the presence of the contents of a rat's small intestine and much slower with cecal material, stomach contents, or human feces. When DBP was incubated with the contents of rat intestines, MBP was the only product of metabolism, and complete hydrolysis to phthalic acid did not occur.

One hour after intravenous dosing of ^{14}C -DBP to Wistar rats, Tanaka et al. (1978) separated rat livers into nuclear, mitochondrial, lysosomal, microsomal, and cytosol fractions. The maximum hydrolysis of DBP to MBP was found in the microsomal fraction of rat liver. These researchers also analyzed the urinary metabolites of rats, hamsters, and guinea pigs that were orally dosed with 60 mg/kg of ^{14}C -DBP. The primary metabolite was MBP in all three species, minor amounts of intact DBP and phthalic acid were also

identified. They also noted the possible occurrence of MBP glucuronide, which was unstable. In later work, Foster et al. (1982) found that MBP was excreted primarily as a glucuronide conjugate in the urine of rats and hamsters receiving oral doses of ^{14}C -DBP.

Excretion. The main route of elimination of orally administered DBP in rodents is urinary excretion. Urinary metabolites include MBP and MBP glucuronide, phthalic acid, intact DBP, and MBP oxidation products. Fecal excretion (8 to 9%) is small when compared with urinary excretion after oral or intravenous administration of DBP to rats (Tanaka et al., 1978). Biliary excretion is another pathway of elimination. Twenty-four hours after an oral dose (60 mg/kg) of ^{14}C -DBP, biliary excretion was much higher than excretion via feces (Tanaka et al., 1978). Kaneshima et al. (1978) administered a single 500-mg/kg dose of ^{14}C -DBP in ethanol to male rats by gastric intubation, and bile was collected every hour for 6 h. A total of 4.5% of the radiolabel was recovered in bile by the end of the collection period. Major rat-bile metabolites included MBP and an MBP glucuronide.

Toxic Effects on Organs and Systems

Hepatic effects. Nikonorow et al. (1973) administered 0.12 and 1.2 g/kg-d of DBP by gavage (in olive oil) for 3 mo to 10 female and 10 male Wistar rats. Both levels of DBP produced a statistically significant increase in the mean liver weight of the animals (p-value was not given). However, no pathologic changes were found in any of the tissues examined. Perwak et al. (1981) cited studies by Yamada (1974) and Ota et al. (1974) in which hepatotoxicity was observed. According to Perwak et al., Yamada (1974) reported increased mortality and significant ($p < 0.01$) enlargement of the liver and spleen when rats were fed 1 or 5 mL/kg-d DBP for 3 wk. Ota et al. (1974) observed liver lesions in mice receiving 5.0 or 0.5 g/kg-d of DBP orally for 1 to 3 months. Walseth et al. (1982) gave 3.8 mM/kg (1.06 g/kg) of DBP (i.p.) to Sprague-Dawley rats for 5 d. DBP significantly increased the concentration of cytochrome P-450 in livers as well as the ratio of liver weight to body weight ($p < 0.05$). Post-treatment serum showed a significant decrease ($p < 0.05$) in alanine aminotransferase (ALAT), albumin, and total protein. Takahashi (1977) used the mitochondrial fraction of livers from male

Wistar rats to study the effect of DBP on mitochondrial respiration of rat liver and demonstrated that DBP inhibited both oxygen uptake and phosphorylation.

Dermal and ocular effects. Several studies involving dermal and eye irritation of DBP were reviewed by the CTFA (1985). In general, DBP caused only slight irritation when applied to the skin of laboratory animals. Intradermal irritation of DBP to rabbits has also been studied. Calley et al. (1966), for example, injected DBP in 3% acacia (0.2 mL of 100 mg/mL) into the skin of the shaven backs of rabbits. DBP produced a mild irritation after 10 min and a moderate response after 26 min. In another study (Lawrence et al., 1975), DBP was not found to be irritating to mice after intradermal injections.

Respiratory effects. In humans, breathing DBP vapors has an irritating action on mucous membranes of nasal passages and upper respiratory systems (Sittig, 1985). Men'shikova (1971) exposed three human subjects to 0.12 and 0.15 mg/m³ of DBP and observed abnormal encephalographic responses in the subjects; at 0.093 mg/m³, no abnormalities were noted. In the same study, rats were exposed continuously to DBP concentrations of 0.098, 0.256, 0.98 mg/m³ in air. No behavioral changes nor weight loss were noted by the researcher. However, gamma globulin was increased and appeared to be dose-related (p-value was not given).

Walseth et al. (1982) exposed male Sprague-Dawley rats to concentrations of DBP in air ranging from 0.5 to 7.0 ppm for five days. The concentration of cytochrome P-450 in the lungs of the exposed rats decreased by as much as 63%, compared with the controls, at a concentration of 7 ppm. Kawano (1980) exposed rats to 0.5 and 50 mg/m³ of DBP mist for 6 h/d for 6 months. Smaller weight gain and greater brain (p < 0.01) and lung weights (p < 0.01) were observed at the 50 mg/m³ DBP mist level.

Reproductive effects. Cater et al. (1977) administered 2000 mg/kg-d of DBP dissolved in corn oil by oral intubation to 3- to 4-week-old male Sprague-Dawley rats. Treated rats exhibited a progressive decline in testes weight, 30 to 40% loss at 4 d (p < 0.01) and 60 to 70% loss at 14 d (p < 0.001), when compared with the control animals. Histological examination of testes tissue revealed that morphological damage had occurred. Since zinc is essential for the maintenance of normal testicular function, it is not

surprising that the researchers also found DBP treatment adversely affected zinc metabolism. Urinary excretion of zinc was increased, and the zinc content in the testes was markedly decreased. DBP treatment did not significantly alter the zinc content in the kidney and liver. Interestingly, coadministration of zinc was found to protect against DBP-produced testicular damage. MBP, the major metabolite of DBP, was shown to be more effective than DBP in causing testicular atrophy. Oishi and Hiraga (1980) also studied the effect of MBP on young male Wistar rats. Animals were fed 2 wt% MBP in feed for 1 wk. MBP caused a significant decrease in zinc concentration ($p < 0.05$) and an increase in testosterone concentration in the testes ($p < 0.05$). A study by Gangolli (1982) showed that oral administration of DBP produced uniformly severe seminiferous tubular atrophy in rats and guinea pigs, but caused only focal atrophy in mice, while hamsters appeared to be resistant to the gonadal effects.

Teratogenicity

Teratogenic studies in rats, mice, and chick embryos have demonstrated that DBP causes increased embryo mortality, decreased birth weight, and teratogenic effects. Singh et al. (1972) administered DBP by intraperitoneal injection (i.p.) to five pregnant Sprague-Dawley rats on days 5, 10, and 15 of gestation. The doses administered on each of those days were 1/10, 1/5, and 1/3 of a previously determined i.p. LD50 (3.05 mL/kg for DBP). Control rats were untreated or were treated with 10 mg/kg of distilled water, 10 mL/kg of normal saline, 10 mL/kg of cottonseed oil, or 5 mL/kg of cottonseed oil. All the rats were sacrificed on day 20. DBP did not interfere with fertility. No fetal deaths or gross abnormalities were noted in any DBP-treated group. However, there were significant effects upon embryonic and/or fetal development. Fetal weight was significantly reduced in all DBP-treated groups ($p < 0.01$). Skeletal abnormalities were increased in 30 to 50% of the fetuses examined (33, 24, and 21% for 1/3, 1/5, and 1/10 of LD50 dose, respectively). Elongated and fused ribs, absence of tail bones, and abnormal or incomplete skull and leg bones were the most prominent skeletal abnormalities.

Peters and Cook (1973) also studied the teratogenic effects of DBP on Sprague-Dawley rats injected with DBP (treatments of 2 and 4 mL/kg) on days 3,

6, and 9 of gestation. DBP injections resulted in a 46 and 61% reduction in the number of pups weaned per litter (in the 2 and 4 mL/kg treatment groups, respectively). In addition, two male pups, one from each of the two litters in the 2-mL/kg group, had no eyes. In a study by Nikonorow et al. (1973), female rats received 120 or 600 mg/kg-d of DBP by gavage for 3 months prior to being mated. Additional groups of female rats received the same doses for 21 d of gestation. Before gestation, DBP administration did not cause any significant changes, whereas postgestational administration did result in lower placental weights at both treatment levels ($p < 0.05$). Fetal weights were significantly lower in the 600-mg/kg-d group ($p < 0.05$). Hamano et al. (1977) (as cited in Perwak et al., 1981) observed increased embryo mortality in mice when "0.5% DBP" was given orally on days 0 to 18 of gestation. Shiota and Nishimura (1982) administered DBP in various doses (80, 180, 370, 660, or 2100 mg/kg-d) in the feed to pregnant mice throughout gestation. Neural tube defects, increased resorptions, decreased fetal weight, and delayed ossification were observed in the 660 and 2100 mg/kg-d DBP-treatment groups. High doses of DBP were embryotoxic and possibly teratogenic in mice. In another study, Onda et al. (1974) (as cited in CTFA, 1985) administered DBP in the diet (10 and 100 mg/kg-d) of two mouse strains (ddY and ICR) for three generations. The formation of renal cysts was increased in the F1 and F2 generations.

In a study with chicks, Bower et al. (1970) injected fertile chick embryos with 0.1 mL and 0.05 mL of undiluted DBP. Increased embryo mortality was observed (79.1 and 66.6%) when compared with uninoculated, sesame oil, and vegetable oil controls (31.1, 44.3, and 53.4%, respectively). No teratogenic defects were noted.

Genotoxicity

A summary of the genotoxicity studies completed on DBP is presented in Table 6-5. The mutagenicity of DBP on different S. typhimurium strains is negative with metabolic activation. DBP was not mutagenic for E. coli (Omori, 1976) or the yeast S. cerevisiae (Shahin and Von Borstel, 1977). DBP was reported as both negative and positive for chromosome aberrations and sister chromatid exchanges (SCE) in Chinese hamster cell. In one study, Abe and Sasaki (1977) observed a significant increase ($p < 0.05$) in SCE in Chinese

Table 6-5. Summary of DBP Genotoxicity.

Assay	Genetic endpoint	Dosage	Results	Comments	Reference
<u>Salmonella</u> plate incorporation TA98, TA100 +S9	Reverse mutation	0.3 mg/mL	-		Omori, 1976
<u>Salmonella</u> plate incorporation TA98, TA100 ± rat S9	Reverse mutation	1000 µg/plate	-S9 +S9 - -		Rubin et al., 1979
<u>Salmonella</u> TA100	8-azaguanine resistance	not reported	+ -	liquid suspension assay	Seed, 1982
<u>Salmonella</u> TA98, TA100 ± rat S9	Reverse mutation	not reported	- -	both histidine and biotin were added to agar	Kozumbo et al., 1982
<u>Salmonella</u> TA98, TA100 TA1535, TA1537 ± rat, hamster S9	Reverse mutation	10-1000 µg/plate (99% purity)	-	preincubation method	Zeiger et al., 1985
<u>Escherichia coli</u> (uvrA ⁻ , pol A ⁻ , rec A ⁻)	DNA repair	0.3 mg/mL	-		Omori, 1976
<u>Bacillus subtilis</u> (rec A ⁻)	DNA repair	0.3 mg/mL	-		
<u>Escherichia coli</u> (Wild, uvrA ⁻)	Mutation	0.3 mg/mL	-		Omori, 1976

Table 6-5. (continued)

Assay	Genetic endpoint	Dosage	Results	Comments	Reference
<u>Saccharomyces</u> 1977 (XV185-14C)	Reverse mutation	10, 20, 100 $\mu\text{L/mL}$	-		Shahin and Von Borstel,
Chinese hamster cells	chromosomal aberration	0.0157, 0.0313 0.0625 mg/mL	0, 1.5, 0% at 48 h		Omori, 1976
Chinese hamster cells	chromosomal aberration	1×10^{-6} , 1×10^{-5} $1 \times 10^{-4}\text{M}$	All positive for SCE at 26 h	$p < 0.05$	Abe and Sasaki, 1977
Chinese hamster cells	chromosomal aberration	0.03 mg/mL	6% at 24 h	control: 1.8% at 24 h	Ishidate and Odashima, 1977
Human leukocyte	chromosomal aberration	0.25 mg/mL	-		Tsuchiya and Hattori, 1976 (as cited in CFTA, 1985)

hamster cells. DBP has no effect on chromosome aberrations in human leukocyte cultures (Tsuchiya and Hattori, 1976; as cited in CFTA, 1985).

Carcinogenicity

No chronic bioassays have been completed with laboratory animals that specifically focus on the carcinogenicity of DBP.

Estimation of Intake Limits to Protect Public Health

The only suitable study to base an acceptable intake level on is a chronic toxicity study performed by Smith (1953) with Sprague-Dawley rats. In that study groups of ten rats were fed DBP in their diet at concentrations of 0.01, 0.05, 0.25, or 1.25 wt%. The highest no-observed effect level was at the dietary concentration of 0.25% wt. This level is equivalent to an intake of 187.5 mg/kg-d of DBP, based on a daily food consumption of 75 g/kg-d (McNamara, 1976), or

$$\begin{aligned}\text{Daily intake} &= \frac{75 \text{ g}}{\text{kg-d}} \times \frac{2500 \text{ mg}}{\text{kg}} \times \frac{\text{kg}}{1000 \text{ g}} \\ &= 187.5 \text{ mg/kg-d}\end{aligned}$$

The U.S. EPA (1980a) assumed that rats consumed 5 wt% of their weight per day, and thus a 200 g rat would consume 50 g/kg-d of feed, yielding an intake of 125 mg/kg-d of DBP. With a safety factor of 100, the intake limits for human would range from 1.25 to 1.88 mg/kg-d.

TOXIC EFFECTS TO AQUATIC SPECIES

Table 6-6 summarizes data on the acute toxicity of DBP to aquatic vertebrates. For vertebrate species the LC50 values range from 0.7 to 6.5 mg/L. Sugawara (1974) reported that DBP caused a decrease in the hatchability of brine-shrimp eggs at levels of 10 mg/L. At 5 mg/L, it was reported that DBP decreased the heart rate of goldfish (Pfuderer and Francis,

Table 6-6. Acute toxicity of DBP to aquatic organisms.

Species ^a	Concentration (mg/L)	Effect	Reference
<u>Aquatic vertebrates</u>			
Bluegill	0.7	96 h LC50	Mayer and Sanders (1973)
Bluegill	1.2	96 h LC50	Buccafusco et al. (1981)
Fathead Minnow	1.3	96 h LC50	Mayer and Sanders (1973)
Fathead Minnow larvae	2.0	96 h LC50	McCarthy and Whitmore (1985)
Channel Catfish	2.9	96 h LC50	Mayer and Sanders (1973)
Rainbow Trout	6.5	96 h LC50	Mayer and Sanders (1973)
<u>Aquatic invertebrates</u>			
Dinoflagellate	0.1	96 h LC50	Wilson et al. (1978)
Scud	2.1	96 h LC50	Mayer and Sanders (1973)
Crayfish	10.0	96 h LC50	Mayer and Sanders (1973)

^a Species: bluegill, Lepomis macrochirus; fathead minnow, Pimephelas promelas; channel catfish, Ictalurus punctatus; rainbow trout, Salmo gairdneri; marine dinoflagellate, Gymnodinium perve; scud, Gammarus pseudolimnaeas; crayfish, Orconectes nais; and brine shrimp, Artemia salina.

(1975). DBP can also affect the growth of phytoplankton: at 5 mg/L, it decreases the growth rate of Skeletonema (Medlin, 1980), whereas, reduction of the growth rate of Gymnodinium was observed at 0.2 mg/L (Wilson et al., 1978).

McCarthy and Whitmore (1985) conducted an early life-stage (ELS) test with fathead minnows and a reproductive potential test with Daphnia magna. In the ELS test fathead minnows were exposed to DBP in the concentrations of 0.1, 0.18, 0.32, 0.56, 1.0, and 1.8 mg/L. Larval survival was greater than 80% for organisms exposed to concentrations of 0.56 mg/L or lower. Hatching rate was significantly reduced at 1.0 or 1.8 mg/L of DBP. At the 1.8 mg/L level, none of the embryos succeeded in hatching to viable larvae. The no-observed-effect-concentration (NOEC) in this ELS test with fathead minnows was 0.56 mg/L and the lowest-observed-effect-concentration (LOEC) was 1.0 mg/L. In the reproductive test with Daphnia magna, organisms were exposed to DBP concentrations of 0, 0.056, 0.18, 0.56, 1.8, and 3.2 mg/L.

Reproductive potential of Daphnia was stimulated at low concentrations and inhibited at high concentrations of DBP; exposure to 0.056 to 0.56 mg/L of DBP increased the number of young produced, and at 1.8 mg/L of DBP, reproduction was significantly impaired. The NOEC was determined to be 0.56 mg/L, and the LOEC was 1.8 mg/L.

TOXIC EFFECTS TO PLANTS

Lokke and Bro-Rasmussen (1981) found that spraying a fine mist of DBP to the leaves of terrestrial plants caused bleaching of the leaves. Dibutyl phthalate caused chlorosis on the leaves but diethylhexyl- and diisobutyl phthalates did not. The combination of DBP vapor and light disturbed carotenoid synthesis in green plants resulting in chlorophyll deficiency (Virgin et al., 1981). No bleaching was observed when plants were exposed to DBP vapor in the dark. Growth and photosynthesis were also inhibited in aquatic algae when the concentration of DBP in the water was near or greater than the solubility of DBP (Melin and Egneus, 1983).

7. DATA-BASE ASSESSMENT FOR DIETHYL PHTHALATE

Diethyl phthalate (DEP) is one of several phthalate esters used as plasticizers in plastic products and has been detected in environmental media across the world. DEP is also an ingredient in single- and double-base propellant formulations and as such represents a possible contaminant at OB/OD sites. The primary environmental transformation process for DEP is microbial degradation. The available data on the partitioning of DEP in environmental media indicate that DEP will be more mobile than DBP.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

Chemical identifiers for DEP are found in Table 7-1 and pertinent physicochemical properties are shown in Table 7-2. The partitioning of DEP (see Table 7-3) between soil/water and soil organic carbon/water has been studied by Russell and McDuffie (1986). The K_d for DEP in a Broome County, New York soil composite containing 1.59 wt% organic carbon was 1.1 and the associated K_{oc} was 69. These values were determined from the equilibrium partitioning of DEP between water and soil in sealed flasks. The average K_{oc} value calculated from data obtained from soil-column experiments was 98. Our estimated K_{oc} value from water solubility, shown in Table 7-3, is 200. Barrows et al. (1980) determined the steady-state bioconcentration factor (K_{fw}) for bluegill sunfish (Lepomis macrochirus) as 117, a factor of five higher than our estimated value (see Table 7-3).

