TOXICOLOGICAL PROFILE FOR
OTTO FUEL II AND ITS COMPONENTS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and the Environmental Protection Agency (EPA) and in support of Department of Defense information needs. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, when known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are significant to protect public health will be identified by ATSDR and the EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) When appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that might present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities.

Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

Foreword

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Bonier review assures consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for Otto Fuel II and its components. The panel consisted of the following members:

1 . Steven Godin, Ph.D., DABT, Research Scientist, Drug Metabolism, CEPHALON, Inc., West Chester, Pennsylvania;

2 . Dr. Arthur Gregory, Private Consultant, Techto Enterprises, Sterling, Virginia; and

3 . Dr. Richard Stewart, Private Consultant, Racine, Wisconsin.

These experts collectively have knowledge of Otto Fuel II and its components' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about Otto Fuel II and its components, and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,397 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Otto Fuel II has been found at two of the sites on the NPL. However, the number of NPL sites evaluated for Otto Fuel II and its components is not known. As EPA evaluates more sites, the number of sites at which Otto Fuel II and its components are found may increase. This information is important for you to know because Otto Fuel II and its components may cause harmful health effects and because these sites are potential or actual sources of human exposure to Otto Fuel II and its components.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating or drinking substances containing the chemical, or from skin contact with it.

If you are exposed to a hazardous chemical such as Otto Fuel II and its components, several factors will determine whether harmful health effects will occur, and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life-style, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT ARE OTTO FUEL II AND ITS COMPONENTS?

Otto Fuel II is a distinct-smelling, reddish-orange, oily liquid that the U.S. Navy uses as a fuel for torpedo and other weapons systems. It is a mixture of three synthetic substances. It contains mostly propylene glycol dinitrate, but it also contains dibutyl sebacate and 2-nitrodiphenylamine.

Propylene glycol dinitrate is the explosive part of Otto Fuel II. It is a colorless liquid with an unpleasant odor. Other names for propylene glycol dinitrate are PGDN, 1,Zpropylene glycol dinitrate, and 1,2-propanediol dinitrate.

Dibutyl sebacate is a clear liquid. It is most often used for making plastics, many of which are used for packaging food. It is also used to enhance flavor in foods such as ice cream, candy, baked goods, and nonalcoholic drinks. Some shaving creams also contain dibutyl sebacate. Other names for dibutyl sebacate are decanedioic acid, dibutyl ester; sebacic acid, dibutyl ester; and dibutyl decanedioate.

2-Nitrodiphenylamine is a solid. Otto Fuel II contains 2-nitrodiphenylamine to control the explosion of propylene glycol dinitrate. It is also used as a solvent dye. Other names for 2-nitrodiphenylamine are 2-nitrobenzenamine, 2-nitro-N-phenyl; 2-nitro-N-phenylaniline; and Sudan Yellow 1339.

See Chapters 3 and 4 for more information.

1.2 WHAT HAPPENS TO OTTO FUEL II AND ITS COMPONENTS WHEN THEY ENTER THE ENVIRONMENT?

Otto Fuel II enters the environment mainly in waste water from Navy facilities that produce it or are involved in torpedo rework operations. Otto Fuel II may also be spilled by accident or be disposed of improperly and contaminate soil. We do not have much information on what happens to Otto Fuel II and its components when they enter the environment. We do know that Otto Fuel II enters the environment as a mixture of three separate components. A large portion of the propylene glycol dinitrate will evaporate very rapidly from the water or the surface of wet soil, but a small portion of it will be broken down by light to other chemicals. Propylene glycol dinitrate that enters the air is probably also broken down by light. Some studies suggest that propylene glycol dinitrate in water or soil is broken down by microorganisms that are normally present, but not all studies agree about this point. It is unlikely that 2-nitrodiphenylamine will evaporate from water or soil into the air. 2-Nitrodiphenylamine will also probably not stay dissolved in water because it does not dissolve easily in water and because it most likely sticks to particles in the water or soil. 2-Nitrodiphenylamine that enters the water is broken down by light. A portion of 2-nitrodiphenylamine in the water or soil also is broken down by microorganisms. We do not know which of the two processes (light- or microorganism-assisted) is more important in breaking down this chemical in the environment. Many microorganisms in water and soil have the capability to break down dibutyl sebacate. We do not have any information on other ways that dibutyl sebacate might be broken down in water or soil. There is no evidence that dibutyl sebacate evaporates into the air from soil or water. You will find more information about the fate and movement of Otto Fuel II and its components in the environment in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO OTTO FUEL II AND ITS COMPONENTS?