ENVIRONMENTAL TRANSFORMATION PROCESSES

Diethyl phthalate will undergo biotransformation in natural waters, soils, and sediments, with aerobic degradation occurring faster than anaerobic. In aqueous solutions hydrolysis of the ester linkage (primary degradation) occurs with a half-life of a few hours to days under aerobic conditions and weeks under anaerobic conditions. Biotransformation takes place at a more rapid rate under aerobic conditions than under anaerobic conditions. When the microbial population has not previously been exposed to DEP, a lag time for microbial adaptation occurs before biotransformation

Table 7-1. Chemical identifiers of DEP.

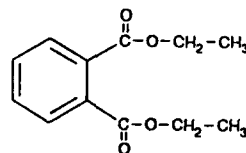
Empirical formula: $\text{CH}_2\text{N}_4\text{O}_4$

Structural formula:

Molecular weight: 222.24

CAS reg. no.: 84-66-2

RTECS no.: TI1050000



begins. Organic carbon content and nutrients do not affect the biotransformation rate. Photolytic degradation and hydrolysis will not be significant transformation processes.

Photolysis

All phthalate esters have similar light absorption spectra in distilled water at 20°C. Although they absorb light in the UV region, little absorption occurs above 300 nm in the visible region (Leyder and Boulanger, 1983). We therefore expect limited degradation of DEP by sunlight because very little sunlight below 300 nm reaches the earth's surface (Lyman et al., 1982). Further evidence that DEP is not degraded by sunlight is provided by the experiments of Mansour et al. (1985) and Hustert et al. (1983), both of whom used DEP as a nonphotoreactive substance that could only be made photosensitive by the addition of hydrogen peroxide or titanium dioxide.

Lewis et al. (1984b) studied the photolytic degradation of DEP using fluorescent lamps with light output between 300-400 nm of the visible light spectrum. They measured less than 1% degradation of DEP dissolved in UV-sterilized water over a five-day period in a flow-through system. Wolfe et al. (1980a) predicted that photolysis of DEP would only be a significant environmental degradation pathway in oligotrophic (clear with little organic content) lakes. A half-life for DEP disappearance was predicted in oligotrophic lakes of 120 d with 94% of the degradation due to photolysis. They based their photolysis rates on unpublished measurements by R.G. Zepp of the photolysis of dimethyl phthalate in natural water exposed to sunlight for one week.

Table 7-2. Chemical and physical proerties of DEP. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source	
Boiling point	°C	295	Windholz et al., 1983	
Freezing/Melting point	°C	-40.5	Verschueren, 1983	
Density	g/mL	1.12	Verschueren, 1983	
Vapor pressure	torr	1.6 x 10 ^{-3a}	Howard et al., 1985	
Aqueous solubility	mol/L	4.18 x 10 ⁻³	Leyder and Boulanger (1983)	
	mg/L	928		
	mol/L	4.86 x 10 ^{-3a}	Howard et al., 1985	
	mg/L	1080		
Henry's law constant	(L-torr)/mol	0.33	Calculated as the ratio of vapor pressure to aqueous solubility at 25°C	
Diffusion coefficients:	Air	m ² /s	5.3 x 10 ⁻⁶	Estimated ^b
	water	m ² /s	5.2 x 10 ⁻¹⁰	Estimated ^b
Log octanol/water partition coefficient (K _{OW})	log K _{OW}	2.24	Howard et al., 1985	

^a Measured at 25°C

^b See Appendix A

Table 7-3. Partition coefficients for use in estimating human exposures to DEP.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^a /(mg/kg soil)	2	Calculated ^b from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	2.9×10^{-3}	Calculated ^b from water solubility and log K_{ow}
Fish/water	K_{fw}	(mg/kg fish) ^a /(mg/kg water)	23.4	Calculated ^b from log K_{ow}
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	200	Calculated ^b from water solubility
			69	Calculated from a measured K_d value of 1.1 and a soil organic carbon content of 1.59 wt%, from Russell and McDuffie, 1986

^a Wet-weights for plant and fish

^b See Appendix A

Biotransformation

Microbial degradation is the major route of DEP transformation in the environment (see Table 7-4 for an overview of biotransformation rate data). Studies on the biodegradation of organic pollutants showed that DEP degraded readily using domestic wastewater as the microbial inoculum in a 5 mg/L aqueous yeast medium (Tabak et al., 1981). Lewis and Holm (1981) concluded that bacteria are the transforming organisms, not fungi, protozoa, or algae.

Russell et al. (1985) studied the biotransformation of DEP in water amended with soil. They found that after a lag time of approximately 2 to 3 d, DEP disappeared rapidly from both the flask containing a composite of natural Broome County soils and one containing composite soils that had been sprayed with sewage leachate. Half-lives for the disappearance of DEP were 17 h (0.7 d) for leachate-sprayed soil and 23 h (0.95 d) for the natural Broome Co. soil. Although the controls had been sterilized with 0.1% formaldehyde, after 72 h, they too began to show loss of DEP. The observed DEP loss in controls could be due to sorption and/or loss of soil sterility with time.

Sugatt et al. (1984) measured both primary (ester hydrolysis) and ultimate biodegradation (mineralization) under aerobic conditions. They used soil and sewage organisms in an aqueous mineral salts medium. For DEP they calculated a half-life of 2.21 d for primary degradation, which was much faster than the half-life for DBP (15.4 d). After 28 days, ultimate degradation was 95% complete and primary degradation of DEP was > 99% complete.

Biotransformation of DEP under anaerobic conditions was measured by Shelton et al. (1984) using sewage sludge and 10% sewage sludge in an aqueous mineral salts medium. In undiluted sludge the anaerobic half-life was less than a week. In the 10% sludge the half-life was approximately 2 weeks and more than 90% had disappeared after 6 weeks. They collected 76% of the theoretical amount of CH₄ from the DEP degradation in 10% sludge as a measure of ultimate degradation over the 70 d course of the experiment (we estimated the half-lives shown in Table 7-4 by extrapolation from graphs of the decreasing concentrations of DEP).

Lewis et al. (1984b) studied how different parameters affected the aerobic biodegradation of DEP in water. They found that bacterial activity associated with submerged surfaces or suspensions of aquatic microbial growth caused rapid microbial degradation of DEP over large ranges of dissolved

Table 7-4. Microbial transformation rates for DEP.

DEP Concentration	Media	Temp. °C	pH	Conditions	Results	Lag-time d	Half-life ^a d	Reference
Primary degradation---hydrolysis to monoester								
3-10 mg/L	Broome Co. soil	25		aerobic	60% to 14% 72-120 h	---	0.95 (1.7)	Russell et al., 1985
3-10 mg/L	Leachate + soil	25		aerobic	89% to 33% 24-48 h	---	0.7 (1.2)	Russell et al., 1985
3-10 mg/L	Sterile soil	25		aerobic	191% to 66% 72-120 h	---	4.3 (8.3)	Russell et al., 1985
20 mg/L	soil/sewage in mineral salts medium	22	7.0	aerobic	76% lost after 7 d	2.3	2.21 (3.4)	Sugatt et al., 1984
20 mg/L	sludge	35		anaerobic	50% lost at about 3.5 d	---	3.5	Shelton et al., 1984
Unstated	10% sludge in mineral salts	35		anaerobic	50% lost at about 10 d	---	10	Shelton et al., 1984
0.191 mg/L	bacteria/water	20		aerobic	decay rate constant = 0.25 h ⁻¹	---	0.1	Lewis et al. 1984b
Ultimate degradation---conversion to CH ₄								
Unstated	10% sludge	35		anaerobic	50% recovered (approx)	---	18	Shelton et al. 1984

^a Half-lives were calculated from the straight-line portion of the graph of concentration decrease vs. time where possible. Values in parentheses are time from addition of DEP to disappearance of one-half of the initial concentration.

organic carbon, nitrogen, chlorophyll phosphorous, ATP, and biomass content. Their experiments were designed to be representative of various nutrient conditions that may be found in water bodies at 20°C. The average first-order rate constant for DEP disappearance was approximately 0.12 h^{-1} , from which we calculate a half-life of 5.8 h (0.24 d). Parker et al. (1984) used two outdoor lysimeters containing 1.52 m of soil to study the biodegradation/leachability of DEP when municipal wastewater containing DEP was sprayed once a week on two soils over a period of two years. Of the 16 organic substances that they monitored, only PCB's were more persistent than DEP. Periodic measurements of DEP concentrations in core samples showed that DEP concentrations decreased rapidly with depth, but DEP was found at all depths in the 150 cm soil at different times. However, it was found only once in leachate samples, although water-travel time was 30 to 50 d through the lysimeters. They found that DEP accumulated in the sandy loam to a greater extent than in the silty loam and suggested that the lower moisture content in the sandy loam decreased the amount of biodegradation of DEP.

Reactions with Humic Substances

Although DEP, like DBP, binds to some extent with organic material in soils, sediments and water, less DEP is removed from water by these complexes. DEP association with humic acids was shown by the persulfate oxidation experiments of Martin et al. (1981). After treating the oxidation products with diazomethane to produce methyl esters of the acids, they isolated DEP among the products. Because DEP is a diethyl ester, it must have been physically and not chemically bound to the humic substances.

Hydrolysis

Hydrolysis will be a very slow process at the pH's encountered in most natural waters. Wolfe et al. (1980b) measured the alkaline hydrolysis of several phthalate esters in 0.01 to 0.0001 M NaOH. They derived hydrolysis rate constants from these measurements that were second order in hydroxide concentration. We calculated hydrolysis half-lives of 10.4 months at pH 8 and 8.9 years at pH 7 for DEP from their second-order rate constant of $0.025/M_{OH}\text{-s}$. Additional evidence for the slow hydrolysis of DEP comes from

Lewis et al. (1984b). In a flow-through system operated at pH 10, they observed "barely measurable" hydrolysis in 12 h (approximately 5%).

TOXIC EFFECTS ON ANIMALS AND HUMANS

Previous reviews on the toxicity of DEP include those of U.S. EPA (1980a), Perwak et al. (1981), Thomas and Thomas (1984), and the Cosmetic, Toiletry, and Fragrance Association (CFTA) (1985).

Toxicokinetics

Absorption and distribution. There is little quantitative data available on the absorption of DEP via different routes. Autian (1973), in a review article, summarized unpublished data (Dillingham and Pesh-Innam, University of Tennessee) on the uptake of radiolabeled DEP applied to the skin of rabbits and then covered with cotton patches. Urinalysis showed that 9% of the radioactivity associated with the applied DEP was excreted after 24 h, 14% after 48 h, and 16 to 20% within 72 h. Three days after the dermal exposure of labeled DEP, radioactivity was detected in the lung, heart, liver, kidney, gonads, spleen, and brain. However, skin and subdermal fatty tissue at the site of dermal exposure showed no radioactivity. According to Autian, the presence of DEP or its metabolites in the brain indicated that this chemical can cross the blood-brain barrier. It has also been shown to penetrate the placental barrier, for example, Singh et al. (1975) administered ^{14}C -DEP intravenously to pregnant rats on day 5 or day 10 of gestation. DEP and metabolites were present in maternal blood, fetal tissue, amniotic fluid, and placentas after day 8 or day 11, respectively, and throughout gestation.

Metabolism. Although information on metabolism of DEP is minimal, the pattern of metabolism is similar for all the members of the homologous series of phthalate esters. DEP is hydrolyzed to the monoester with subsequent oxidation of the remaining alkyl chain (Brown et al., 1978). Several in vitro hydrolysis studies of DEP (Lake et al., 1976; Lake et al., 1977; Rowland et al., 1977) showed that DEP was hydrolyzed to monoethyl phthalate (MEP) in tissues and organs such as liver and small intestines. Lake et al. (1976) incubated ^{14}C -DEP with rat, ferret, and baboon hepatic and intestinal-mucosal

cell homogenates. DEP was hydrolyzed by all the preparations, and MEP constituted more than 90% of the metabolites formed. In a later study, Lake et al. (1977) also demonstrated that human intestinal preparations catalyzed DEP monohydrolysis. Rowland et al. (1977) incubated 1 mg/mL of DEP with the contents of rat stomach, small intestines, cecum, and human feces for 16 h at 37°C. The rate of in vitro hydrolysis of DEP was greatest in the presence of the contents of a rat's small intestine and slower with cecal contents. DEP was barely hydrolyzed by stomach contents or human feces. When the contents of rat intestines were used, MEP was the only metabolic product, and hydrolysis to phthalic acid was incomplete.

Excretion. Kitanaka et al. (1977) reported that more than 80% of the radioactivity of orally ingested ^{14}C -DEP was excreted in the urine of rats and mice.

Toxic Effects on Organs and Systems

Hepatic effects. Subchronic and chronic studies show that DEP does not produce severe toxicity to organs or systems. However, reduction of animal weight gain and enlargement of the liver and other organs were noted in several experiments. Brown et al. (1978) fed male and female rats DEP at dietary concentrations of 0.2, 1.0, and 5.0 wt% for 16 wk. At 16 wk, both female and male rats receiving 5.0 wt% DEP in their feed had a significant reduction of body weight ($p < 0.001$). Significant ($p < 0.001$) liver enlargements were also noted in both males and females at the 5.0 wt% dietary level of DEP. Histological examination of liver tissues showed fatty degeneration and slight vacuolation.

In a study by Moody and Reddy (1978), four male F-344 rats consumed feed containing 2 wt% DEP for 3 wk. Although body weight increases in the treated group were not significantly different from those in the control group, liver weight (% of body weight), liver catalase, and liver carnitine acetyltransferase activity were all increased significantly ($p < 0.01$) when compared with controls. Takahashi (1977) studied the effects of DEP and other phthalate esters on liver mitochondrial respiration of male Wistar rats and found that DEP inhibited both oxygen uptake and phosphorylation.

Dermal and ocular effects. DEP produces little irritation when placed in contact with animal or human skin. However, intradermal injections of DEP in rabbits can lead to a significant degree of irritation. Calley et al. (1966) injected 0.2 mL of DEP in 3% acacia at a concentration of 100 mg/mL into the shaven back skin of rabbits. DEP produced a rapid and marked inflammatory response. Significant irritation of peritoneal tissue at sacrifice was noted when mice were injected (i.p.) with 2 mL/kg of DEP with cottonseed oil as a diluent (Lawrence et al., 1975). Lawrence et al. (1975) also demonstrated no grossly observable eye irritation after application of undiluted DEP to the eyes of rabbits.

Respiratory effects. In humans, exposure to heated DEP vapor may produce transient irritation in mucous membranes of the nasal passage and the upper respiratory tract (U.S. EPA, 1980a). No animal studies of respiratory effects have been reported.

Reproductive effects. Two studies (Gray et al., 1977; Cater et al., 1977) have shown that diethylhexyl phthalate and DBP produce testicular atrophy in the rats and mice. This effect has not been observed in toxicity studies with DEP. Foster et al. (1980) fed young male Sprague-Dawley rats 1600 mg/kg-d of DEP by gavage in corn oil for 4 d. No testicular atrophy was observed. Urinary zinc excretion and the zinc content of testes were unaffected.

Teratogenicity

In animals, DEP has caused increased embryo mortality, decreased birth weight, and teratogenic effects in rats, mice, and chicks (Singh et al., 1972; NTP, 1984; Bower et al., 1970). Singh et al. (1972) administered DEP (i.p.) to groups of five pregnant Sprague-Dawley rats on days 5, 10, and 15 of gestation. The doses administered to each group on each of those days were 1.686, 1.012, or 0.506 mL/kg per injection. No fetal deaths or gross abnormalities were noted in any DEP-treated dams. However, average fetal weight was significantly ($p < 0.01$) reduced in all DEP-treated groups. Skeletal abnormalities (mainly incomplete or missing skull bones) were

increased in 30 to 50% of the fetuses examined (81.3, 47.1, and 26.3% in the 1.686-, 1.012-, and 0.506-mL/kg treatments, respectively).

In a study conducted as part of the National Toxicology Program (NTP) (NTP, 1984), DEP was administered in feed (0.25, 1.25, and 2.5 wt% in feed) for 7 d before pairing and then to breeding pairs of CD-1 mice for 98 d of cohabitation and 21 d thereafter. Dietary DEP did not appear to affect the numbers of litters produced, the average litter size, or the mean pup weight when compared with controls. The only exception was a significant increase ($p < 0.05$) in average litter size in the low-dose group (0.25 wt% DEP in the feed) relative to controls. Assessment of reproductive effects on high-dose (2.50 wt% DEP in the feed) offspring relative to control offspring was also performed. Average litter size was significantly ($p < 0.05$) smaller for the treated group. Mean pup weight of the high-dose offspring was depressed relative to controls ($p = 0.056$). Second-generation breeding pairs exhibited statistically significant ($p < 0.01$) physiological effects, namely, decreased body weights and increased liver weights ($p < 0.01$) in the high-dose groups (2.50 wt% of DEP in the feed) when compared with controls.

Bower et al. (1970) injected 0.025 mL of DEP into fertilized chicken eggs. Embryo mortality was increased significantly ($p < 0.01$) in the DEP-treated group when compared with sesame oil, vegetable oil, and uninoculated controls (44.3, 53.4, and 31.1%, respectively). One out of 10 live chicks in the DEP-treated group had malrotation of the leg (no statistical tests reported). None of the control groups had congenital malformations. Iijo (1975) reported that DEP injected into fertilized chicken eggs produced teratogenic and toxic effects. DEP injection did not suppress the body weight of the chicks that developed. No further information was available on this study.

Genotoxicity

A summary of microbial assay, DNA repair, and chromosomal aberration studies on DEP is presented below in Table 7-5. The mutagenicity of DEP to strains of S. typhimurium has been reported as both negative and positive, depending on the assay protocol. DEP was not mutagenic for E. coli (Omori,

Table 7-5. Summary of DEP genotoxicity (derived from CTFA, 1985).

Assay	Genetic endpoint	Dosage	Results ^a		Comments	References
<u>Salmonella</u> TA 98, TA 100 + S9	Reverse mutation	0.3 mg/mL				Omori, 1976
<u>Salmonella</u> TA 98 ± rat S9	Reverse mutation	1000 µg/plate	-S9 -	+S9 -		Rubin et al., 1979
TA 100 ± rat S9	Reverse mutation	1000 µg/plate	+	-		
<u>Salmonella</u> TA 100	8-azaguanine resistance	not reported	+	+	Liquid Suspension Assay, results were dose-related	Seed, 1982
<u>Salmonella</u> TA 98, TA 100 ± rat S9	Reverse mutation	1000 µg/plate	+	-	Histidine and biotin were both added to agar	Kozumbo et al., 1982
<u>Salmonella</u> TA 98, TA 100, TA 1535, TA 1537 ± rat, hamster S9	Reverse mutation	100-1000 µg/plate (99.9% purity)	-	-		Zeiger et al., 1985

Table 7-5. (continued).

Assay	Genetic endpoint	Dosage	Results ^a	Comments	References
<u>Escherichia coli</u> (uvr A ⁻ , pol A ⁻ , rec A ⁻)	DNA repair	0.3 mg/mL	-		Omori, 1976
<u>Bacillus subtilis</u> (rec A ⁻)	DNA repair	0.3 mg/mL	-		
<u>Escherichia coli</u> (Wild, uvr A ⁻)	Mutation	0.3 mg/mL	-		Omori, 1976
Chinese hamster cells	Chromosomal aberration	0.125, 0.25, 0.5 mg/mL	NOAEL 0.125 mg/mL, cell death occurred at 48 h, 0.5 mg/mL		Omori, 1976
Chinese hamster cells	Chromosomal aberration	0.25 mg/mL	1.0% at 24 h		Ishidate and Odashima, 1977
Human leukocytes	Chromosomal aberration	0.25 mg/mL	-		Tsuchiya and Hattori, 1976 (as cited in CFTA, 1985)

^a + = positive - = negative

1976) and was negative for chromosomal aberration in Chinese hamster cells (Omori, 1976; Ishidate and Odashima, 1977). DEP has no effect on chromosome aberrations in human leukocyte cultures (Tsuchiya and Hattori, 1976).

Carcinogenicity

No evidence has yet been found that DEP produces carcinogenic effects in animals or humans.

Estimation of Intake Limits to Protect Public Health

In order to estimate safe intake limits for DEP, we examined dose-response data from both subchronic and chronic toxicity studies. Table 7-6 presents the results of the two subchronic toxicity studies for DEP in rodents. Calley et al. (1966) administered 125 mg/kg-d of DEP to mice i.p. for 6 wk. Results of body weight gain, organ/body weight ratios, hematology and pathology studies showed that DEP-treated animals were similar to those of the controls. In another subchronic study, Brown et al. (1978) administered 0, 0.2, 1.0, and 5.0 wt% DEP in feed to groups of 15 rats (CD strain) of both sexes for 16 wk. According to the researchers, the mean DEP intakes over the entire study were approximately 150, 770, and 3160 mg/kg-d in the male rats of the test groups and 150, 750, and 3710 mg/kg-d in the females. At the end of the 16 wk, male rats showed a significant ($p < 0.001$) reduction in body weight and increase in liver weight at the 3160 mg/kg-d level. At the 770 mg/kg-d level, significant ($p < 0.05$) increases in the relative stomach weight were observed. No adverse effects were observed at 150 mg/kg-d level (NOAEL). For female rats, significant ($p < 0.001$) body-weight reductions were observed at the end of 16 wk at 3710 mg/kg-d dose rate. Liver weights were significantly increased at all three dose levels ($p < 0.05$, $p < 0.01$, and $p < 0.001$ for the 150, 750, 3710 mg/kg-d groups, respectively). Thus, 150 mg/kg-d can be considered as a subchronic lowest-observed-adverse-effect-level (LOAEL).

The ADIs derived from the two subchronic toxicity studies mentioned above are listed in Table 7-7. In the study by Calley et al. (1966) the NOAEL was 125 mg/kg-d and by using an uncertainty factor of 5 to 10 (10 is used in this

Table 7-6. Results of subchronic toxicity studies for DEP.

Species (Strain)	Route	No. of animals	Dose rate or wt% in feed	Duration (wk)	Effects	References
Mice (Swiss- Webster)	i.p.	20-30	125 mg/kg-d	6	NOAEL	Calley et al. (1966)
Male rats (CD)	oral	15 per group	0, 0.2, 1.0, 5.0 wt% DEP in feed	16	NOAEL at 0.2 wt% DEP; increase of stomach weights ($p < 0.05$) at 1.0 wt% DEP	Brown et al. (1978)
Female rats (CD)	oral	15 per group	0, 0.2, 1.0, 5.0 wt% DEP in feed	16	Significant reduction of body weight and liver enlargements were observed in 0.2, 1.0, 5.0 wt% of DEP	Brown et al. (1978)

Table 7-7. Estimated acceptable daily intakes for DEP derived from subchronic toxicity studies.

Study	Species	Duration (wk)	Dose Rate mg/kg-d	Safety Factor	Estimated ADI mg/kg-d
Calley et al. (1966)	mice (Swiss- Webster)	6	125 ^a	1000	0.125
Brown et al. (1978)	Male rats (CD)	16	150 ^a	1000	0.15
	Female rats (CD)	16	150 ^b	1000	0.15 (lower-bound)

^a Dose rate for a NOAEL

^b Dose rate for a lowest-observed-adverse-effect-level

125 mg/kg-d and by using an uncertainty factor of 5 to 10 (10 is used in this case) to adjust a subchronic NOAEL to a chronic NOAEL (Layton et al., 1987b), and a safety factor of 100, the ADI becomes 0.125 mg/kg-d. In the study by Brown et al. (1978), the NOAEL for male rats was 150 mg/kg-d. If we also use an uncertainty factor of 10 to adjust the subchronic NOAEL to a chronic NOAEL (Layton et al., 1987b), and a safety factor of 100, the ADI becomes 0.15 mg/kg-d. Thus, from the above two subchronic toxicity studies the estimated ADI ranges from 0.125 to 0.15 mg/kg-d.

The U.S. EPA (1980a) chose a chronic study conducted by Food Research Laboratories, Inc. (1955) to derive an ADI for DEP instead of using one of the subchronic toxicity studies. In this chronic study (as reviewed by U.S. EPA (1980a)), groups of 30 rats were fed 0.5, 2.5, and 5.0 wt% DEP in their feed for two years. At the 5.0 wt% DEP level, a small but significant decrease in the growth rate of rats were noted (p-value was not given). No adverse effects were observed for the groups receiving 0.5 and 2.5 wt% DEP in their feed. The NOAEL of 2.5 wt% DEP equals a dose rate of 1250 mg/kg-d, assuming that rats consume 5% of their body weight (200 g) per day. By using a safety factor of 100, an ADI can be calculated as 12.5 mg/kg-d, and this is the level recommended by U.S. EPA (1980a). Interestingly enough, the NOAEL of 2.5 wt% DEP in feed defined in the chronic study was higher than the level that produced toxicity in the female rats used in the subchronic study conducted by Brown et al. (1978). The resulting ADI of 12.5 mg/kg-d is more than 80 times higher than the estimated ADI range derived from our calculation based on the two subchronic studies mentioned above (i.e., 0.125 to 0.15 mg/kg-d) that were calculated using an uncertainty factor of 1000.

TOXIC EFFECTS TO AQUATIC SPECIES

Acute toxicities of DEP to fish and aquatic invertebrates are listed on Table 7-8. No chronic toxicity studies were available for this compound. Only two studies reported no-observed-effect concentrations (NOEC) during acute toxicity tests. Heitmuller et al. (1981) reported a NOEC of 22 ppm for sheepshead minnows and LeBlanc (1980) reported a NOEC of 10 ppm for water fleas.

Table 7-8. Acute toxicity of DEP to aquatic organisms.

Species ^a	Concentration (mg/L)	Effect	Reference
Sheepshead Minnow	30.5	96 h LC ₅₀	Heitmuller et al., 1981
Bluegill	110	96 h LC ₅₀	Buccafusco et al., 1981
Marine Dinoflagellate	28.8	96 h LC ₅₀	Wilson et al. (1978)
Marine Dinoflagellate	4.5 (3.0-6.1)	Median growth limit concentration	Wilson et al. (1978)
Daphnia	52	48 h LC ₅₀	LeBlanc, (1980)
Brine Shrimp	50.0	Hatching success lower than controls (p < 0.05)	Sugawara (1974)

^a Species: Sheepshead Minnow = Cryrnodon variegatus; Bluegill = Lempomis macrochirus; Marine Dinoflagellate = Gymnodinium breve; Daphnia = Daphnia magna; Brine Shrimp = Artemia salina.

8. DATA-BASE ASSESSMENT FOR DIPHENYLAMINE

Diphenylamine (DPA) is a non-explosive stabilizer and antioxidant for propellants. The role of DPA in stabilization of single- and double-based propellants is that of an NO scavenger. Without a stabilizer, these propellants deteriorate rapidly; the free NO becomes oxidized to NO₂ with a simultaneous release of heat. This reaction catalyzes further degradation. The scavenging of NO by DPA results in a series of progressively more nitrated diphenylamines (see Fig. 8-1). Most of these amines are better stabilizers than DPA itself (Apatoff and Norwitz, 1973). When the DPA has been converted to dinitrodiphenylamine, the propellant is usually no longer stable. Therefore, depending on when propellants are demilitarized, some or all of the original DPA will have been converted to its nitrated analogues. When DPA itself is distributed in water and soils, it will degrade both photolytically and microbially. It may also react with oxygen as well as form metal salts with cations.

ENVIRONMENTAL PARTITIONING AND TRANSPORT

Chemical identifiers of DPA are found in Table 8-1 and pertinent physicochemical properties are shown in Table 8-2. The Henry's law constant for this compound is quite high, indicating that it will tend to move to the atmospheric compartment. Partitioning parameters, shown in Table 8-3, indicate that DPA will sorb to soils and sediments to a limited extent when organic matter is present. The estimated value for K_{OC} (see Appendix A) is about a factor of two lower than the measured value reported by Briggs (1981)(see Table 8-3).

ENVIRONMENTAL TRANSFORMATION PROCESSES

Photolysis

Diphenylamine is unstable in direct sunlight and air, becoming first tan, then blue, and purple. Zbozinek (1984) suggested that the products responsible for forming these colors included photoproducts ranging from dimers of DPA (joined at the para position of the phenyl groups) to oxidation products of the phenyl groups. Another possible product suggested was carbazole.

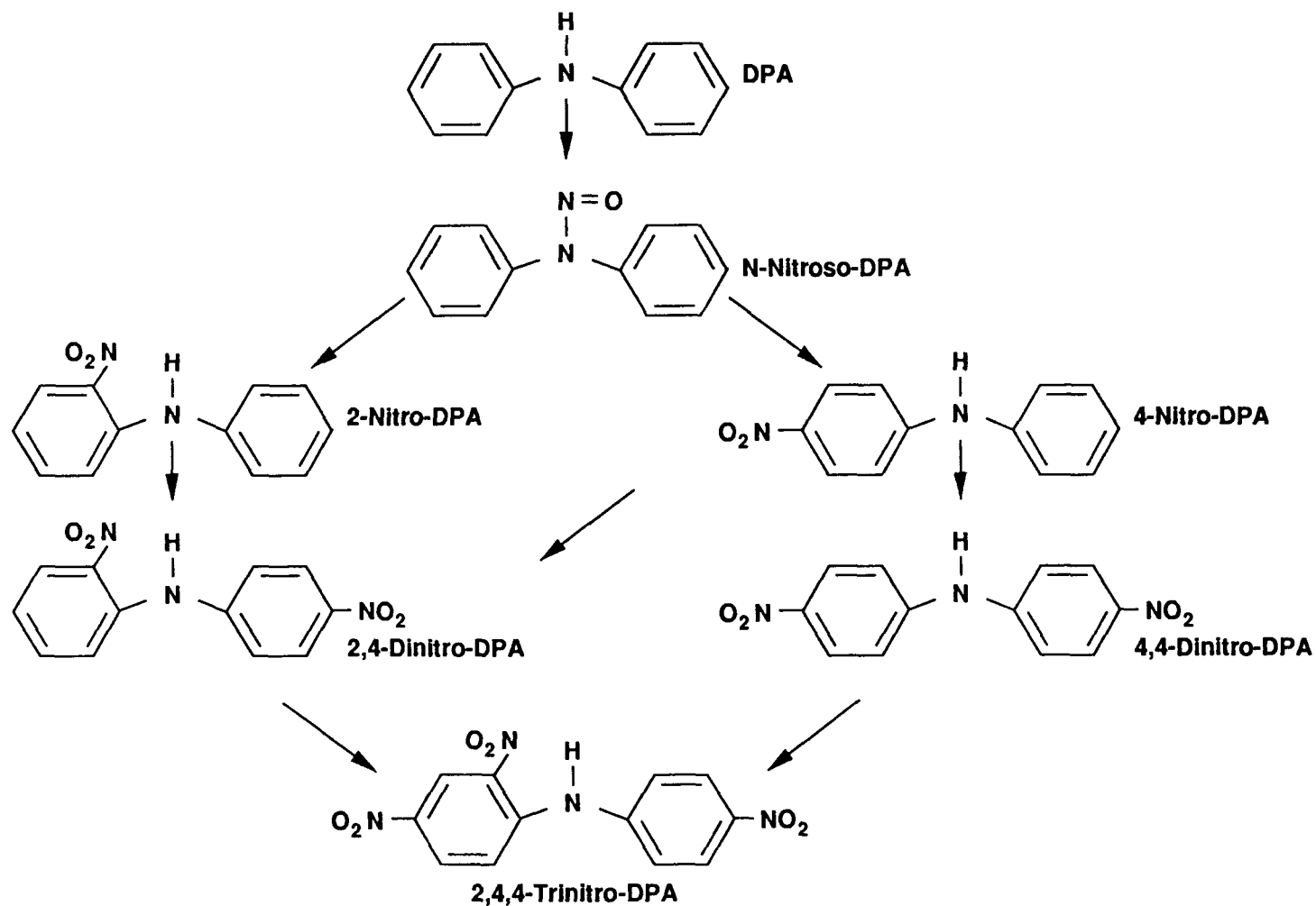


Figure 8-1. Progressive nitration of DPA as a stabilizer for single and double based propellants (adapted from Apatoff and Norwitz, 1973).

Table 8-1. Chemical identifiers of DPA.

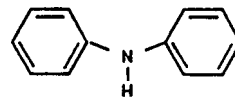
Empirical formula: $\text{CH}_{12}\text{N}_{11}\text{O}$

Molecular weight: 169.23

CAS reg. no.: [122-39-4]

RTECS no.: JJ7800000

Structural formula:



Lopez et al. (1980) found that DPA was completely converted to carbazole when 2.5×10^{-5} M DPA solution was irradiated with monochromatic visible light at 313 nm in an oxygenated "aqueous solution" at pH 7 at 25°C. In deoxygenated solutions they found that carbazole accounted for only 50% of the product with tetrahydrocarbazole formed as well (see Fig. 8-2). In addition, they reported that photolysis of DPA proceeded more readily between pH of 5 and 9. They proposed that these reactions proceeded through an excited singlet state of the DPA molecule.

Biotransformation

Gardner et al. (1982) measured the microbial degradation of ^{14}C -labeled DPA in a sewage sludge-mineral salts medium and isolated the products. After 24 h, they noted no decrease in DPA concentration in the heat-sterilized medium and a 96% loss in the active medium. The products isolated were 4-hydroxy-DPA and an isomer, aniline, indole, and CO_2 (see Fig. 8-2). The water soluble metabolites increased rapidly during the first 7 h of the experiment and the CO_2 evolution commenced thereafter. The experiment by Gardner et al. indicates that DPA will degrade by microbial action in environmental waters, sediments, and soils. However, the rate of environmental transformation will be much slower than in sewage sludge.

Table 8-2. Chemical and physical properties of DPA. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling point	°C	302 (explodes)	Berkowitz et al., 1978
Freezing/Melting point	°C	52.9	Berkowitz et al., 1978
Density	g/mL	1.159	Berkowitz et al., 1978
Vapor pressure (25°C)	torr	0.0027	Vriens and Hill, 1952
Aqueous solubility (25°C)	mol/L mg/L	0.000327 55.4	Takano et al., 1982
Henry's law constant	(L-torr)/mol	8.2	Calculated as the ratio of vapor pressure to aqueous solubility
Diffusion coefficients:	Air m ² /s Water m ² /s	5.9 x 10 ⁻⁶ 5.8 x 10 ⁻¹⁰	Estimated ^a Estimated ^a
Log octanol/water partition coefficient (K _{ow})	log K _{ow}	3.5	Hansch and Leo, 1979

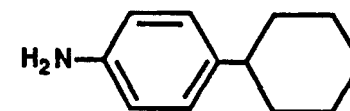
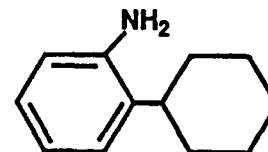
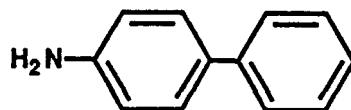
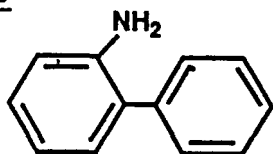
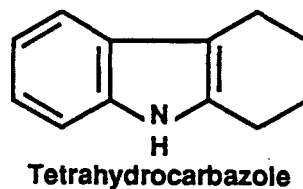
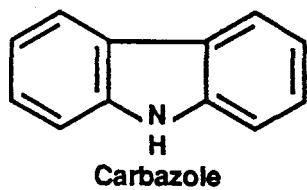
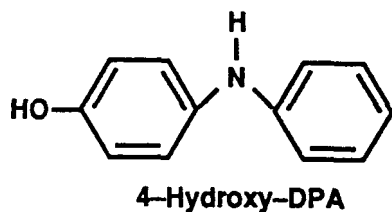
^a See Appendix A.

Table 8-3. Partition coefficients for use in estimating human exposures to DPA.

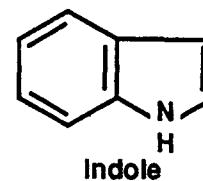
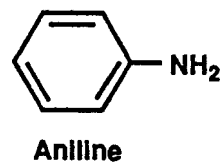
Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K _{sp}	(mg/kg plant) ^a /(mg/kg soil)	4	Calculated ^b from molecular weight
Beef-fat/diet	K _{fd}	(ppm in fat)/(ppm diet)	0.011	Calculated ^b from water solubility and log K _{ow}
Fish/water	K _{fw}	(mg/kg fish) ^a /(mg/kg water)	30	Measured value for fathead minnow, Veith et al., 1979
			232	Calculated ^b from log K _{ow}
SOC/water	K _{oc}	(mg/kg SOC)/(mg/kg water)	316	Calculated ^b from solubility in water and melting point.
			597	Adjusted from measured value, Briggs, 1981 ^b

^a Wet-weights for plant and fish

^b See Appendix A

ImpuritiesPhotolysis productsBiotransformation products

Isomer of
4-Hydroxy-DPA



CO₂

Figure 8-2. Co-contaminants of DPA from manufacturing (from Berkowitz et al., 1978), photolysis (from Lopez et al., 1980), and biotransformation (from Gardner et al., 1982).

Hydrolysis

No information was found on the hydrolysis of DPA.