Humans are most likely to be exposed to Otto Fuel II or its components in areas where Otto Fuel II is used as a torpedo fuel or where it is made. The most likely ways these people will be exposed to Otto Fuel II are by breathing contaminated air and by touching the fuel during handling. One of the chemicals that makes up Otto Fuel II, propylene glycol dinitrate, was measured at levels of less than 1 part per million (ppm) parts of air in a facility where Otto Fuel II was used. Another chemical found in Otto Fuel II, 2-nitrodiphenylamine, was measured at levels of 1-14 ppm in waste water released from a plant where torpedo fuel was being manufactured. This chemical was also measured at levels of 0.5-12.2 ppm in the sediment of the river where the waste water was dumped. Almost nothing is known about levels of Otto Fuel II or its components at hazardous waste sites or at other places. It is not known whether exposure of persons living or working near hazardous waste sites occurs. Exposure to 2-nitrodiphenylamine also may occur as the result of its manufacture and use as a solvent dye. Exposure to dibutyl sebacate also may occur as a result of its manufacture and use as a flavor enhancer, as an ingredient in plastic food containers, and as an ingredient in shaving lotions. See Chapter 5 for more information.

1.4 HOW CAN THE COMPONENTS OF OTTO FUEL II ENTER AND LEAVE MY BODY?

Propylene glycol dinitrate, the explosive chemical in Otto Fuel II, enters your bloodstream when you breathe it in, when you drink water containing it, eat food or soil containing it, and when your skin comes in contact with it. 2-Nitrodiphenylamine and dibutyl sebacate, the other two components in Otto Fuel II, enter your bloodstream when you drink water or eat food with either of these two chemicals in it. We do not know how much of these two chemicals can enter your bloodstream by breathing or touching them. Within a day, propylene glycol dinitrate is rapidly and completely broken down in your blood to chemicals that are normally found in your body. Some of the breakdown products leave your body in your urine, and others are used by your body to make other chemicals. One study reported that dibutyl sebacate is rapidly broken down in your body by the same process that your body uses to break down fat. We do not know what happens to the breakdown products of dibutyl sebacate in your body. We also do not know what happens to 2-nitrodiphenylamine in your body or how it is eliminated. Chapter 2 contains more information on how the chemicals in Otto Fuel II enter and leave your body.

1.5 HOW CAN OTTO FUEL II AND ITS COMPONENTS AFFECT MY HEALTH?

People who work around Otto Fuel II report experiencing a number of effects which include headaches, loss of balance, poor eye-hand coordination, eye irritation, congested noses, nausea, dizziness, and difficulty breathing. The most common side effect of overexposure is headache. It can occur when there are no other reported side effects, even when the degree of overexposure is minimal. The greater the overexposure, the larger the number of reported

1. PUBLIC HEALTH STATEMENT

symptoms. Some people who work around Otto Fuel II get used to being around it, and after a period of time, they do not seem to experience discomfort. People who have worked around Otto Fuel II, but later are no longer exposed to this chemical, might feel chest pain or rapid beating of the heart, or have heart attacks. We do not know if Otto Fuel II affects the ability of people to have children or if it causes children to have birth defects. We also do not know if this chemical affects the ability of people to fight disease or if it causes cancer in people. Most of the effects of Otto Fuel II on people's health are believed to be caused by its major component, propylene glycol dinitrate. Exposure to levels of propylene glycol dinitrate as low as 0.2 ppm in the air for several hours causes headaches in some persons. At 0.2 ppm, some brain wave patterns are also altered, and at 0.5 ppm, dizziness and nausea are common. We do not know anything about the effects of propylene glycol dinitrate on the ability of people to have babies or to fight disease. We also do not know whether propylene glycol dinitrate causes birth defects or cancer. Very little is known about the other two components of Otto Fuel II, 2-nitrodiphenylamine or dibutyl sebacate. We do not know anything about the human health effects of the component 2-nitrodiphenylamine. The only thing we know about the human health effects of the component dibutyl sebacate is that it was not irritating to the skin of volunteers who were tested.

Animal studies show effects of propylene glycol dinitrate that are related to the effects seen in people. Results from animal studies also show additional effects of propylene glycol dinitrate that have not been reported in people exposed to this chemical. Exposure of animals to moderate-to-large amounts of propylene glycol dinitrate for several weeks causes problems in blood, like anemia and a decreased ability of the blood to carry oxygen. The livers and kidneys of some animals exposed to moderate levels of propylene glycol dinitrate all day, every day, for several months showed some damage. We do not know whether these effects might also occur in persons exposed to sufficiently high concentrations. We also do not know whether propylene glycol dinitrate affects the ability of animals to have babies or whether it causes birth defects in animals. However, we know that rats that had Otto Fuel II applied to their skin during pregnancy gave birth to babies with low birth weights. Propylene glycol dinitrate has not been sufficiently tested to see whether or not it causes cancer in animals.