TOXIC EFFECTS ON ANIMALS AND HUMANS

The pharmacology and toxicology of DPA have been reviewed by Opdyke (1978) and Berkowitz et al. (1978). In the following section, we discuss the important aspects of studies cited in those publications; this discussion is supplemented by a review of studies published since 1978.

Toxicokinetics

Absorption. Virtually nothing is known about the rate or extent of absorption of DPA in humans or animals. However, experimental administration of DPA in the diet has consistently elicited toxicity in laboratory animals, which demonstrates that DPA is absorbed across the gastrointestinal mucosa. Furthermore, as is apparent from the dermal LD50 for rabbits (5 g/kg) reported by Levenstein (1976) (as cited in Berkowitz et al., 1978), some absorption of DPA can take place through intact skin. Because there are no equivalent data for oral administration (in rabbits) it is not known whether there are route-dependent differences in absorption.

Distribution. The principal target organ of DPA-induced toxicity is the kidney (see following discussion). Adverse effects have also been documented in the liver, blood, and central nervous system. Although it can be inferred from these findings that DPA is widely distributed in the body, it is not known whether DPA preferentially distributes to specific organs or tissues.

Metabolism. Diphenylamine undergoes oxidative metabolism to form 4-hydroxydiphenylamine (4-hydroxy-DPA) and 4,4'-dihydroxydiphenylamine (4,4'-hydroxy-DPA). These metabolites have been recovered in the urine of humans, rats, dogs, and rabbits (Alexander et al., 1965; BIBRA, 1963; Sander and Schweinsberg, 1972; Gutenman and Lisk, 1975). Biliary excretion of 4-hydroxy-DPA and 4,4'-hydroxy-DPA have been documented in rats, and 2'-hydroxydiphenylamine (2-hydroxy-DPA), O-glucuronide, and O-sulphate

conjugates of DPA were isolated from the urine of rabbits dosed with DPA (Alexander et al., 1965).

Toxic Effects on Organs and Systems

Central nervous system effects. In his review of DPA's toxicity, Opdyke (1978) cited Russian authors who reported that DPA (100 mg/kg) had anticholinesterase activity when administered orally to rats and mice (Selivanova et al., 1972).

Hematological effects. Hemoglobin concentration, leukocyte counts, and red blood cell counts were unaffected in rats fed 1.0 wt% DPA in the diet for 463 days (Thomas et al., 1967a). However, Thomas et al. (1967b) found that long-term dietary administration of 1.0 wt% DPA (224 days) caused overt anemia in dogs. Because of poor survival (deaths due to distemper) in other treatment groups (i.e., 0.01, 0.10 wt%), it was not possible to determine if this effect was concentration-dependent. In their review of DPA-toxicity, Berkowitz et al. (1978) cited a Russian study (Volodchenko, 1975) that documented a decrease in hemoglobin and oxyhemoglobin, and an increase in methemoglobin and Heinz bodies in rats dosed orally with 1600 mg/kg DPA. A single oral dose of 169 mg/kg of DPA also caused methemoglobinemia in cats (Alexander et al. (1965).

Dermal effects. In patch tests with over 1000 individuals, Calnan (1978) showed that DPA was not allergenic to humans.

Hepatic effects. One of the earliest studies of DPA-induced toxicity found pigmentation in the liver (indicative of hemolysis) in rats who received 0.5, 1.0, or 1.5 wt% DPA in the diet for 226 days (Thomas et al., 1957). In a later study, Thomas et al. (1967b) fed dogs 0.01, 0.10, or 1.0 wt% DPA in their diet for 737 days. Tests of liver function conducted on days 618 to 627 of treatment showed an apparent correlation between administration of DPA and an increase in retention of sulfobromophthalein; this association was not statistically significant, however. Upon sacrifice, peripherolobular fatty change was evident in the livers of animals treated with 1.0 wt% DPA. These animals also had a "marked" increase in liver weight, and in the quantity

of "ether-extractable" lipids. Slight amounts of intracellular bilirubin were also noted. Interestingly, in similar studies with albino rats, Thomas et al. (1967a) found no evidence of hepatic injury due to DPA.

Renal effects. In the kidneys, DPA-induced toxicity is manifested as tubular dilation and polycystic disease. The etiology, pathogenesis, and underlying mechanism of DPA-induced renal disease has been relatively well studied. This is a consequence of the fact that the polycystic disease caused by administration of DPA appears to be a valid model for a similar (hereditary) disease in humans. In a two-year feeding study of DPA in rats (0.001 to 1.0 wt% DPA in feed), Thomas et al. (1967a) observed cystic dilation and inflammation of renal tubules accompanied by some accumulation of interstitial lymphocytes. Proteinaceous fluid and blood-derived iron-positive pigment were present in the renal pelvis, and were associated with "mild" epithelial hyperplasia or squamous metaplasia. By using a qualitative ranking system to compare the extent of renal cystic change and/or the degree of inflammation, Thomas et al. concluded that chronic nephritis occurred at doses of DPA between 0.1 and 0.5 wt%, and that cystic change was induced at doses of DPA > 1.0 wt%. Parallel studies with dogs (0.01, 0.10, and 1.0 wt% DPA in the diet, for 2 y) found no effect of DPA on renal function. However, at autopsy, all animals treated with DPA had slightly greater kidney weights than untreated controls. There was no evidence of overt morphologic or histologic change (Thomas et al., 1967b). Gardner et al. (1976) suggested that the renal cyst formation typical of treatment with DPA results from partial obstruction of the renal tubules, an increase in intratubular pressure caused by epithelial degeneration, accumulation of intraluminal debris, tubular narrowing, and eventually, compression of tubules from adjacent dilated nephrons. Experimental confirmation of these events was obtained by measuring a 5 to 30% increase in the size of surface nephrons, and an increase in intraluminal pressure in rats fed 1 wt% DPA for 5 to 20 months. Similar considerations led Eknoyan et al. (1976) to study the morphological alterations in the kidneys of rats fed DPA for 3 to 6 weeks (2.5 wt%). Approximately 10% of all animals treated with DPA had grossly visible renal cysts in the corticomedullary region. All rats exhibited morphological changes of the kidneys - the most common being cystic dilation of the collecting ducts in the medulla. Within two weeks of treatment, all animals

that received DPA also developed defects in their ability to concentrate urine, with an average reduction of capacity to 50% of control values. Kime et al. (1962) also speculated that narrowing of the tubular lumen combined with degeneration of the nephron are involved in the pathogenesis of DPA-induced renal disease. They observed tubular dilation, cyst formation, a decrease in glomerular filtration rate, and a decrease in maximum urinary osmolality in all rats who were treated with 2.5 wt% DPA in the diet for 1 y.

Evan and Gardner (1976) found similarities between DPA-induced cystic disease in rats and human polycystic kidney disease. After inducing renal cysts in rats by providing DPA in the diet for 12 to 18 months (1.0 wt%), electron microscopy showed that this disease is characterized by changes in the renal corpuscles and by thickening of the basement membrane. Cysts were observed along the entire nephron; those which developed in collecting ducts were lined with irregularly-formed cells, indicative of cell hypertrophy and/or hyperplasia. Kidneys from humans with polycystic disease exhibited a similar distribution of cysts and tubule dilation.

To study the evolution of renal cystic disease, Evan et al. (1978) fed rats 1.0 wt% DPA in their diet for up to 78 weeks. Histologic examination of animals sacrificed at regular intervals (2, 4, 5, 10, 20, or 78 weeks) found evidence of morphological changes in the medullary collecting tubules within five weeks of treatment. These changes progressed over time so that by 20 weeks "numerous" collecting ducts were dilated and contained cast material. By 24 weeks, animals had advanced renal cystic disease, with cysts present in the cortex and medulla, and necrotic cells in the collecting duct. Although some animals were maintained on a DPA-containing diet for 78 weeks, there was little progression of disease beyond that noted at 20 weeks. Darmady et al. (1970) and Safouh et al. (1970) also observed a similar progression of renal disease in rats fed DPA at 2.5 wt% in the diet over a 19-week period.

Reproductive effects. Thomas et al. (1967a) conducted a two-generation study of the reproductive toxicity of DPA to rats. DPA was given in the diet at 0.1, 0.25, or 0.5 wt%. Treatment was initiated when rats were 35 days old, and animals were mated at 100 days of age (65th day of treatment). Each dose group consisted of 12 females and three males. Following three weeks of

cohabitation, females were isolated until parturition. After pups were weaned, the adult rats were remated. The offspring from the first mating were also mated for a second-generation study. Treatment with DPA caused a statistically significant ($p < 0.05$) decrease in the average litter size from females that received 0.5 wt% DPA (first generation, first mating). This effect became more pronounced among litters from the second mating ($p < 0.01$). In second generation pups, the average litter size was significantly less than controls only in the 0.1 wt% dose group ($p < 0.05$).

Although cystic renal disease has been repeatedly induced in laboratory animals, Crocker et al. (1972) had experienced difficulty in reproducing a specific incidence of the disease. They speculated that the variability in response may be due to differences in composition of the samples - specifically, that DPA degenerates as it ages. To examine this hypothesis, Crocker et al. separated samples of fresh and aged DPA by thin-layer chromatography. While the fresh samples were essentially pure, the aged DPA contained three unidentified contaminants. Subsequent to this analysis, groups of pregnant rats were fed either a commercial (aged) preparation of DPA or fresh (unaged) DPA in the diet (1.5 or 2.5 wt%) for the last six days of gestation. Separate groups of rats were given one of the three contaminants (50 μ g daily). Newborn rats from all DPA-treated groups developed cystic dilation and degeneration of the proximal convoluted tubule. These lesions were more common and of greater severity in pups that received aged DPA at 2.5 wt%. Furthermore, Crocker et al. found an apparent correlation between the incidence and severity of renal cystic change in the newborn rats and the age of the DPA. (No statistical analysis was performed.) However, the most severe histological damage was observed in the kidneys of pups whose mothers received one of the contaminants (designated only as 'contaminant E').

Genotoxicity

Diphenylamine has given consistently negative results in short-term tests with Salmonella typhimurium, Escherichia coli, and Saccharomyces cerevisiae. DPA was also inactive in the rat hepatocyte assay, which measures induction of DNA repair synthesis.

Ferretti et al. (1977) examined the mutagenicity of DPA in a single strain of S. typhimurium (TA 1538). DPA was tested using a plate incorporation

protocol at a single concentration (100 μ g), in the presence and absence of S9. Although no data on background revertant counts were provided, DPA reportedly gave negative results both with and without S9. Florin et al. (1980) also attempted to study the mutagenicity of DPA to S.typhimurium. However, DPA precipitated out of solution, and no results were obtained. McGregor (1980) tested a series of compounds used in conventional ordnance for activity in the DNA repair assay with E.coli, the Ames reverse-mutation assay with S.typhimurium, and for mitotic recombination in S.cerevisiae. The authors reported that DPA gave negative results in all test systems, although specific data were not given. Probst et al. (1981) compared the activity of a series of 200 compounds in the Ames assay and in the rat hepatocyte assay for induction of unscheduled DNA synthesis (UDS). Mutagenicity in the Ames test was evaluated by inoculating eight separate tester strains of S.typhimurium and two strains of E.coli across agar, in plates containing a 10-fold concentration gradient of DPA (specific concentrations were not given). Exogenous metabolic activation (S9) was incorporated into the agar for half of the tests. In addition, primary cultures of rat hepatocytes were incubated with DPA (0.5 to 1000 nmol/mL) and ^{3} H-Thymidine for 23 to 25 h. Following development of autoradiograms, UDS was quantified by measuring the uptake of ^{3} H-Thymidine into the nucleus. Tests were repeated if a compound initially gave negative results; 2-acetylaminofluorene and methyl-N-nitrosoguanidine served as positive controls. DPA was one of 88 compounds (of the 200 tested) that was inactive in both the Ames test and UDS assay.

Oral administration of sodium nitrite and various secondary amines has reportedly produced carcinogenic N-nitroso compounds in the stomach of mammals (Druckrey et al., 1963). To examine the mutagenicity of N-nitroso compounds formed in vivo, Braun et al. (1977) used an intraperitoneal (i.p.) host-mediated assay with S.typhimurium. Mice received a single i.p. injection of bacteria along with a nearly simultaneous gavage dose of DPA (1450 to 2900 μ mol/kg) and an equimolar amount of sodium nitrite. Three to five hours after treatment, the contents of the peritoneal cavity were recovered and plated on agar to determine the viability of S.typhimurium. Although positive mutagenic responses were observed for several other cyclic secondary amines, DPA was inactive in this assay.

Carcinogenicity

There are no data to indicate that DPA is carcinogenic to humans (see reviews by Opdyke, 1978; Berkowitz et al., 1978). Three carcinogenicity studies conducted in animals have provided no evidence of carcinogenic activity. However, an impurity of commercially-available DPA, 4-biphenylamine, has been implicated in the development of human bladder cancer (Koss et al., 1969). In addition, Berkowitz et al. (1978) reviewed a German study (Sander and Seif, 1969) that examined the formation of potentially carcinogenic nitrosamines in the stomach as a result of the bacterial reduction of nitrates and secondary amines. Following ingestion of 10 mg DPA and 300 mg of sodium nitrate, nitrite was identified in samples of gastric fluids from all volunteers who had a pretreatment stomach pH less than 4. Nitrosamines (2 to 10 μ g) were detected in 11 of 31 volunteers.

Griswold et al. (1966) administered a single oral dose of 300 mg/kg DPA (the maximum tolerated dose) to 20 young female rats. Animals were observed for six months thereafter, but received no further treatment. After sacrifice, tissues were examined for the presence of neoplasms or preneoplastic changes. Under the conditions of this study, DPA was reported to be non-carcinogenic. However, no details of the actual study results were given, and this fact, combined with the single dose level, single treatment, and small number of animals combine to make the validity of these results questionable.

Over the course of a chronic toxicity study, Thomas et al. (1967a) gave weanling albino rats DPA in their diet for approximately two years (734 days). Doses of DPA ranged from 0.001, 0.01, 0.10, 0.50, to 1.0 wt%. Sixty animals were used for each dose level, including 20 untreated controls. At the termination of the study, histological examination of animals reportedly did not reveal any statistically significant changes in the incidence of specific tumors (benign or malignant) or in the incidence of total tumors in animals treated with DPA.

The most recent bioassay of DPA was conducted by Holmberg et al. (1983). NMRI mice were given 300 mg/kg of DPA in soy bean oil by gavage once a week for 18 months (78 doses total). Animals were observed for 48 weeks after treatment was discontinued. In an English-language summary of the results, Holmberg et al. noted that lymphomas and alveolar adenomas were found in DPA-treated animals (8.3 and 16.5% incidence, respectively). Both tumor types

were also found in vehicle controls in approximately the same frequency as in treated animals (11.1% incidence for both tumor types). Although these negative findings indicate that DPA did not significantly affect tumor incidence, the discontinuous dosing protocol and less-than-lifetime duration of the experiment make this study inadequate for any critical evaluation of DPA's carcinogenicity.

Estimation of Intake Limits to Protect Public Health

Among the various toxicity studies discussed in the preceding paragraphs, only one (Thomas et al., 1967a) is adequate to estimate an acceptable daily intake (ADI) of DPA. Thomas et al. (1967a) began their long-term toxicity study of DPA with weanling albino rats. DPA was given in the feed at 0.001, 0.01, 0.10, 0.50, or 1.0 wt% beginning at approximately 10 days of age, and continuing for 734 days. Each of the five dosage groups contained 20 males and 20 females. An additional 20 animals of each sex were included as untreated controls. Detailed records of food consumption and body weight were maintained throughout the study. Statistical analysis of these data for day 240 indicated that ingestion of DPA at 0.5 and 1.0 wt% caused a statistically significant inhibition of growth among males ($p < 0.01$) as well as in females in the 0.1 wt% group. Daily food consumption of animals in the 0.5 and 1.0 wt% treatment groups were significantly lower ($p < 0.01$) than in other treated groups. The authors concluded that DPA affected growth indirectly, that is, as a consequence of inadequate caloric intake. Upon autopsy of animals at the end of treatment, Thomas et al. (1967a) documented a number of urinary tract lesions attributable to treatment with DPA. These included cystic dilation and inflammation of the renal tubules, and accumulation of proteinaceous fluid. In some animals, the renal pelvis and bladder displayed evidence of mild epithelial hyperplasia or squamous metaplasia. The severity of pathological changes of the kidney (chronic nephritis and tubular cysts) were scored qualitatively (ranked 1 to 4) for each animal. In animals of both sexes given 0.001 wt% DPA, the extent of chronic nephritis and tubular cyst formation was less than or equal to control values. Both sexes in the 0.01 wt% dose group had chronic nephritis that was less severe than controls; however, in males of this group, there was a slight increase in the mean severity of cyst formation. This increase was due to data from two additional

animals only, and is probably not statistically significant. No statistical analysis of data was performed, however. Animals from the 0.1, 0.5, and 1.0 wt % DPA groups had an apparent dose-related increase in the incidence and severity of nephritis and cyst development. Although we acknowledge that this treatment of data is subjective, it presents a picture of DPA-induced toxicity that is consistent with a number of other reports (see Renal Effects). Therefore, these results identify a chronic no-observed-adverse-effect-level (NOAEL) for dietary administration of DPA to rats of 0.01 wt%.

To convert the dietary intake of DPA to an equivalent value in mg/kg, we used the data provided by Thomas et al. (1967a) on average daily consumption of feed, and on the average body weight of males and females (both parameters were tabulated by dosage group). Male rats given 0.01 wt% DPA consumed an average of 11.68 g/d of food, and females, 9.57 g/d. This corresponds to 1.168 mg/d of DPA for males and 0.957 mg/d of DPA for females. The average body weight of these animals was 0.33 kg and 0.21 kg, respectively. Dividing the daily consumption of DPA (mg) by the body weight (kg) gives a NOAEL of 4.6 mg/kg-d (females) and 3.5 mg/kg-d (males). An acceptable daily intake can be calculated by dividing the animal NOAEL by a safety factor (SF). Generally, when a NOAEL is identified from a well-conducted, long-term study, a SF of 10 is applied to account for interspecies variability, and an additional SF of 10 is used to adjust for intraspecies variability (U.S.EPA 1980b, 1985). Applying these SFs to the NOAELs listed above gives a range for an ADI between 0.035 to 0.046 mg/kg-d. We note that this value is extremely close to the recommended maximum acceptable daily intake of 0.02 mg/kg-d established by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (1977).

TOXIC EFFECTS TO AQUATIC SPECIES

Hartley (1976) (reviewed by Berkowitz et al., 1978) completed acute toxicity tests using bluegill sunfish and an invertebrate (Clyclocyprid sp.). The 96-h LC50 for the bluegill sunfish was 1.18 mg/L and for the invertebrate species the 48-h LC50 was 2.53 mg/L.

9. DATA-BASE ASSESSMENT FOR ETHYL CENTRALITE

Ethyl centralite (EC) dissolves, gelatinizes, and stabilizes nitrocellulose and TNG. When the amount of EC is approximately 1 wt% of the composition, it acts as a stabilizer for propellants. In concentrations of 3 to 10 wt%, it gelatinizes nitrocellulose and sometimes reduces flash (Fedoroff and Sheffield, 1962).

ENVIRONMENTAL PARTITIONING AND TRANSPORT

Chemical identifiers for EC are found in Table 9-1, and Table 9-2 contains information on relevant chemical and physical properties. The estimated partition coefficients for EC are presented in Table 9-3. Its log K_{OW} (see Appendix A) is high (>4), and consequently it should tend to be adsorbed to organic material in sediments and soils. In addition, its fish bioconcentration factor should be relatively high (estimated to be over 1000).

ENVIRONMENTAL TRANSFORMATION PROCESSES

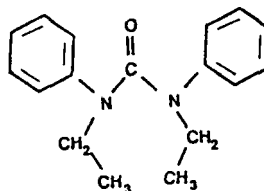
The environmental fate of EC has not been investigated. However, because the degradation pathways for EC are probably similar to those of other substituted urea compounds, we will use data on their degradation in the environment to assess the fate of EC. Propellants subject to demilitarization are likely to have EC present in them as well as products formed by the reactions of EC with nitrogen oxides (see Fig. 2-1). The environmental fate of the degradation products of EC are therefore at least as important as those of EC itself.

Photolysis

The light absorption maxima for EC are at wavelengths near 250 and 203 nm (Wentzel et al., 1979). We therefore do not expect direct photolytic degradation of EC to occur because only a small portion of the natural sunlight spectrum falls in this range. But, because EC is expected to complex with humic substances, it may be degraded photolytically as the humic materials absorb light and subsequently transfer energy to the EC. Evidence

Table 9-1. Chemical identifiers of EC.

Empirical formula:	C ₁₇ H ₂₀ N ₂ O	Structural formula:	
Molecular weight:	268.35		
CAS reg. no.:	[85-98-3]		
RTECS no.:	FE0350000		



for the photosensitization of EC by humic acids comes from dye sensitization photoreactions with carbanilide, a possible surrogate for EC. In an experiment by Dubey (1985), carbanilide was found to undergo photorearrangement to the aryl formamide in the course of the dye-sensitized photooxidation of sym-diphenylthiourea, as show in Fig. 9-1.

Biotransformation

No information is available on the biotransformation of EC. However, there is some information on the herbicide, Fenuron (N,N-dimethyl-N'-phenylurea, shown in Fig. 9-2), a reasonable surrogate for EC. Attaway et al. (1982) studied the anaerobic degradation of Fenuron by pond sediment microorganisms. They found no degradation products after 41 d of incubation at 30°C. However, unexplained losses of Fenuron from the active media were noted (they did not compare the losses from the active cultures to those of controls). Attaway et al. suggested that Fenuron was either adsorbed and complexed to sediments or that degradation products were not detected by their methods. In other work, Talakin and Voloshina (1986) found that the application of Fenuron at "high concentrations" reduced the number of microorganisms in soil. They found that nitrifying organisms were relatively insensitive to Fenuron. Lechner et al. (1982) isolated a bacterium that was capable of hydrolyzing the amide bond of some phenyl ureas, but not of Fenuron. Likewise Minney et al. (1985) found that an estuarine microbial

Table 9-2. Chemical and physical properties of EC. Properties are for an ambient temperature of 20°C unless otherwise noted.

Property	Units	Value	Source
Boiling point	°C	325-330	Fedoroff and Sheffield, 1962
Freezing/Melting point	°C	72.4 (sublimes)	Fedoroff and Sheffield, 1962
Density at (25°C)	g/mL	1.14	Fedoroff and Sheffield, 1962
Vapor pressure	torr	1.3×10^{-4}	Estimated ^a
Aqueous solubility	mol/L mg/L	3×10^{-4} 80	Fedoroff and Sheffield, 1962
Henry's law constant	(L-torr)/mol	0.4	Calculated as the ratio of vapor pressure to aqueous solubility
Diffusion coefficients:	Air Water	m^2/s m^2/s	Estimated ^a Estimated ^a
Log octanol/water partition coefficient (K_{ow})	log K_{ow}	4.5	Estimated ^a

^a See Appendix A.

Table 9-3. Partition coefficients for use in estimating human exposures to EC.

Partition coefficient	Parameter	Units	Value	Source
Plant/soil	K_{sp}	(mg/kg plant) ^a /(mg/kg soil)	1	Calculated ^b from molecular weight
Beef-fat/diet	K_{fd}	(ppm in fat)/(ppm diet)	0.03	Calculated ^b from water solubility and log K_{ow}
Fish/water	K_{fw}	(mg/kg fish) ^a /(mg/kg water)	1400	Calculated ^b from log K_{ow}
SOC/water	K_{oc}	(mg/kg SOC)/(mg/kg water)	1000	Calculated ^b from solubility in water and melting point

^a Wet-weights for plant and fish

^b See Appendix A

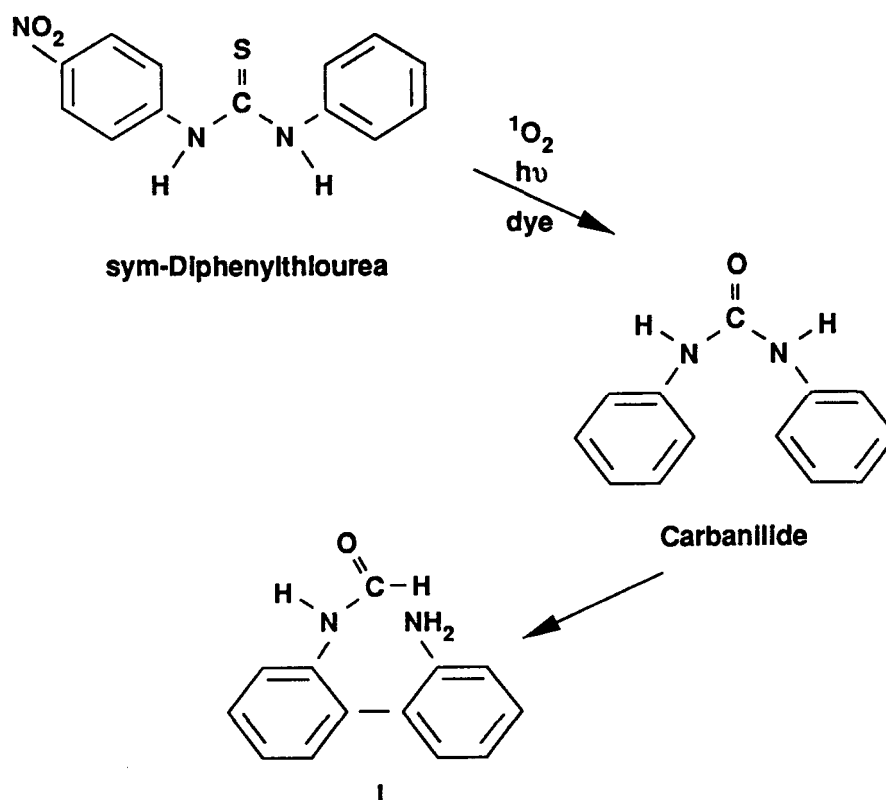
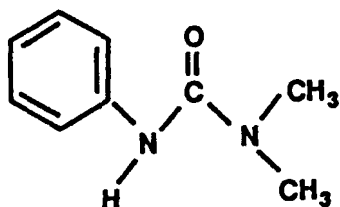


Figure 9-1. Dye-sensitized photorearrangement of sym-diphenyl urea (adapted from Dubey, 1985).

community did not degrade Fenuron. Based on the assumption that Fenuron is an adequate surrogate, the existing studies suggest that EC will not readily undergo biotransformation.

Binding to Humic Substances

Although the binding of EC to humic acids has not been studied, the binding of the surrogate compound, Fenuron has been investigated. Senesi and Testini (1984) studied the possible binding between herbicides and humic acids in an attempt to better understand the action of the herbicides on chloroplasts. They found that the free radical content of complexes of two humic acids with Fenuron were approximately double that of the humic acids



Fenuron

Figure 9-2. Structure of Fenuron, N,N-diethyl-N'-phenylurea.

alone. However, the free radical content of a third humic acid only showed a slight increase when complexed with Fenuron.

Attaway et al. (1982) suggested that the loss of extractable Fenuron from their anaerobic microbial degradation experiments was probably the result of adsorption or complexing with sediment. Motuzinskii et al. (1982) found that it took more than a year for Fenuron to disappear from soils after application. They also reported that Fenuron leached to the ground water.

In addition to binding with humic acids by chemical reactions, EC may adsorb to humic acids. This adsorption is directly related to the octanol/water and soil/water partition coefficients. EC has more lipophilic substituents than Fenuron and is therefore expected to have a higher octanol/water partition coefficient. This implies that EC will be more strongly adsorbed to humic materials than Fenuron.

Hydrolysis

Wentzel et al. (1979), citing the work of Roy (1968), noted that the hydrolysis of EC did not occur under basic conditions and occurred only with difficulty under acidic ones. Hydrolysis required heating EC in 60% sulfuric acid for 3 h at 160°C. This result is somewhat surprising because hydrolysis of EC is part of the mechanism proposed for the scavenging of nitrous acid produced by the decomposition of nitrocellulose and TNG (see Impurities section, Fig. 2-1). If hydrolysis of EC in water proceeds in the same fashion as it does in the stabilization of propellants, we expect the slow hydrolysis to ethylaniline and carbon dioxide in natural waters.

TOXIC EFFECTS ON ANIMALS AND HUMANS

Acute and subchronic exposures to EC can cause skin and eye irritation as well as hematological effects.

Toxicokinetics

No studies have directly addressed the uptake, distribution, metabolism, and excretion of EC.

Effects on Organs and Systems

Dermal effects. Weeks and McCreesh (1977) conducted a skin irritation experiment using New Zealand white rabbits. A single 0.5-g dose of dry EC was applied to either the intact or abraded skin of six rabbits in each treatment group. No primary irritation of intact or abraded skin was observed at 24 and 72 h after the initial application. When 0.5 g of EC (in acetone) was applied to both types of skin, the rabbits suffered from mild irritation in both treatment groups at 25 and 72 h, but recovered in 7 d. In another experiment conducted by Weeks and McCreesh, EC was administered in a sensitization test using Hartley guinea pigs. The test protocol consisted of the administration of EC, followed by a known sensitizer, dinitrochlorobenzene. EC was administered to 10 guinea pigs by intradermal injection. The sensitizer was administered in the same manner as EC and at the same dose, but did not elicit a sensitization reaction. Weeks and McCreesh (1977) also noted in their report that occupational exposures to EC have caused skin irritation, but did not provide any supporting references.

Hematological effects. Korolev et al. (1976), cited by Wentzel et al. (1979), fed an unspecified number of rats 22, 110, and 550 mg/kg of EC for 25 d. These doses corresponded to 1/125, 1/25, and 1/5 of a previously determined oral LD50 of 2750 mg/kg. Parameters measured in the experimental animals included erythrocyte, leukocyte, and reticulocyte counts; amount of hemoglobin and methemoglobin; cholinesterase, aldolase, and peroxidase activity; composition of blood protein fractions and color intensity of the urine. No animals died during the exposure period. The treated rats were

sacrificed at the end of 25 days and the internal organs were weighed and liver cholinesterase activity was measured. At the highest dose, 550 mg/kg, statistically significant ($p < 0.05$ to 0.01 level) changes in several parameters were observed (no details were given of which parameters). A change in the number of erythrocytes and in peroxidase activity was observed (no details) at the 110 mg/kg level. Korolev et al. considered the 110 mg/kg dose of EC to be the threshold dose. Wentzel et al. commented that the Korolev et al. study lacked many experimental details, and therefore the validity of the results was highly suspect.

A chronic study was also conducted by Korolev et al. (1976). The review by Wentzel et al. (1979) indicated that white rats were fed a diet of 0.05, 0.5, and 5 mg/kg body weight of EC (no duration or frequency of administration was provided). The same parameters in the subacute study were measured in this study, plus the following parameters: conditioned reflex activity, ceruloplasmin, beta-lipoprotein in the blood serum during fat metabolism, sulfhydryl groups, transaminase and phosphatase activity, and liver excretory function. No changes were noted at the two lower dose levels, 0.05 and 0.5 mg/kg. However, statistically significant changes (no p -value given) in the conditioned-reflex activity, liver excretory function, peroxidase activity, and ceruloplasmin and sulfhydryl groups in the blood were observed in rats receiving 5-mg/kg dose. Wentzel et al. commented that even though Korolev et al. monitored a large number of parameters in this study, the lack of information on specific protocols in the experiment makes it difficult to evaluate the results.

Ocular effects. In the study by Weeks and McCreesh (1977), no corneal opacity was observed in New Zealand rabbits after a single 24-h application of 0.1 g of dry (technical-grade) EC, which was applied to one eye of each rabbit. Five out of six rabbits had conjunctival redness, chemosis, and discharge and then recovered in 3 days.

Reproductive effects. There have been no experimental studies conducted directly on the reproductive effects of EC. However, Korolev et al. (1976), while conducting the subacute and chronic studies mentioned above, also observed gonadotropic effects. No signs of any gonadotropic effects (functional state of the spermatozoa, the morphology of the seminal canal

epithelium, the number of chromosomes showing reorganization in the anaphase, and the absolute number of fragmented types being recombined) were found at 5 mg/kg of EC. Wentzel et al. again criticized this work because of the lack of experimental details.

Genotoxicity

McGregor (1980) tested EC and 14 other compounds in these in vitro test systems: mitotic recombination, Escherichia coli, Salmonella typhimurium, and Saccharomyces cerevisiae. However, details of the test conditions were not discussed in this article because EC was negative in the four assays. Consistent with the work of McGregor, Weeks and McCreesh (1977) reported negative genotoxicity of EC in Saccharomyces cerevisiae strain D4, a reverse mutation/gene conversion assay, and the Salmonella (strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538) reversion mutation assay. EC was tested at dose levels of 0.5, 5, 50, and 250 µg/plate, with and without metabolic activation (S9 from rats pretreated with Aroclor). Both microbial assays showed no genotoxic activity of EC.

Carcinogenicity

There are no data currently available on the carcinogenicity of EC.

Estimation of Intake Limits to Protect Human Health

Without a clearly defined NOEL from a chronic toxicity study, it is not possible to estimate a safe intake for EC. We have therefore estimated a provisional ADI from an oral LD50 following the methodology of Layton et al. (1987b). Weeks and McCreesh (1977) reported an LD50 of 2560 mg/kg for rats that had been administered EC orally. With an application factor of $1 \times 10^{-5} \text{ d}^{-1}$, the lower-bound ADI would be 0.026 mg/kg-d. This intake has a high probability (~ 95%) of being below the true value.

TOXIC EFFECTS TO AQUATIC SPECIES

Little work has been completed on the aquatic toxicity of EC. Wentzel et al. (1979) reviewed two studies; one conducted by MacPhee and Ruelle (1969) and the other by Applegate et al. (1957). Those studies showed that EC was acutely toxic at levels of 10 ppm and rapidly stressed fish at levels of 5 ppm (exposure duration not given). A no-effect concentration was not defined in those studies.

10. HEALTH AND ENVIRONMENTAL DATA AVAILABLE ON PROPELLANTS AND ASSOCIATED CO-CONTAMINANTS

Of the seven compounds we examined, NSGu and EC had the least amount of data available to support assessments of their potential health and environmental effects. There were no data on the toxic effects of NSGu and only an oral LD50 (rat) was available for EC. We were unable to estimate the vapor pressure or log K_{ow} for NSGu, making it difficult to determine how it will behave in environmental media. Whether NSGu truly represents a hazard following demilitarization operations remains to be proved, as there are few data on its occurrence in soils or waters at OB/OD sites. More work is needed to focus on measurements of this NGu degradation product at locations where propellants have been destroyed.

Although the available information on the environmental fate of EC is limited, the primary issue associated with this propellant stabilizer is the extent to which it reacts over time with NO in propellants. If it is completely consumed in such reactions, then it does not directly pose an environmental problem, but its reaction by-products might. Therefore, we recommend that samples of new and aged propellants be analyzed to determine the composition of stabilization products. In a similar fashion, the stabilizer DPA will also be converted in propellants, and consequently, its hazard may be minimal. The occurrence of DPA stabilization products (e.g., dinitrodiphenylamine) in propellants should be studied as well. Until such additional data are available, the existing information on DPA's toxicity and environmental properties is probably adequate.

The two propellant plasticizers reviewed have a considerable amount of information available on their toxic effects and environmental properties. Our review indicates that the health and environmental effects data base on DBP and DEP is adequate at this time. However, additional toxicity studies may eventually be needed to define a chronic NOAEL in laboratory animals for DEP. The chronic study that the U.S. EPA (1980a) based their acceptable intake on contains a NOAEL that is higher than one derived from a subchronic test.

The other two compounds we addressed, NGu and TNG, are important components of multi-base propellant formulations. TNG has been extensively

studied, and only selected topics should be considered for future work. In this regard, we believe that future research should focus on its potential carcinogenicity to humans. One potentially useful effort would be a retrospective epidemiologic study to examine whether there is a significant relationship between doses of TNG administered chronically to angina patients and the age-adjusted cancer incidence among that cohort. Nitroguanidine has only recently been the subject of special studies involving its environmental properties and toxicity. Existing acute and subchronic toxicity studies with laboratory animals show that it is not very toxic. Moreover, its genotoxic potential is low. Even though chronic toxicity studies have not been conducted on NGu, there is no evidence for widespread contamination of NGu at OB/OD grounds, and therefore the benefit of conducting such toxicity studies must be weighed against the magnitude of potential exposures.

Generic deficiencies in the data bases of all the compounds considered were the absence of data on plant uptake of the contaminants and their partitioning between feed and fat of cattle. Plant uptake studies are not routinely carried out for environmental contaminants, and this is unfortunate because the consumption of fruits and vegetables grown on contaminated sites does represent a possible exposure pathway. We recommend that plant uptake studies be conducted on each of the compounds and that work also focus on methods for predicting uptake. The bioconcentration of the compounds in beef fat was estimated using a regression equation that was based on only a limited number of compounds. Again, the options are either to complete compound-specific studies on the seven propellants and co-contaminants or to develop improved methods of estimating the biouptake of the contaminants in cattle. Finally, most of the data on the aquatic toxicity of the compounds were 96-h LC50 levels, with little data on chronic toxicity. However, OB/OD operations do not normally result in direct contamination of surface waters, thus the need for detailed data on the aquatic toxicity of the compounds considered here seems minimal.