Animal studies also examined the effects of dibutyl sebacate. These studies showed that eating large amounts of this chemical for long periods did not affect the health of the animals that ate it. The babies of animals that ate large amounts of this chemical grew more slowly than babies of animals that did not eat it. We do not know whether dibutyl sebacate causes cancer in animals.

We do not know anything about the health effects of 2-nitrodiphenylamine in animals.

The Department of Health and Human Services, the International Agency for Research on Cancer, and the Environmental Protection Agency have not reviewed Otto Fuel II to determine what classification of carcinogenicity it should receive.

More information on the health effects of the chemicals found in Otto Fuel II is given in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO OTTO FUEL II AND ITS COMPONENTS?

There is no routinely available test that can directly measure an individual's exposure to Otto Fuel II. Sensitive methods have been used to measure propylene glycol dinitrate, the major component in Otto Fuel II, in both the blood and the exhaled air of the exposed individual. Tests that measure the amount of a breakdown product of propylene glycol dinitrate in your urine could give some information about whether a person has been exposed to this chemical. These tests, which assume the same breakdown products for humans and animals, could be easily performed by clinical laboratories. Your body rapidly breaks down propylene glycol dinitrate, and the breakdown products leave your body in your urine within a day. Therefore, the tests are only helpful if given within a few hours of exposure. The tests also are not specific for exposure to propylene glycol dinitrate. Many other chemicals, such as those found in fertilizers, explosives, some heart and diarrhea medications, and, some food preservatives, also raise the amount of this breakdown product in the urine. No tests are known for measuring the other two components of Otto Fuel II in your body. Chapters 2 and 6 contain more information on these tests.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The government has developed regulations and guidelines for Otto Fuel II and the chemicals in it. These are designed to protect the public from potential harmful health effects of the chemical. The Department of Transportation regulates the transportation of Otto Fuel II because of its potential health effects.

The National Institute for Occupational Safety and Health (NIOSH) recommends that workers not be exposed to air containing more than 0.05 ppm propylene glycol dinitrate during an 8-hour workday, 40-hour workweek. For more information, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of Otto Fuel II and its components, and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies, and presents levels of significant exposure for Otto Fuel II and its components based on toxicological studies and epidemiological investigations.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal-and then by health effect-death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with “serious” effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Otto Fuel II is a torpedo propellant that is composed of a mixture of approximately 75% propylene glycol dinitrate, 2% 2-nitrodiphenylamine, and 23% dibutyl sebacate. The studies described in this section include both those concerning exposures to the mixture, Otto Fuel II, as well as those concerning exposures to the individual components of this mixture.
Propylene glycol dinitrate is the only component of Otto Fuel II with significant volatility. However, inhalation exposures to the other components of Otto Fuel II are considered in this section because mists of Otto Fuel II may be generated, and inhalation of aerosol particles in the mists is possible.

Occupational exposure to Otto Fuel II may result in simultaneous inhalation and dermal exposures. Thus, many of the effects reported in occupational studies in this section may be due, in part, to dermal exposure to Otto Fuel II.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to Otto Fuel II or its individual components.

No studies were located regarding death in animals after inhalation exposure to either Otto Fuel II or two of its components, 2-nitrodiphenylamine, and dibutyl sebacate. However, information was available regarding death in animals following inhalation exposure to propylene giycol dinitrate. These studies indicate that differences in species sensitivity to the lethal effects of propylene glycol dinitrate may exist.

For example, exposure to concentrations of propylene glycol dinitrate as high as 200 ppm.for 4 hours has been tolerated in rats without any toxic signs, and continuous (24 hours/day) exposure of rats, guinea pigs, and dogs to 35 ppm for 90 days produced no treatment-related deaths in any of these species (Jones et al. 1972). However, continuous exposure of a rabbit to 35 ppm of propylene glycol dinitrate resulted in the death of the rabbit on the 4th day (Jones et al. 1972). The rabbit appeared to be cyanotic 6 hours prior to death. One out of 9 squirrel monkeys exposed.continuously to 35 ppm died on the 31st day of exposure, and a squirrel monkey exposed to 61 ppm of propylene glycol dinitrate for 23 hours/day died on the third day of exposure (Jones et al. 1972).

In longer-term studies, intermittent (6 hours/day, 5 days/week) exposure of rats and mice to 35 ppm of propylene glycol dinitrate for 1 year resulted in no increase in deaths over the death rates of controls in either species during the exposure period or in the l-year postexposure observation period (Air Force 1985a). Also, a 14-month exposure of dogs to 0.2 ppm propylene glycol dinitrate for 6 hours/day, 5 days/week, caused no treatment-related deaths (Air Force 1985a). Test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each study for each end point for propylene glycol dinitrate are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to 2-nitrodiphenylamine or dibutyl sebacate. However, information was available regarding respiratory end points following inhalation exposure to Otto Fuel II and propylene glycol dinitrate.