APPENDIX A

CHEMICAL/PHYSICAL PROPERTIES AND ENVIRONMENTAL PARTITION COEFFICIENTS: CALCULATIONS AND SUPPORTING DATA

In this Appendix we present estimates of the chemical properties and environmental partition coefficients that are needed to predict the transport of propellants and their co-contaminants in the environment and to predict food-chain transfers to man. The chemical and physical properties considered include vapor pressure, octanol/water partition coefficient, aqueous solubility, Henry's law constant, and molecular-diffusion coefficients in air and in water. Vapor pressure and aqueous solubility are estimated at a reference temperature of 20°C; estimates are based on extrapolations or interpolations of these parameters at various temperatures, as well as on predictions derived from other chemical properties. Partition coefficients for the individual compounds include soil/water (K_d), soil or sediment organic carbon (SOC)/water (K_{oc}), plant/soil (K_{sp}), fish/water (K_{fw}), and beef-fat/diet (K_{fd}). Estimates of these parameters are based on regression equations relating various properties (e.g., water solubility, octanol/water partition coefficient, or molecular weight) to the partition coefficient of interest.

VAPOR PRESSURE

The vapor pressure of a solid or liquid chemical is the pressure of the gas phase that is in equilibrium with the solid or liquid phase at any given temperature. The evaporative escape, or volatilization, of a chemical depends on the vapor pressure of the compound, as well as the environmental conditions that influence diffusion from the solid or liquid surface. Combined with aqueous solubilities at the same temperature, vapor-pressure data permit the calculation of Henry's law constants that can be used along with the diffusion coefficient of a compound in water to determine the volatilization rate of organic chemicals dissolved in water. Organic chemicals with relatively low vapor pressure, high aqueous solubility, or high adsorptivity to solids are less likely to vaporize and become airborne than compounds with high vapor pressure, low solubility in water, or low adsorption to solids and sediments.

Most of the equations and correlations in the literature for estimating vapor pressure are designed for accuracy between the normal boiling point (T_b) and the critical temperature (T_c), a range of primary interest in process engineering. However, environmental studies usually involve temperatures below the boiling point, where the above-mentioned estimation methods are less accurate. Hence, there is a need for reliable vapor-pressure estimates for a wide variety of explosive and propellant compounds, preferably at 20°C. There is a particular need for a method of estimating very low vapor pressures (i.e., $\ll 1$ torr), where it is very difficult to determine accurate pressure values experimentally.

Vapor-Pressure Equations

Many equations have been proposed that relate the pressure and temperature of the gas phase in equilibrium with the condensed phase. Good correlation with the experimental values is obtained with the Antoine equation:

$$\log P_v = A - \frac{B}{t + C} \quad (A-1)$$

A simpler equation is frequently suitable over limited temperature ranges:

$$\log P_v = A - \frac{B}{T} \quad (A-2)$$

In these equations, the P_v term is the vapor pressure of the compound in torr (mm Hg), t is the temperature in °C, T is the absolute temperature in K, and A , B , and C are empirical constants that are unique for each chemical compound (see, for example, Lange's Handbook of Chemistry (Dean, 1985), 13th ed., pp. 1028-1053, for a tabulation of these constants, based on least-square fits of experimental data, and applicable temperature ranges of several hundred organic compounds). In Table A-1 we provide a summary of P_v - T equations for the propellants and co-contaminants from various literature sources.

A second technique, which is equivalent to graphical extrapolation of the data, involves the insertion of a selected temperature (i.e., 20°C) in an Antoine equation even though the equation is valid for a different temperature range, and calculation of the corresponding vapor pressure. Again, it should be noted that the resultant estimated value of vapor pressure will be less

Table A-1. Vapor-pressure/temperature equations for selected military propellants and co-contaminants.

Propellant or co-contaminant	Equation ^a	Temperature range (°C)	Ref.
TNG	$\log P_v = 17.27 - \frac{8453.4}{t + 385}$	20 to 60	Jordan, 1954
DBP	$\log P_v = 6.6398 - \frac{1744.2}{t + 113.69}$	126 to 202	Dean, 1985
DPA	$\log P_v = 8.6755 - \frac{3242.9}{t + 265.5}$	108 to 200	Jordan, 1954
NGu	$\log P_v = 16.27 - 7452/T$	129.2 to 199.8	Cundall et al., 1981

^a In the equations for TNG, DBP, and DPA, P_v represents vapor pressure in torr, and t , temperature in °C. For NGu, P_v is in Pascals and temperature, T , is Kelvin.

reliable the greater the discrepancy between 20°C and the applicable temperature range. Table A-2 contains measured vapor-pressure data for propellants and co-contaminants.

Vapor-Pressure Estimation with Limited Data

The literature did not contain the data needed to derive Antoine-type equations for EC thus Eq. A-3 developed by Mackay et al. (1982) was used:

$$\ln P = -(4.4 + \ln T_b)[1.803(T_b/t - 1) - 0.803 \ln(T_b/T)] - 6.8(T_m/T - 1) \quad (A-3)$$

where P = vapor pressure (atm), T_b = normal boiling point (K), T = temperature (K) corresponding to estimated pressure, and T_m = melting point (K).

Table A-2. Measured vapor pressures for selected propellants and co-contaminants.

Propellant or co-contaminant	Measured values		Ref.
	Vapor pressure (torr)	Temperature (°C)	
TNG	0.00025	20	Jordan, 1954
	0.00083	30	
	0.0024	40	
	0.0073	50	
	0.0188	60	
	0.043	70	
	0.098	80	
	0.23 (some decomp.)	90	
DBP	0.000073	25	Howard et al., 1985
	0.0002	40	
	0.0018	60	
	0.014	80	Hoyer and Peperle, 1958
	0.1	89	
	0.4	98.8	
	0.8	111.3	
	1.0	132	
	1.5	153.5	
	2.1	162.9	
	2.8	168	
	4.1	176.3	
DEP	0.000002	-20	Hoyer and Peperle, 1958
	0.000009	-10	
	0.00004	0	
	0.00017	10	
	0.0006	20	
	0.002	30	
	0.006	40	
	0.00165	25	
			Howard et al., 1985
DPA	1.0	108.3	Jordan, 1954
	5	141.7	
	10	157.0	
	17	170.0	
	20	175.2	
	25.4	180.0	
	40	194.3	
	51.2	200.0	
	60	206.9	
	100	222.8	

Table A-2. (continued)

Propellant or co-contaminant	Measured values		Ref.
	Vapor pressure (torr)	Temperature (°C)	
DPA	200	247.5	Vriens and Hill, 1952
	400	274.1	
	760	302.0	
	840	310.0	
	0.0027	25.0	

For EC, the published temperature values are $T_b = 326\text{--}330^\circ\text{C}$ (Meyer, 1981) and $T_m = 79^\circ\text{C}$ (Windholz et al., 1983). Thus the vapor pressure of this compound at 20°C can be calculated as follows:

$$\ln P_v = -(4.4 + \ln 601) \left[1.803 \left(\frac{601}{293} - 1 \right) - 0.803 \ln \left(\frac{601}{293} \right) \right] - 6.8 \left(\frac{353}{293} - 1 \right) \quad (\text{A-4})$$

$$= -15.606$$

$$P_v = 1.67 \times 10^{-7} \text{ atm} = 1.3 \times 10^{-4} \text{ torr.}$$

There was no boiling point data available for NGu. We obtained an estimate of the vapor pressure at 20°C by using the equation in Table A-1, which is for the temperature range 129.2 to 199.8°C :

$$\log P_v (\text{Nm}^{-2}) = 16.27 - 7452/293$$

$$= -9.16$$

$$\log P (\text{Torr}) = -11.27$$

$$= 6.9 \times 10^{-10}$$

or

$$P_v (\text{torr}) \cong 5 \times 10^{-12}.$$

Vapor Pressures for Propellants and Co-contaminants

Although Tables A-1 and A-2 provide vapor-pressure/temperature equations and measured vapor-pressure data for the contaminants of concern over a wide range of temperature, the primary interest in this report is in pressures at

20°C. In Table A-3, P_V values at 20°C are summarized for the propellants or co-contaminants under consideration, and the source or estimation method used in each case is identified.

ESTIMATION METHODS FOR K_{OW}

The only compounds for which we were unable to obtain a measured K_{OW} value were ethyl centralite and nitrosoguanidine (see Table A-4). We estimated the K_{OW} values for these compounds using alternative methods based on fragment constants, retention time on reverse phase HPLC, or from regression equations with other parameters (e.g., solubility in water) (see Lyman et al. (1982) for a more detailed discussion of alternative estimation techniques).

Estimation of Log K_{OW} Values for Ethyl Centralite and NSGu

For most compounds the fragment constant method or π calculations of Hansch and Leo (1979) yield the most accurate log K_{OW} estimates. Unfortunately, such calculations require an "isolating carbon atom" that is not present in the two compounds for which we need to estimate log K_{OW} . The π value calculations are influenced by resonance and steric interactions and yield a wide range of log K_{OW} values when different ureas are used as the starting points and to which the appropriate π values for substituent groups are added.

The linear relationship between the logarithm of reverse-phase HPLC retention time and log K_{OW} can be used to calculate unknown log K_{OW} 's for compounds chromatographed with compounds with known log K_{OW} and similar functional groups. The same type of relationship with solubility should give the same values for log K_{OW} except that the solubilities of many of the propellants and stabilizers are not well established. Therefore, because the retention times on HPLC are well defined for ethyl centralite and NSGu and the log K_{OW} 's of the other compounds chromatographed were measured, we favor log K_{OW} estimates for these two compounds based on retention times on reverse phase HPLC.

Table A-3. Summary of vapor-pressure data at 20°C for selected military propellants and their co-contaminants.

Propellant or co-contaminant	Vapor Pressure (torr)	Reference
TNG	2.5×10^{-4}	Jordan, 1954
NGu	$\cong 5 \times 10^{-12}$	Estimated from equation in Cundall et al., 1981 (see text)
NSGu	Not available	
DBP	7.3×10^{-5a}	Howard et al., 1985
DEP	1.6×10^{-3a}	Howard et al., 1985
DPA	2.7×10^{-3a}	Vriens and Hill, 1952
Ethyl centralite	1.3×10^{-4}	Calculated from equation of Mackay et al., 1982

^a Measured at 25°C

Table A-4. Summary of log K_{ow} values for selected military propellants.

Compound	log K_{ow}	Method	Reference
TNG	1.62	Measurement	Roberts et al. (1983)
NGu	-0.83	Measurement	Spanggord et al. (1985)
NSGu	less than -0.83	Estimation ^a HPLC	
DBP	4.79	Measurement	Howard et al. (1985)
DEP	2.24	Measurement	Howard et al. (1985)
DPA	3.50	Measurement	Hansch and Leo (1979)
Ethyl centralite	4.5	Estimation ^a HPLC	

^a See calculation in this appendix.

Ethyl centralite. Wentzel et al. (1979) estimated the $\log K_{OW}$ for ethyl centralite by the π constant method of Leo et al. (1971). By using two different reference compounds, they estimated $\log K_{OW}$ values of 4.37 and 5.22. The large range in these $\log K_{OW}$ estimates results from the use of π values derived from substituted amines to calculate $\log K_{OW}$ for compounds with a carbonyl adjacent to the groups being substituted. This can lead to error because of resonance and steric interactions (Hansch and Leo, 1979).

$\log K_{OW}$ has been shown to be proportional to the retention volume of the compounds on reverse phase HPLC (Doucette and Andren, 1988; Garst and Wilson, 1984). The retention volume is approximately proportional to retention time of the compound minus the retention time of the mobile phase (Garst and Wilson, 1984). We used two reverse phase HPLC chromatograms containing ethyl centralite, propellants, and stabilizers (Sjobom and Oresten, 1980; Ryder and Knowlton, 1983) to derive a regression equation for $\log K_{OW}$ vs $\log$ retention time. The Sjobom and Oresten (1980) chromatogram contained four compounds with known $\log K_{OW}$ values obtained from Table A-4 and Hansch and Leo (1979). From these $\log K_{OW}$'s and retention times (RT) we derived the regression equation: $\log K_{OW} = 5.83 \log RT - 2.70$, $r^2 = 0.99$. Our $\log K_{OW}$ estimate for ethyl centralite from this regression equation is 4.64.

We also used the regression equations of Chiou et al. (1977) and Mackay et al. (1980) to predict ethyl centralite's $\log K_{OW}$ from its aqueous solubility. The $\log K_{OW}$ value calculated from the Chiou et al. formula^a is 3.3 and that calculated from the formula of Mackay et al.^b, which includes a melting point correction, is 3.05. These equations were not based on compounds similar to ethyl centralite, however.

We considered the $\log K_{OW}$ estimated from HPLC to be the most reliable and selected a value of 4.5 as the best estimate for the $\log K_{OW}$ of ethyl centralite.

^a $\log K_{OW} = 5.0 - 0.67 \log S$; where S is aqueous solubility, $\mu\text{mol/L}$.

^b $\ln K_{OW} = 7.494 - \ln \text{Sol} + 6.79 \left(1 - \frac{T_m}{T}\right)$; where Sol is mole fraction solubility, T is ambient temperature in K; and T_m is melting point in K.

Nitrosoguanidine. Estimation of the $\log K_{OW}$ of NSGu is more difficult. Again, the sole carbon atom in the molecule is "non-isolating" so calculations from substituent values are not possible. The π constants are not derived for N-substituted nitro and nitroso groups. The solubility equations were derived from compounds of very different chemical nature and therefore also would not be reliable for computing $\log K_{OW}$.

The calculation from reverse-phase HPLC retention time is probably the best method for estimating the $\log K_{OW}$ of NSGu and should be pursued. At this time, several reverse-phase HPLC spectra are available in the literature. All of these show NSGu to have a shorter retention time than nitroguanidine (NGu) (Kaplan and Kaplan, 1985; Burrows et al., 1984a,b). Therefore, the $\log K_{OW}$ of NSGu should be lower than the -0.83 value measured for NGu (Spanggord et al., 1985). Unfortunately, only the chromatograms of Burrows et al. (1984a,b) included additional compounds besides NGu and NSGu, and none had a measured $\log K_{OW}$. Though it was not possible to calculate the $\log K_{OW}$ from the reverse-phase HPLC retention time, from the HPLC data it is clear that the $\log K_{OW}$ of NSGu will be less than the $\log K_{OW}$ of NGu, that is, less than -0.83.

WATER SOLUBILITY

The aqueous solubility of a chemical compound is an important parameter in predicting its environmental transport and distribution. The aqueous solubility of a chemical can be defined as the maximum amount of that chemical that will dissolve in pure water at a specific temperature. For consistency in the calculation or estimation of vapor pressures, solubilities, and Henry's law constants, we have expressed solubilities in moles/L and mg/L at 20°C, unless vapor pressure and solubility were measured at 25°C. In general, chemicals that are highly soluble in water are distributed more easily and rapidly in surface and ground waters than are chemicals of low solubility. Very soluble compounds tend to have relatively low adsorption coefficients for soils and sediments, as well as comparatively low bioconcentration factors in aquatic life. They are also more susceptible to biodegradation by microorganisms in soils and surface waters. Water solubility can also affect transformation by hydrolysis, photolysis, oxidation, and reduction in water. Experimental values were available for the aqueous solubilities of all the propellants and associated co-contaminants. Table A-5 summarizes the aqueous solubilities of the compounds of interest.

Table A-5. Summary of aqueous solubilities of selected military propellants at 20°C unless noted otherwise.

Compound	Aqueous solubility		Ref.
	mol/L	mg/L	
TNG	7.9E-03	1800	Dean (1985)
NGu	2.6E-02	2660	Urbanski (1965)
	2.5E-02	2600 ^a	Spanggord et al. (1985)
NSGu	2.0E-02	1760	Richter (1961)
DBP	3.63E-05	10.1	Leyder and Boulanger (1983)
	4.02E-05	11.2 ^a	Howard et al. (1985)
DEP	4.18E-03	928	Leyder and Boulanger (1983)
	4.86E-03	1080 ^a	Howard et al. (1985)
DPA	3.27E-04	55.4	Takano et al. (1982)
Ethyl centralite	3 E-04	80	Fedoroff and Sheffield (1962)

^a Measured at 25°C

DIFFUSION COEFFICIENTS OF CHEMICALS IN AIR AND WATER

The diffusion coefficient of a compound in air is used in GEOTOX to estimate the flux of a compound from soil to the atmosphere, and the diffusion coefficient of a compound in water is used to estimate the flux from sediments to water. Methods for estimating the diffusion coefficients of chemical compounds in air have been reviewed by Tucker and Nelken (1982). One method they suggest is both simple and accurate for nonpolar species at low to moderate temperatures. The method is based on the following correlation:

$$D_G = \frac{10^{-7} T^{1.75} M_r^{0.5}}{P \left[V_A^{1/3} + V_B^{1/3} \right]^2} \quad (A-5)$$

where

D_G = diffusion coefficient of species B in air, m^2/s ;

T = temperature, K;

M_r = $(M_A + M_B)/M_A M_B$ in which M_A and M_B are respectively, the molecular weights of air and species B;

P = pressure, atm;

V_A = molar volume of air, $cm^3/mole$; and

V_B = molar volume (gas) of species B, $cm^3/mole$.

The method recommended by Tucker and Nelken (1982) for estimating the diffusion coefficient of a compound in water is

$$D_L = \frac{13.26 \times 10^{-9}}{(\eta_w) 1.14 (V_B') 0.589} \quad (A-6)$$

where

D_L = diffusion coefficient of species B in water, m^2/s ;

η_w = viscosity of the water, cP; and

V_B' = Le Bas molar volume of species B, $cm^3/mole$ in water.

Table A-6 contains the estimates of D_G and D_L for the propellants and associated co-contaminants. Calculations were based on the following parameter values: $T = 293$ K; $V_A = 20.1$ cm^3/mol ; $M_A = 29$ g/mol; $P = 1$ atm; and $\eta_w = 1.0023$ cP.

COEFFICIENTS FOR EQUILIBRIUM DISTRIBUTIONS OF CHEMICALS BETWEEN SOIL/WATER (K_d) AND SOIL-ORGANIC-CARBON/WATER (K_{OC})

A key parameter in the analysis of the transport and fate of organic contaminants in surface soils (or sediments) is the equilibrium partitioning of those substances between soil and water. The distribution of a chemical between the solid and liquid phases in soil is described by the partition coefficient K_d that relates the amount of chemical sorbed to soil particles to the concentration in water, or

$$K_d = \frac{C_s}{C_w} = \frac{mg/kg(soil)}{mg/kg(water)} \quad (A-7)$$

Table A-6. Diffusion coefficients in air and water for propellants and co-contaminants.