Approximately 6% of a group of 87 torpedo maintenance workers with 1-132 months (average 47 months) of occupational exposure to Otto Fuel II reported experiencing dyspnea during past exposures (Horvath et al. 1981). However, it is unknown whether the incidence of this effect was increased relative to controls. Airway irritation was reported by incinerator workers with between I7 months and 3 years of experience (ATSDR 1990). In addition, one individual living near the incinerator was reported to have had bronchiolar obstruction; possibly related to inhaling incinerator fumes. However, only approximately 10% of the material incinerated was Otto Fuel II; other solvents and corrosive materials were also incinerated. Thus, the irritation and bronchiolar damage described in the report by ATSDR (I 990) cannot be entirely attributed to Otto Fuel II exposure with certainty.

Nasal congestion was reported by approximately 31% of the torpedo maintenance workers in the study by Horvath et al. (1981). Although respiratory tissues were affected, this symptom is most likely due to a direct vasodilatory effect of the propylene glycol dinitrate on blood vessels of the nasal mucosa and not to an effect on respiratory function. Therefore, nasal congestion is also discussed below as a symptom of a cardiovascular response.

Volunteers exposed, in a single session lasting between 1and 8 hours, to propylene glycol dinitrate atmospheres generated by volatilizing Otto Fuel II experienced no effects on respiratory function as measured using computerized spirometry (Stewart et al. 1974). Exposure levels in the study by Stewart et al. (I 974) were measured by monitoring atmospheric concentrations of propylene glycol dinitrate. Exposure to concentrations of propylene glycol dinitrate in this study as high as I.5 ppm for a single 3.2-hour period or 0.2 ppm for 7.5-8 hours/day for 5 days caused no measurable decrease in the respiratory function parameters measured.

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
ACUTE EXPOSURE									
Systemic									
1	Human	5 d 7.5-8hr/d	Resp	0.2					Stewart et al. 1974
			Cardio	0.2					
			Hemato	0.2					
			Ocular	0.2					
2	Human	1-8 hr	Resp	1.5					Stewart et al. 1974
			Cardio	0.35	0.5	(12 mm Hg increase diastolic blood pressure)			
			Hemato	1.5					
			Ocular	0.5	1.5	(definite eye irritation in 8/8)			
3	Rat (NS)	4 hr	Hemato		200	(23.5% methemoglobin)			Jones et al. 1972
4	Dog (Beagle)	2 wk 5d/wk 6hr/d	Hemato		0.2	(decreased hematocrit and hemoglobin)			Air Force 1985a
Neurological									
5	Human	once 30-60 min (occup)			≤0.22	(decreased performance in oculomotor and ataxia tests)			Horvath et al. 1981
6	Human	5 d 7.5- 8 hr/d			0.2	(altered visual evoked response; headache)			Stewart et al. 1974
7	Human	1-8 hr		0.1[b]	0.2	(altered visual evoked response; headache)	0.5	(ataxia)	Stewart et al. 1974

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
8	Monkey (Squirrel)	90 d 24hr/d	Resp	35 M			Jones et al. 1972
			Cardio	35 M			
			Hemato	10 M		16 M (hemolysis)	
			Hepatic	10 M	16 M (hemosiderin deposits in the liver, fatty changes)		
			Renal	10 M		16 M (hemosiderin deposits in the kidneys, elevated BUN)	
			Bd Wt	35 M			
9	Rat (Fischer 344)	2-51 wk 5d/wk 6hr/d	Hemato			35 (increased methemoglobin; decreased red blood cells)	Air Force 1985a
			Bd Wt	35			
10	Rat (Sprague-Dawley)	90 d 24hr/d	Resp	35			Jones et al. 1972
			Cardio	35			
			Hemato			10 (hemolysis)	
			Hepatic		10 (fatty change in liver)	35 F (focal necrosis)	
			Renal		10 (hemosiderin deposits in the kidneys)	35 F (tubular necrosis)	
			Bd Wt	35			
11	Dog (Beagle)	2-51 wk 5d/wk 6hr/d	Hemato		0.2[c] (decreased hematocrit, hemoglobin, red blood cells, reticulocytes; increased methemoglobin)		Air Force 1985a