Compound	Empirical formula	V_B Molar volume in air (cm ³ /mol)	V'_B LeBas molar volume (cm ³ /mol)	Coefficient for diffusion in air (m ² /s)	Coefficient for diffusion in water (m ² /s)
TNG	C ₃ H ₅ N ₃ O ₉	125.79	184.4	6.8 x 10 ⁻⁶	6.1 x 10 ⁻¹⁰
NGu	CH ₄ N ₄ O ₂	58.14	98.4	1.0 x 10 ⁻⁵	8.9 x 10 ⁻¹⁰
NSGu	CH ₄ N ₄ O	52.66	90.1	1.0 x 10 ⁻⁵	9.3 x 10 ⁻¹⁰
DBP	C ₁₆ H ₂₂ O ₄	309.48	332.8	4.5 x 10 ⁻⁶	4.3 x 10 ⁻¹⁰
DEP	C ₁₂ H ₁₄ O ₄	227.64	224.0	5.3 x 10 ⁻⁶	5.2 x 10 ⁻¹⁰
DPA	C ₁₂ H ₁₁ N	185.26	200.3	5.9 x 10 ⁻⁶	5.8 x 10 ⁻¹⁰
Ethyl centralite	C ₁₇ H ₂₀ N ₂ O	296.36	334.2	4.6 x 10 ⁻⁶	4.3 x 10 ⁻¹⁰

The actual value of K_d for a chemical in a soil matrix is a function of the properties of the chemical (e.g., hydrophobicity) and the host soil (e.g., organic-carbon content of the soil, pH of the soil, cation-exchange capacity, particle-size distribution, etc.). For discussions of these and other factors, see Lyman et al. (1982). Because of the inherent variability in the soil properties at different sites, the preferred approach for developing values of K_d for assessment of the transport of propellants and related compounds at OB/OD sites is to actually measure K_d for the compounds and soils of interest.

Different studies have shown that the organic carbon content of soils governs the equilibrium distribution of neutral organic compounds between soil water and soil solids. More precisely, the K_d of these types of organic compounds increases as the soil organic carbon (SOC) content increases (Karickhoff et al., 1979; Corwin and Farmer, 1984). From this relationship, K_d can be estimated as the product of the wt% SOC for a given soil (denoted by f_{oc}) and a partition coefficient that describes the partitioning of a chemical between organic carbon and soil water (i.e., K_{oc}). Expressed mathematically,

$$K_d = K_{oc} \times f_{oc}/100 \quad , \quad (A-8)$$

where

$$K_{oc} = \frac{\text{mg chemical/kg of SOC}}{\text{mg chemical/kg of soil water}}$$

and

$$f_{oc} = \text{wt\% SOC.}$$

There are a number of empirical relationships for estimating the K_{oc} of a chemical from its water solubility or log octanol/water partition coefficient, K_{ow} (see Lyman et al., 1982). We selected the following equation reported by Karickhoff (1985) for estimation of K_{oc} when there are no measured values:

$$\log K_{oc} = -0.83 \log SOL - 0.01(MP - 25) - 0.93 \quad , \quad (A-9)$$

where SOL is the mole fraction solubility, and MP is the melting point in °C. This regression equation was based on data for 47 organic compounds representing five chemical families. The r^2 value is 0.93. Table A-7 presents the estimated values of K_{OC} for the propellants and co-contaminants.

When the compound is a liquid, a better correlation would probably be obtained with water solubility alone. We recommend that the K_{OC} values for TNG and the phthalate esters be calculated from the formula of Briggs (1981):

$$\log K_{Om} = 0.9 - 0.52 \log S \quad (A-10)$$

where S is in mol/L. Briggs measured K_{Om} (partition coefficient based on the organic matter content of soil) instead of K_{OC} . To convert K_{Om} to K_{OC} , K_{Om} must be multiplied by 1.724. Briggs reported a measured value for the K_{Om} of DBP as 346, equivalent to a K_{OC} value of 597.

PLANT/SOIL PARTITION COEFFICIENT (K_{Sp})

The uptake of a soil contaminant by a food-chain crop can be estimated by a partition coefficient, K_{Sp} (or plant concentration factor), that is defined as

$$K_{Sp} = \frac{\text{Concentration of contaminant in crop (mg/g fresh wt)}}{\text{Concentration of contaminant in soil (mg/g dry wt)}} \quad (A-11)$$

Values of K_{Sp} are available for a relatively small number of organic compounds, primarily pesticides and herbicides that are used in agricultural applications. The plant concentration factor is a complex function of several dynamic processes. The availability of a soil contaminant for subsequent uptake, for example, depends largely on the binding or adsorption of the contaminant to the soil matrix and the rate of depletion from processes (e.g., leaching, biotransformation, volatilization, etc.) that lower the concentration of the organic contaminant in the root zone. Consequently, the bioavailability of a contaminant is controlled by its chemical/physical properties and the properties of the soil environment (e.g., organic-carbon content, particle size, etc.), and the climate at a specific site (e.g., OB/OD grounds). Plant uptake of contaminants occurs not only through the root system, but also through the deposition of vapors and particles on foliage.

Table A-7. Values of K_{OC} measured and calculated from Eqs. A-9 or A-10.

Propellant or co-contaminant	Solubility in water (moles/L)	Melting point, °C	Solubility, ^a (mole fraction)	$\log K_{OC}$ ^b	Measured $\log K_{OC}$
TNG	7.90E-03	13.2 (stable)	1.42E-04	2.2(A-10)	2.77 ^c
NGu	2.6E-02	245	4.61E-04	-0.23(A-9)	
NSGu	2.0E-02	161 (explodes)	3.60E-04	0.57(A-9)	
DBP	3.63E-05	-35	7.21E-07	3.4 (A-10)	3.14 ^d
DEP	4.18E-03	-40.5	8.83E-05	2.3(A-10)	1.8 ^d
DPA	1.8E-03	53 to 54	3.2E-05	2.5(A-9)	2.78 ^e
Ethyl centralite	3 E-04	72.4	5 E-06	3.0(A-9)	

^a At low concentrations, the solubility in mole fractions is equal to the ratio of moles of solute to the moles of water. A liter of water contains 55.5 moles.

^b Presented to two significant figures, applicable equation noted within parentheses. The K_{Om} values derived from Eq. A-10 have been converted to the equivalent K_{OC} value.

^c Spanggord et al., 1980b (average of 3 measured values).

^d Russell and McDuffie, 1986 (calculated from K_d and 1.59 wt% soil organic content).

^e K_{OC} calculated from K_{Om} reported in Briggs, 1981.

The concentration of a contaminant in a plant will change with time in response to differences in the rates of uptake and loss. Generally, the uptake rate is greatest during the early growth of a plant and subsequently slows as the plant matures (Casterline et al., 1985; Scheunert et al., 1985). Losses of a contaminant can occur through transpiration and metabolism. Because the concentrations of a contaminant in soil and plant vary with time, the values of K_{sp} also change. In fact, it can take most of the growing season before equilibrium is reached between plant and soil concentrations. Kloskowski et al. (1986) also have shown that the uptake of a soil contaminant is influenced by the "aging" of the contaminant; that is, plant uptake of a freshly added organic compound is different from uptake of a substance that has resided for a long period in soil.

Given the variability in the different chemical, soil, climate, and plant properties that affect the uptake of organic chemicals by plants, it is not surprising that little work has focused on the development of techniques for estimating plant uptake of organic chemicals. Topp et al. (1986), however, have examined some of the factors affecting the uptake of organic chemicals by plants and have derived a regression equation in which the K_{sp} for barley is calculated as a function of the molecular weight of an organic chemical, that is,

$$\log K_{sp} = 5.943 - 2.385 \log MW \quad , \quad (A-12)$$

where MW is the gram-molecular weight of an organic compound. This equation was based on measured uptake values for 14 different compounds, and the r^2 value is 0.89. These researchers examined other regression equations, using K_{oc} ($r^2 = 0.70$) and K_{ow} ($r^2 = 0.80$), but MW had the highest correlation coefficient. The uptake measurements, though, are for short-term (i.e., 7-d) uptake experiments, and therefore Eq. A-12 may not be generally applicable to the estimation of the uptake that occurs over the entire period of plant growth prior to harvest. Furthermore, the estimate of K_{sp} is for barley, and its applicability to other crops is unknown. Despite these limitations, the K_{sp} predicted from Eq. A-12 represents the best estimate we have found of plant uptake, and for the purposes of the data-base assessments, we have adopted these values as default K_{sp} values in lieu of measured data. In

Table A-8 we have listed the estimated uptake factors for all of the different compounds addressed here. These values are within the range of plant bioconcentration factors recommended by Small (1984) for different classes of organic chemicals.

BIOCONCENTRATION FACTORS FOR FISH (K_{fw})

The ratio between the concentration of an organic compound in fish (units of mg contaminant/kg fish weight) and the concentration of the contaminant in water (mg/kg) under steady-state conditions is commonly known as the bioconcentration factor, which is denoted as K_{fw} in our notation (the more common term is BCF, and we shall use it interchangeably with K_{fw}). The BCF for an organic chemical is a function of dynamic uptake and elimination processes in fish that are in contact with the chemical dissolved in water; see Bysshe (1982) and Spacie and Hamelink (1982) for details. As might be expected, this partition coefficient is positively correlated with the lipophilicity of a compound (as measured by its octanol/water partition coefficient, K_{ow}) and inversely correlated with its aqueous solubility.

Many regression equations have been published that predict bioconcentration as a function of K_{ow} . These equations are of the general form $\log K_{fw} = a \log K_{ow} + b$. A review of the literature on the predictive equations for K_{fw} by van Gestel et al. (1985) indicates that the most reliable equation is one developed by Veith and Kosian (1983), or

$$\log K_{fw} = 0.79 \log K_{ow} - 0.40 \quad . \quad (A-13)$$

Equation A-13 was based on bioconcentration data for 122 chemicals and has an r^2 of 0.86 ($r = 0.928$). This is an improvement over an earlier equation by Veith et al. (1980) for 84 compounds (i.e., $\log K_{fw} = 0.76 \log K_{ow} - 0.23$, with $r^2 = 0.82$).

In Table A-9 we have tabulated the values of K_{fw} for the compounds considered in this report.

Although regression equations like Eq. A-13 are valid for many organic compounds, some exceptions should be noted. First of all, organic compounds incorporated in sediments are also available for fish uptake -- a pathway that is not directly accounted for in this equation. Knezovich et al. (1987), in a

Table A-8. Estimated barley uptake factors (K_{sp}) for selected propellants and their co-contaminants. K_{sp} values predicted from Eq. A-12.

Explosive or co-contaminants	Gram-molecular weight	Predicted K_{sp} ^a
TNG	227.09	2
NGu	104.07	14
NSGu	88.09	20
DBP	278.35	1
DEP	222.24	2
DPA	169.23	4
Ethyl centralite	268.35	1

^a Values have been rounded off to the nearest integer.

Table A-9. Estimates of K_{fw} for military propellants and related co-contaminants. K_{fw} values predicted from $\log K_{fw} = 0.79 \log K_{ow} - 0.40$.

Propellant or co-contaminant	$\log K_{ow}$	$\log K_{fw}$	K_{fw}
TNG	1.62	0.88	7.6
NGu	-0.83	-1.06	0.088
NSGu	Not available		
DBP	4.79	3.38	2420
DEP	2.24	1.37	23.4
DPA	3.50	2.36	232.0
Ethyl centralite	4.5	3.1	1400

review of the literature on the bioavailability of organic compounds sorbed to sediments, have shown that the bioaccumulation of xenobiotic compounds from contaminated sediments can be important. Nevertheless, there are presently no methods for predicting bioaccumulation that directly account for the various uptake pathways (i.e., the water column, sediment, or even diet).

BEEF-FAT/DIET PARTITION COEFFICIENT (K_{fd})

Kenaga (1980) has developed regression equations relating the octanol/water partition coefficient and aqueous solubility of organic chemicals to their partitioning between the fat of cattle and their diet, defined by the beef-fat/diet partition coefficient, K_{fd} . Based on 28-d feeding studies for 23 organic chemicals (including eight chlorinated hydrocarbon insecticides and 15 miscellaneous chemicals), the resulting regression equations using K_{ow} and C_{so1} (in mg/L) were:

$$\log K_{fd} = 0.5 \log K_{ow} - 3.457, \quad (n = 23, r^2 = 0.62) \quad (A-14)$$

and

$$\log K_{fd} = -0.495 \log C_{so1} - 1.476. \quad (n = 23, r^2 = 0.67) \quad (A-15)$$

The values of K_{fd} for the propellants and co-contaminants are presented in Table A-10. For the purposes of the data-base assessments, we have taken the average of two K_{fd} values for each compound.

Table A-10. Estimates of the beef fat/diet partition coefficient, K_{fd} , for propellants and their co-contaminants using the two regression equations from Kenaga (1980).

Propellant or co-contaminant	K_{OW} -based estimates			C_{SO1} -based estimates ^a			Average ^b K_{fd}
	$\log K_{OW}$	$\log K_{fd}$	K_{fd}	$\log C_{SO1}$	$\log K_{fd}$	K_{fd}	
TNG	1.62	-2.65	0.0022	3.26	-3.09	0.00082	0.0015
NGu	-0.83	-3.87	0.00013	3.42	-3.17	0.00067	0.00040
NSGu	Not available			3.25	-3.08	0.00083	0.00083
DBP	4.79	-1.06	0.087	1.00	-1.97	0.011	0.049
DEP	2.24	-2.34	0.0046	2.97	-2.94	0.0011	0.0029
DPA	3.50	-1.71	0.020	2.48	-2.70	0.0019	0.011
Ethyl centralite	4.5	-1.20	0.062	-1.9	-2.4	0.0038	0.03

^a C_{SO1} expressed in mg/L.

^b Average of the K_{OW} - and C_{SO1} -based estimates of K_{fd} .

APPENDIX B

CONCENTRATIONS OF PROPELLANTS IN ENVIRONMENTAL MEDIA: MODELING, DETECTION METHODS, AND MEASURED LEVELS

The concentrations of propellants and associated co-contaminants in environmental media resulting from demilitarization operations can be measured directly or predicted using environmental transport models. This appendix provides background information on the GEOTOX model that we have used to estimate the equilibrium distribution of contaminants in reference ecoregions. Later in the appendix we identify the analytical methods available for detecting propellants, and present data on concentrations of propellants and co-contaminants that have been measured in environmental media at different locations in the U.S.

GEOTOX MODEL

The GEOTOX model simulates the transport and transformation of a contaminant in a multi-media system comprised of several environmental compartments (e.g., soil, ground water, atmosphere, etc.) Figure B-1 depicts the compartmental structure of GEOTOX. This model was used in our Phase I effort (Layton et al., 1986) to determine the distribution of demilitarization by-products in environmental media and to estimate human exposures from different pathways (e.g., inhalation, water ingestion, etc.). Here, we use GEOTOX to indicate which environmental media are potentially the most important in terms of transport from the surface soil layer, which is the primary source-term region for residuals associated with the open-burning and open-detonation of propellants.

Table B-1 shows the values used to define the landscapes or compartment properties of the Western and Southeastern ecoregions. These two ecoregions represent humid and arid areas where demilitarization facilities are located. Our Phase I report provides data on the derivation of the various landscape properties. Important differences between the two landscapes are the amount of annual precipitation, thickness of the soil zones, and the ground water inventory. Our estimates of the fractional distributions of propellants and co-contaminants among the compartments are based on the continuous addition to

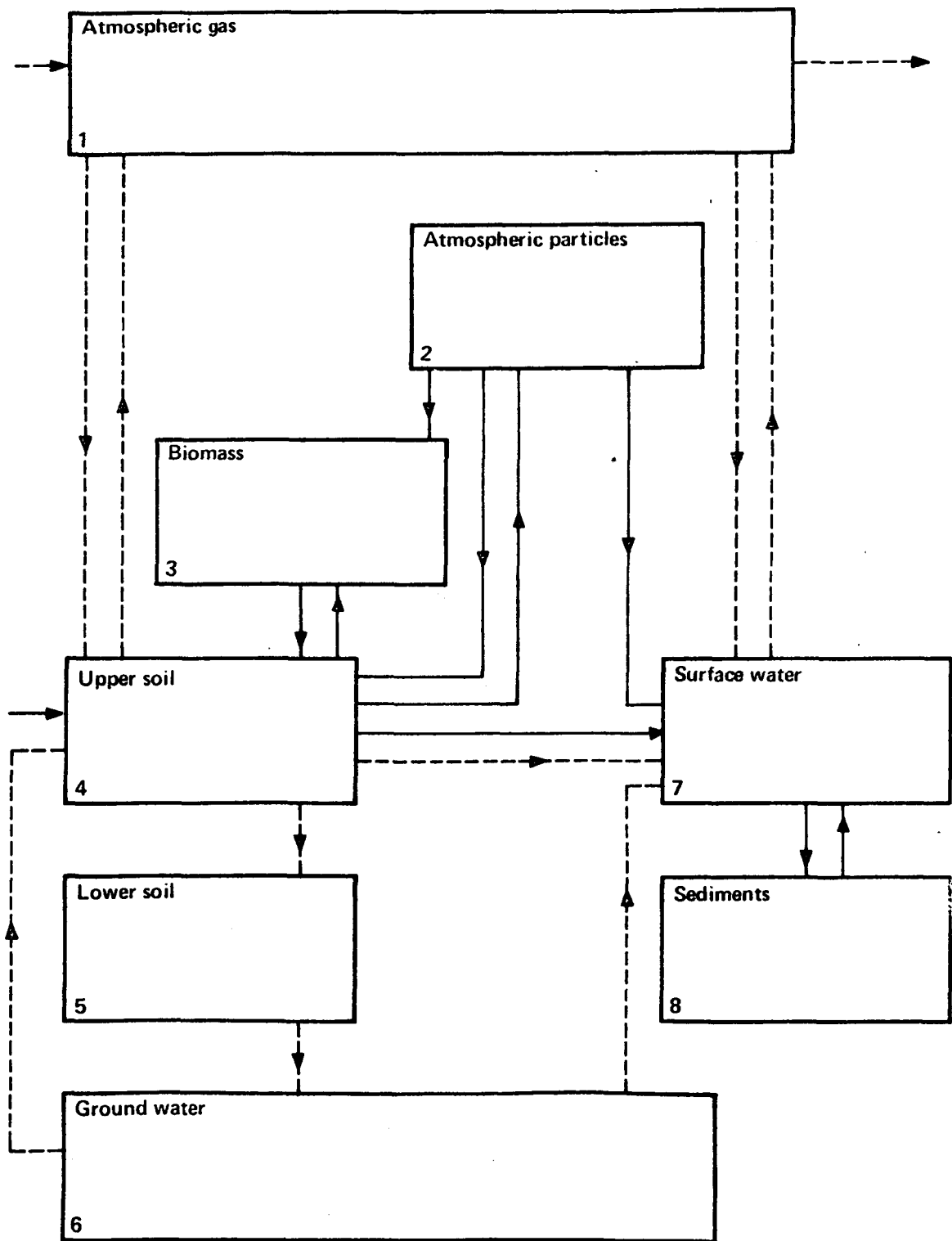


Fig. B-1. Diagram of the eight-compartment structure of GEOTOX. Dashed lines represent flows of liquids and gases, while solid lines represent flows of solids.

Table B-1. Parameter values used in GEOTOX for the Western and Southeastern ecoregions.

Landscape property	Units	Parameter Value	
		Western ecoregion	Southeastern ecoregion
1 area	km ²	1.00 e00	1.00 e00
2 height of the air compartment	m	1.00 e03	1.00 e03
3 humidity	kg/L	5.00 e-6	1.14 e-5
4 precipitation onto land	cm/yr	3.20 e01	9.90 e01
5 precipitation onto surface water	cm/yr	0.30 e00	2.00 e00
6 total surface water runoff	cm/yr	1.26 e01	4.00 e01
7 land surface runoff	cm/yr	1.10 e01	3.50 e01
8 soil flux to lower atmosphere	kg/km ² /yr	7.50 e03	7.50 e03
9 residence time of particles in the lower atmosphere	yr	8.20 e-3	8.20 e-3
10 biota dry mass inventory	kg/km ²	7.00 e05	3.10 e07
11 biota dry mass production	kg/km ² /yr	9.00 e04	1.60 e06
12 biota dry mass fraction		3.30 e-1	3.30 e-1
13 evapotranspiration from soil	cm/yr	1.88 e01	5.98 e01
14 evaporation from surface water	cm/yr	0.16 e00	1.20 e00
15 thickness of the a soil horizon	m	1.60 e-1	2.50 e-1
16 bulk density of the soil in the a horizon	kg/L	1.50 e00	1.50 e00
17 water content of the soil in the a horizon	kg/L	3.80 e-1	4.20 e-1
18 volumetric air content of the soil	L/L	7.00 e-2	3.00 e-2
19 mechanical erosion rate	kg/km ² /yr	1.19 e06	4.11 e05
20 irrigation from ground water	cm/yr	0.68 e00	2.00 e00
21 thickness of the b soil horizon	m	1.00 e01	2.00 e00
22 water content of the soil in the b horizon	kg/L	3.00 e-1	2.80 e-1
23 bulk density of the soil in the b horizon	kg/L	1.70 e00	2.00 e00
24 volumetric air content in the b horizon	l/L	5.00 e-2	2.00 e-2
25 groundwater inventory	kg/km ²	1.10 e10	4.60 e09
26 porosity of rock in the ground water zone	L/L	3.50 e-1	1.00 e-1
27 density of rock in the ground water zone	kg/L	1.70 e00	2.33 e00
28 fraction of the total surface area in surface water		8.42 e-3	1.90 e-2
29 average depth of surface waters	m	6.00 e00	6.00 e00

Table B-1. (Continued)

Landscape property	Units	Parameter Value	
		Western ecoregion	Southeastern ecoregion
30 suspended sediment load in surface water	kg/L	8.90 e-3	8.90 e-4
31 deposition rate of suspended sediment	kg/m ² /yr	3.83 e03	3.90 e02
32 thickness of the sediment layer	m	5.00 e-2	5.00 e-2
33 bulk density of the sediment layer	kg/L	1.50 e00	1.50 e00
34 porosity of the sediment zone		0.20 e00	0.20 e00
35 resuspension rate from the sediment layer	kg/m ² /yr	3.83 e03	3.90 e02
36 ambient environmental temperature	k	2.83 e02	2.90 e02
37 boundary-layer thickness at air/soil interface	m	1.00 e-2	1.00 e-2
38 boundary-layer thickness at water/air interface	m	1.00 e-2	1.00 e-2
39 boundary-layer thickness at sediment/water interface	m	2.00 e-2	2.00 e-2
40 fraction organic carbon in the upper soil zone		1.20 e-2	1.60 e-2
41 fraction organic carbon in the lower soil zone		2.00 e-3	1.00 e-3
42 fraction organic carbon in the groundwater zone		2.87 e-4	2.87 e-4
43 fraction organic carbon in the sediment zone		2.00 e-2	2.00 e-2
44 wet deposition scavenging efficiency		1.00 e00	1.00 e00

the surface soil layer without subsequent chemical transformation of a contaminant. Chemical-specific input parameters consisted of the gram-molecular weight of a compound, Henry's law constant, diffusion coefficients in air and water, and these partition coefficients: K_{sp} , K_{oc} , K_{fw} , and K_{fd} (for both meat- and milk-fat).

Table B-2 presents the estimated fractional distribution of the propellants and co-contaminants among the eight compartments of two landscapes that are representative of areas in the Southeastern and Western U.S. where demilitarization operations occur.

DETECTION METHODS

Trinitroglycerin

Most analyses for trinitroglycerin and its degradation products are made with high performance liquid chromatography (HPLC). HPLC has the advantages of being fast, and quantitative as well as qualitative, and it runs at low temperature. Gas chromatography (GC), on the other hand, is done at high temperatures where nitroglycerin (TNG) is thermally unstable. Experiments by Wu et al. (1981) found that 10% decomposition of TNG occurred on all GC columns tested in their comparison of GC and HPLC methods for separating TNG and its hydrolysis products. Thin layer chromatography (TLC) was used to separate and identify TNG and its degradation products before HPLC became readily available. Although qualitatively the results obtained from TLC are as definitive as those from HPLC, they are not as readily or precisely quantified. Also, TLC requires more time than HPLC (Wendt et al., 1978).

The results of several studies (Severin, 1985; Wu et al., 1981; Spanggord et al., 1980b; and Wendt et al., 1978) on TNG and its degradation products showed that C₁₈ columns with mobile phase solvents of methanol/water, or water are the most popular. As the percentage of water increased, the resolution of di- and mononitroglycerins improved, but the time of analysis increased from less than 10 minutes to an hour. The usual injected concentrations were in the range of 1 to 50 µg/mL (or g/L) for both methods of detection.

UV at approximately 210 nm was the favored method of detection of TNG and its products in the column effluent. For environmental samples, Maskarinek et al. (1984) found electrochemical detection (ED) superior to UV at 210 nm

Table B-2. Fractional distributions of propellants and co-contaminants in environmental landscapes representative of areas in the U.S. where demilitarization operations occur (i.e., denoted Western ecoregion and Southeastern ecoregion). Distributions are based on the steady-state addition to the upper soil layer.

Compartment	TNG	DBP	DEP	DPA	Ethyl Centralite
<u>Western ecoregion</u>					
Air	6.2×10^{-10}	1.8×10^{-4}	1.6×10^{-4}	2.9×10^{-3}	4.8×10^{-5}
Air particles	9.7×10^{-9}	1.2×10^{-8}	2.9×10^{-9}	7.9×10^{-9}	1.1×10^{-8}
Biota	1.8×10^{-4}	1.1×10^{-4}	6.8×10^{-5}	3.0×10^{-4}	1.0×10^{-4}
Upper Soil	3.9×10^{-2}	4.7×10^{-2}	1.5×10^{-2}	3.3×10^{-2}	4.4×10^{-2}
Lower soil	5.1×10^{-1}	5.8×10^{-1}	3.0×10^{-1}	4.6×10^{-1}	5.6×10^{-1}
Ground water	4.4×10^{-1}	3.7×10^{-1}	6.8×10^{-1}	5.0×10^{-1}	4.0×10^{-1}
Surface water	1.2×10^{-3}	6.8×10^{-4}	2.0×10^{-3}	1.6×10^{-3}	8.7×10^{-4}
Sediments	1.7×10^{-4}	1.9×10^{-4}	5.6×10^{-5}	1.4×10^{-4}	1.8×10^{-4}
<u>Southeastern ecoregion</u>					
Air	3.7×10^{-10}	2.3×10^{-4}	2.5×10^{-4}	4.4×10^{-3}	5.1×10^{-5}
Air particles	1.9×10^{-8}	2.2×10^{-8}	8.2×10^{-9}	1.7×10^{-8}	2.1×10^{-8}
Biota	1.6×10^{-2}	8.7×10^{-3}	8.1×10^{-3}	2.8×10^{-2}	8.5×10^{-3}
Upper Soil	1.2×10^{-1}	1.3×10^{-3}	6.3×10^{-2}	1.1×10^{-1}	1.3×10^{-1}
Lower soil	9.8×10^{-2}	9.8×10^{-2}	1.0×10^{-1}	9.6×10^{-2}	9.8×10^{-2}
Ground water	7.6×10^{-1}	7.6×10^{-1}	8.1×10^{-1}	7.6×10^{-1}	7.6×10^{-1}
Surface water	3.7×10^{-3}	1.8×10^{-3}	1.3×10^{-2}	5.4×10^{-3}	2.4×10^{-3}
Sediments	5.5×10^{-4}	6.1×10^{-4}	2.5×10^{-4}	4.8×10^{-4}	5.9×10^{-4}

^a Values do not add to one because of rounding.

for two reasons: first, there are many other organic chemicals that absorb at 210 nm that may mask the absorption of TNG; and second, ED had a smaller detection limit so that less than half the amount required with UV detection gave a larger response. Another detection method for HPLC and GC analysis of nitro compounds is the thermoelectron analyzer (TEA). Goff et al. (1983) achieved linear instrument response for 0.1 to 50 ng injections and a detection limit of 5 pg for TNG with TEA as a detection method. He produced clean separations of TNG and other explosives with both HPLC and GC. Baba et al. (1984) reported a detection limit of 0.2 ng per injection for an HPLC method they developed for tracing the metabolism of radiolabeled TNG. Their detection method incorporated UV detection with radiolable multiplication.

Wyant (1977) derived a simple procedure for the detection of TNG in letters and packages from traces of its vapor. Initially, a reagent is prepared by dissolving 0.35 g of procaine and 0.35 g N,N-dimethyl-1-naphthylamine in 100 mL of 50% acetic acid in distilled or deionized water (because this is a test for NO_2^- ion, tap water may contain nitrates and cause the reagent to be colored). The object to be tested is sprayed first with a suspension of zinc dust (10 g/100 mL of benzene) and then with the above reagent. The presence of nitrate esters results in a red or red-violet color. The test is sensitive down to 0.4 μg of nitrate ester. This reagent is not highly toxic or corrosive and does not deface letters. The shelf-life of the reagent is about 3 months.

Nitroguanidine

Burrows et al. (1984b) found HPLC to be the method of choice for determining the presence and concentration of NGu and some of its co-contaminants in waste water. Contaminated water, without prior extraction or cleanup, was injected directly onto a Zorbax C₈ reverse-phase column using glass-distilled deionized water. Detection limits were 100 $\mu\text{g/L}$ for NGu, 42 $\mu\text{g/L}$ for NSGu, and 170 $\mu\text{g/L}$ for cyanoguanidine. Melamine and ammeline were analyzed with the mobile phase consisting of methanol/octanesulfonic acid. Guanidine does not absorb at 235 nm in the UV, so analysis was of its cation by ion chromatography, and determination was done conductimetrically. Cyanamide likewise could not be detected by UV and was therefore detected spectrophotometrically by complexation with pentacyanoamine.

Kaplan et al. (1981,1982) likewise used HPLC for analysis of NGu and NSGu concentrations. They used a reverse phase Zorbax column with the mobile phase of methanol/water (10/90) and reported detection limits of 100 and 500 µg/L for NGu and NSGu, respectively. Later Kaplan and Kaplan (1985) used water as the mobile phase and a "C₈ cartridge" to achieve separation of the two compounds with retention times of 5.1 and 6.6 minutes and detection limits of 100 µg/L.

Dibutyl phthalate

Dibutyl phthalate (DBP) can be extracted from soils, sediments, and water with organic solvents and the extracts subsequently analyzed by GC and HPLC for both identity and amount. Solvents used by various workers for extraction of DBP from soils and sediments include hexane (Walker et al., 1984; Russell et al., 1985), cyclohexane (Carlberg and Martinsen, 1982), acetonitrile (Shanker et al., 1985), and methanol (Shanker et al., 1985). Because it absorbs in the UV near 254, common UV detectors (Shanker et al., 1985) as well as flame ionization and ⁶³Ni electron capture (ECD) (Carlberg and Martinsen, 1982; Russell et al., 1985) detectors have been used.

Analysis of environmental samples for DBP contamination requires extreme care to exclude background levels of the phthalate ester on laboratory utensils. After scrupulous cleaning of laboratory utensils, Giam et al. (1975) still found that DBP was at background levels. Also the chlorinated hydrocarbons similar to DDT elute with similar GC retention times. Giam et al. removed these chlorinated hydrocarbons by column chromatography. Their detection limit for DBP with GC/ECD was 1 ppb.

In addition to being an ubiquitous contaminant, DBP adsorbs to the sediment, tissue etc. being extracted for analysis of DBP. Recovery from sediment and tissue homogenate was approximately 60% for samples spiked with 2.5 mg/kg of DBP, extracted with acetonitrile, and analyzed by GC. Recovery was enhanced by storage at lower temperatures; at -20°C, 70% of the DBP spike was found in the sediment extracts (Ozretich and Schroeder, 1986).

Diethyl phthalate

Analysis for diethyl phthalate (DEP) was similar to DBP. Recovery was usually somewhat better from environmental samples because DEP is less likely to adhere to organic material than DBP because of its lower K_{OC} . Only one experiment reported low extraction efficiencies for DEP. Ozretich and Schroeder (1986) recovered approximately 65% DEP from marine sediments with acetonitrile independent of storage time from 0.13 to 7 d and temperatures of 4 to -20°C . They spiked the sediments with 2.5 mg/kg of DEP. On the other hand, Lewis et al. (1984b) claimed an extraction efficiency of $97 \pm 3.6\%$ for extraction of bacterial cultures in water with isooctane. Sugatt et al. (1984) stated that they recovered 90 to 100% with hexane extraction of a mineral salts solution of bacterial inoculum. Taylor et al. (1981) claim 92% or better recovery of phthalates from Mississippi River water and XAD-2 resins.

Diphenylamine

Identification of diphenylamine (DPA) in environmental samples is similar to the procedures described above: extraction with an organic solvent followed by GC or HPLC analysis of the condensed extract (Berkowitz et al., 1978). DPA has been isolated from sewage sludge by extraction with ethyl ether and analyzed by GC. An average recovery of 82% for 5 ppm DPA in sludge was reported for this technique by Gardner et al., 1982. Berkowitz et al. (1978) noted quantitative extractions of dilute aqueous dye solutions with isooctane where the DPA concentration was determined spectrophotometrically. Berkowitz et al. suggested that extraction from water into solid "diphenyl oxide" may be a better procedure if extraction with the more common organic solvents of hexane and diethyl ether proves ineffective.

CONCENTRATION REPORTED IN ENVIRONMENTAL MEDIA

Table B-3 contains representative data on the concentrations of propellants and co-contaminants found in environmental media.

Table B-3. Concentrations of propellants and co-contaminants in soils and waters.

Compound	Media	Depth	Description	Concentration (ppm)	Reference
TNG	Building		Indiana AAP Static Test Building	None detected	Wiese, 1981
NGU	Water	unknown	SAAP trailer pH = 9.6	2	Burrows et al., 1984a
	Water	unknown	SAAP NGu SE Sump pH = 11.3	327	Burrows et al., 1984a
	Water	unknown	SAAP Basin 123 pH = 7.3	0.3	Burrows et al., 1984a
	Water	unknown	SAAP Wetr NGu Sump, pH = 8.8	915	Burrows et al., 1984a
NSGu	Water	unknown	SAAP Basin 123 pH = 7.3	< 0.042	Burrows et al., 1984a
	Water	unknown	SAAP Wetr NGu Sump, pH = 8.8	0.43	Burrows et al., 1984a
DBP	Water	1 meter	Mississippi source, Lake Itaska	0.00015	DeLeon et al., 1986
	Water	1 meter	Mississippi River, Cario (stet), Ill.	0.00014	DeLeon et al., 1986
	Water	1 meter	Mississippi River, 20 miles below Memphis	0.00015	DeLeon et al., 1986
	Water	1 meter	Mississippi River, New Orleans	0.000139	DeLeon et al., 1986
	sediment		Chef Menteur Pass, Lake Pontchartrain, LA.	0.015	McFall et al., 1985
	sediment		Inner Harbor Navigation Canal, "	0.0045	McFall et al., 1985
	oyster		Inner harbor Navagation Canal, "	0.570	McFall et al., 1985
DEP	Water	1 meter	Mississippi source, Lake Itaska	0.00019	DeLeon et al., 1986
	Water	1 meter	Mississippi River, Cario (stet), Ill.	0.000084	DeLeon et al., 1986
	Water	1 meter	Mississippi River, 20 miles below Memphis	0.00035	DeLeon et al., 1986
	Water	1 meter	Mississippi River, New Orleans	0.000063	DeLeon et al., 1986
	sediment		Chef Menteur Pass, Lake Pontchartrain, LA.	0.065	McFall et al., 1985
	sediment		Inner Harbor Navigation Canal, "	0.025	McFall et al., 1985
	clams		Chef Menteur Pass, Lake Pontchartrain, LA.	0.45	McFall et al., 1985
	oyster		Inner harbor Navagation Canal, "	1.1	McFall et al., 1985
	clams		Rigolets, "	0.34	McFall et al., 1985

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) The demilitarization of propellants by open burning results in the deposition of residues on soils. Residues can consist of the main ingredients in propellant formulations, namely, nitrocellulose, nitroglycerin, and nitroguanidine. Co-contaminants, consisting of plasticizers and stabilizers present in propellant formulations as well as environmental degradation products of the propellants, represent additional soil contaminants. These substances include nitrosoguanidine dibutylphthlate, diethylphthlate, diphenylamine, and ethyl centralite. To support studies of the health and environmental risks of such by-products, this report presents assessments of data available on parameters that affect the risks posed by propellants and their principal co-contaminants. Specifically, data-base assessments cover factors that influence the transport and fate of the contaminants in environmental media (e.g., soils, water, etc.) and subsequently, human exposures via different pathways (e.g., inhalation, ingestion, and skin absorption). (CONTINUED ON NEXT PAGE)					
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Importantly, information on dose-response relationships for various toxic effects in humans and laboratory animals are evaluated so that acceptable daily intakes for noncarcinogenic substances and virtually safe dose rates for carcinogenic substances can be defined. Toxic effects on plant and aquatic species are also addressed.