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL: Less serious (ppm)	LOAEL: Serious (ppm)	Reference
12	Dog (Beagle)	90 d 24hr/d	Resp	35 M			Jones et al. 1972
			Cardio	35 M			
			Hemato			10 M (hemolysis)	
			Hepatic		10M (hemosiderin deposits in the liver)		
			Renal		10M (hemosiderin deposits in the kidneys)		
			Endocr	35			
			Bd Wt	35			
13	Gn pig (Hartley)	90 d 24hr/d	Resp	10	16 (foci of pulmonary hemorrhage)		Jones et al. 1972
			Cardio	35			
			Hemato		35 (elevated methemoglobin)		
			Hepatic		10 (fatty change in the liver)		
			Renal	35			
			Bd Wt	35			
Immuno./Lymphor							
14	Monkey (Squirrel)	90 d 24hr/d		16 M	35M (hemosiderin deposits in spleen)		Jones et al. 1972
15	Rat (Sprague-Dawley)	90 d 24hr/d		35			Jones et al. 1972
16	Dog (Beagle)	90 d 24hr/d		16 M	35M (hemosiderin deposits in spleen)		Jones et al. 1972
17	Gn pig (Hartley)	90 d 24hr/d		35			Jones et al. 1972

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Neurological							
18	Monkey (Squirrel)	90 d 24hr/d			39 (pupillary dilation)		Jones et al. 1972
19	Monkey (Squirrel)	90 d 24hr/d		35 M			Jones et al. 1972
20	Dog (Beagle)	90 d 24hr/d		35 M			Jones et al. 1972
CHRONIC EXPOSURE							
Systemic							
21	Rat (Fischer 344)	1 yr 5d/wk 6hr/d	Resp		0.2 M (mild degeneration of nasal epithelium) 35 F (pneumonia)		Air Force 1985a
			Cardio	35			
			Gastro	35			
			Hemato		35 (increased methemoglobin)		
			Musc/skel	0.2			
			Hepatic	35			
			Renal	35			
			Endocr	35			
			Dermal	35			
			Bd Wt	35			

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL: Less serious (ppm)	LOAEL: Serious (ppm)	Reference
22	Mouse (C57BL/6)	1 yr 5d/wk 6hr/d	Resp	35			Air Force 1985a
			Cardio	35			
			Gastro	35			
			Musc/skel	35			
			Hepatic	35			
			Renal	35			
			Endocr	35			
			Dermal	35			
			Bd Wt	35			
23	Dog (Beagle)	14 mo 5d/wk 6hr/d	Resp	0.2			Air Force 1985a
			Cardio	0.2			
			Gastro	0.2			
			Hemato		0.2[d] (decreased hematocrit, hemoglobin, red blood cells, reticulocytes; increased methemoglobin)		
			Musc/skel	0.2			
			Hepatic	0.2			
			Renal	0.2			
			Endocr	0.2			
			Dermal	0.2			
			Bd Wt	0.2			
Immuno./Lymphor							
24	Rat (Fischer 344)	1 yr 5d/wk 6hr/d		35			Air Force 1985a

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
25	Mouse (C57BL/6)	1 yr 5d/wk 6hr/d		35			Air Force 1985a
26	Dog (Beagle)	14 mo 5d/wk 6hr/d		0.2			Air Force 1985a
	Neurological						
27	Rat (Fischer 344)	1 yr 5d/wk 6hr/d		35			Air Force 1985a
28	Mouse (C57BL/6)	1 yr 5d/wk 6hr/d		35			Air Force 1985a
29	Dog (Beagle)	14 mo 5d/wk 6hr/d		0.2			Air Force 1985a
	Reproductive						
30	Rat (Fischer 344)	1 yr 5d/wk 6hr/d		35			Air Force 1985a
31	Mouse (C57BL/6)	1 yr 5d/wk 6hr/d		35			Air Force 1985a

TABLE 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
32	Dog (Beagle)	14 mo 5d/wk 6hr/d		0.2			Air Force 1985a

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.003 ppm; dose adjusted from intermittent to continuous dosing (0.1 ppm x 8 hr/24 hr = 0.03 ppm); adjusted dose divided by an uncertainty factor of 10 (for human variability).
[c]Used to derive an intermediate inhalation MRL of 0.00004 ppm; dose adjusted from intermittent to continuous dosing (0.2 ppm x 5 d/7 d x 6 hr/24 hr = 0.036 ppm); adjusted dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[d]Used to derive a chronic inhalation MRL of 0.00004 ppm; dose adjusted from intermittent to continuous dosing (0.2 ppm x 5 d/7 d x 6 hr/24 hr = 0.036 ppm); adjusted dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno./Lympho = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate – Inhalation

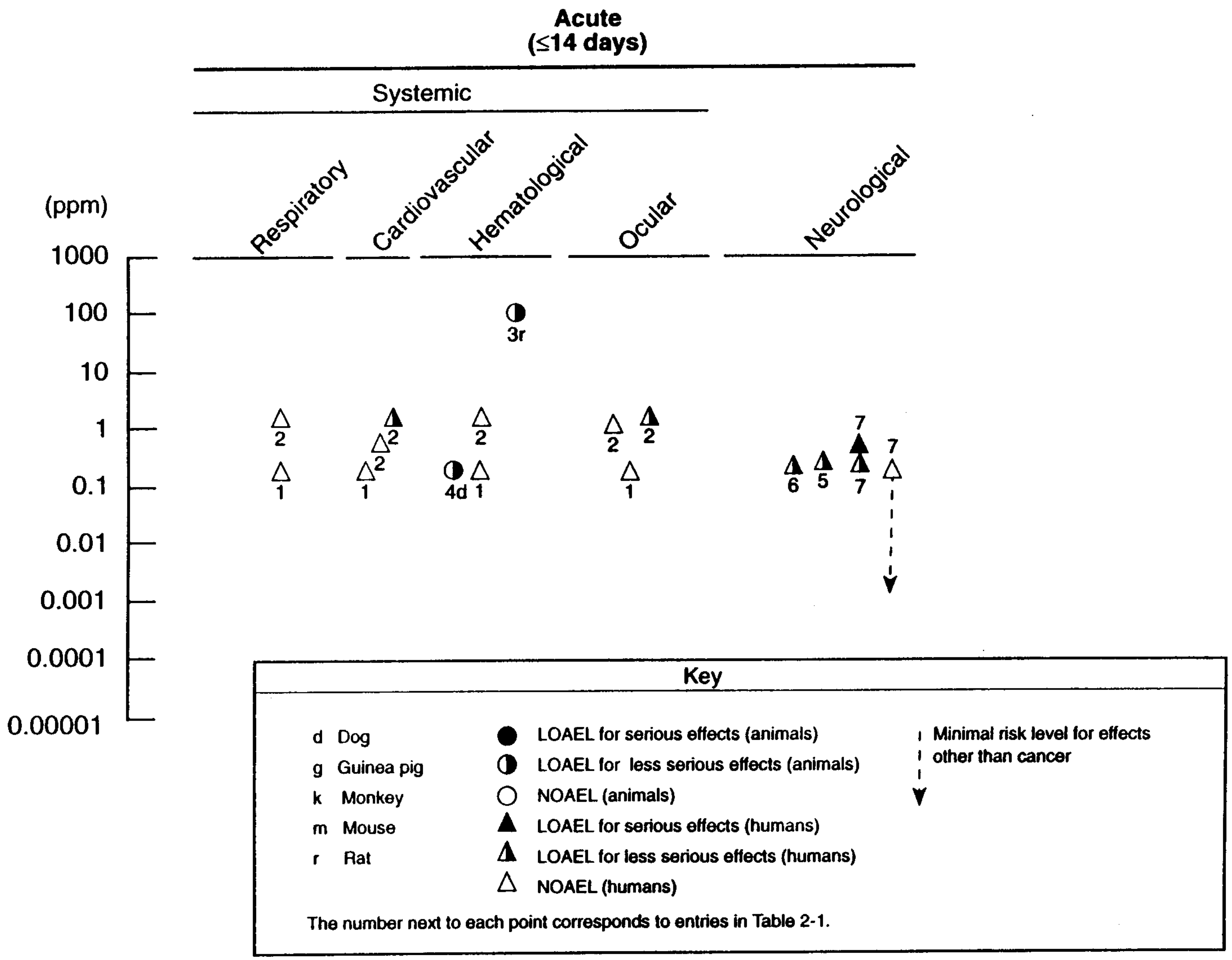


Figure 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate – Inhalation (continued)

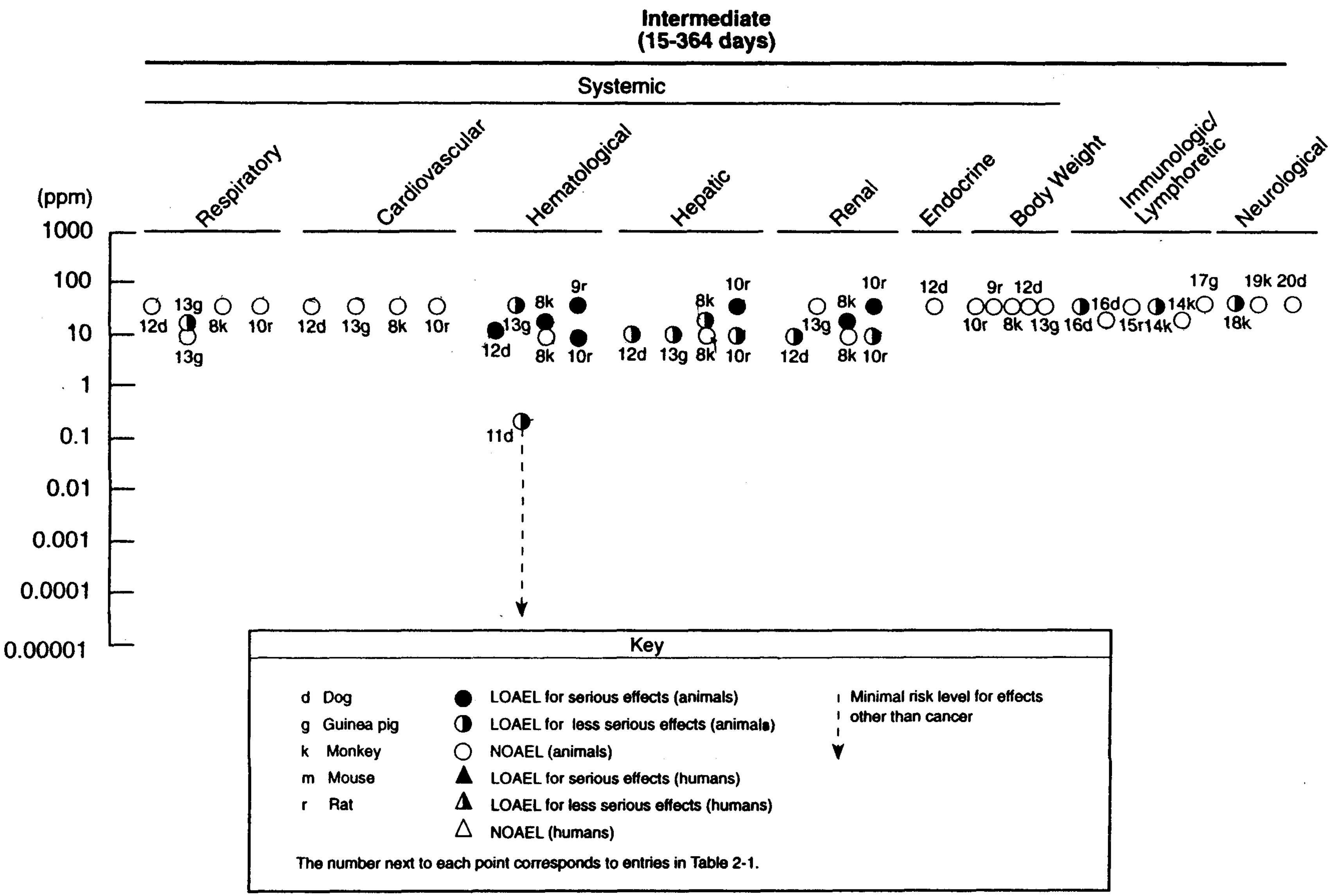
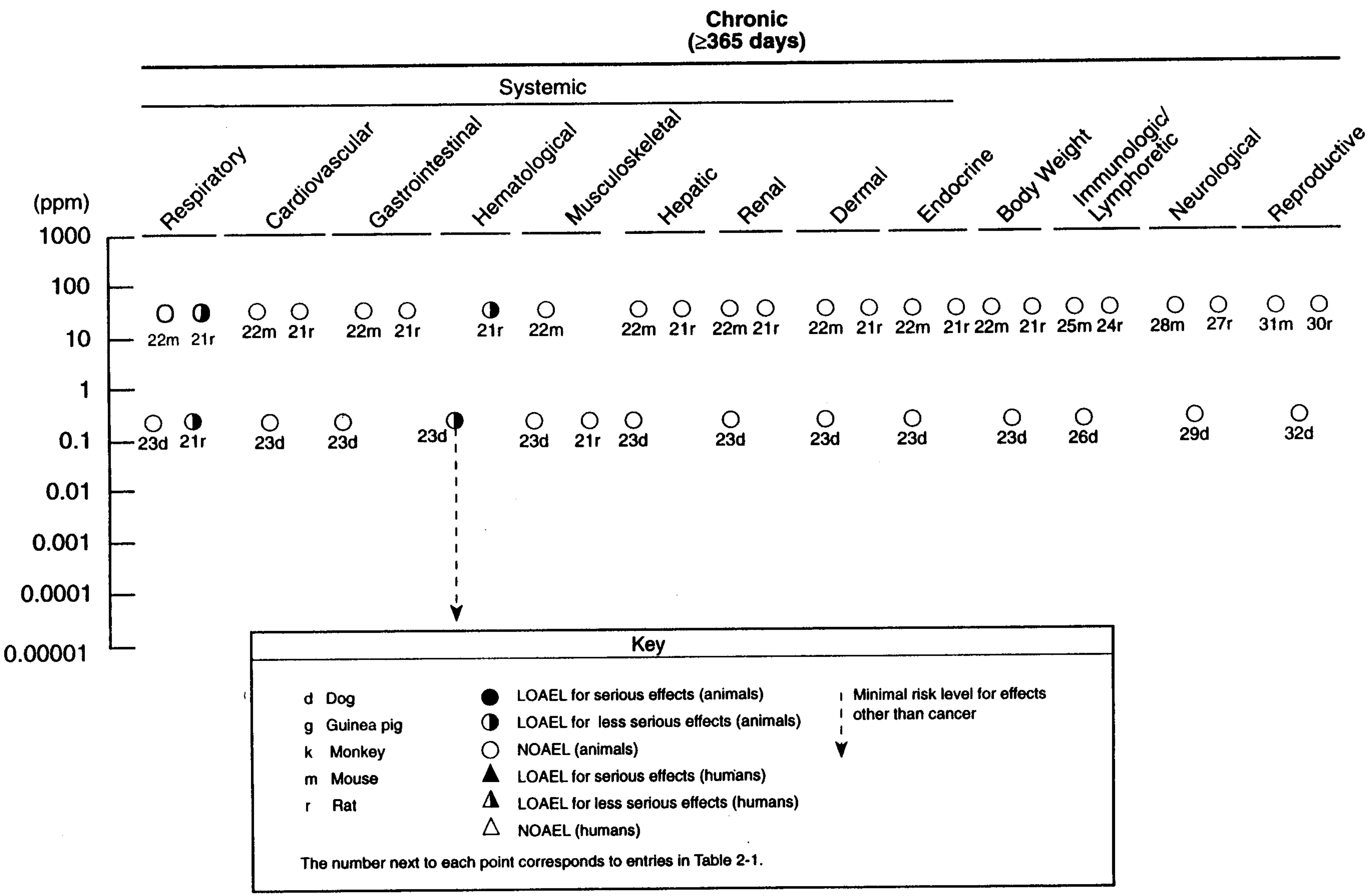


Figure 2-1. Levels of Significant Exposure to Propylene Glycol Dinitrate – Inhalation (continued)



No studies were located regarding respiratory effects in animals after inhalation exposure to Otto Fuel II, 2-nitrodiphenylamine, or dibutyl sebacate. However, studies were located that examined respiratory end points in animals following inhalation exposure to propylene glycol dinitrate.

In general, inhalation exposure of animals to propylene glycol dinitrate resulted in no gross or histologically apparent adverse effects on the tissues of the respiratory system. Studies examining the effects of a 90-day, 24-hour/day exposure of rats, monkeys, and dogs to 35 ppm propylene glycol dinitrate showed no treatment-related gross or histopathological alterations in the lungs (Jones et al. 1972). In addition, a l-year exposure of mice to 35 ppm propylene glycol dinitrate and a 14-month exposure of dogs to 0.2 ppm propylene glycol dinitrate for 6 hours/day, 5 days/week, produced no gross or histopathological changes in the tissues of the nasal cavity, larynx, trachea,. bronchi, or lungs (Air Force 198Sa). In this Air Force study (1985a), the atmosphere containing propylene glycol dinitrate was generated by volatilizing Otto Fuel II. The study is limited, however, in that the controls were not sham exposed. In addition, the control mice developed intercurrent ulcerative dermatitis, thereby confounding the conclusions that can be drawn.

Adverse respiratory effects were, however, observed in two studies. In the first study, exposure of guinea pigs to 16 ppm propylene glycol dinitrate for 24 hours/day for 90 days resulted in foci of pulmonary hemorrhage in both males and females (Jones et al. 1972). In the other study, exposure of rats of both sexes to propylene glycol dinitrate for 6 hours/day, 5 days/week, for I year, resulted in mild degeneration of the nasal epithelium at concentrations as low as 0.2 ppm and pulmonary inflammation only in females at 35 ppm (Air Force 1985a). After a l-year recovery period, the effects on the nasal epithelium and lungs were no longer significantly increased. As noted above, the propylene glycol dinitrate atmospheres in the Air Force study were generated by voIatilizing Otto Fuel II. Also, controls were not sham exposed in this study; thus, it is difficult to determine whether the effects observed on the nasal epithelium and lungs were related specifically to propylene glycol dinitrate exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to 2-nitrodiphenylamine alone or dibutyl sebacate alone. However, information was available regarding cardiovascular end points following inhalation exposure to Otto Fuel II or propylene glycol dinitrate.

2. HEALTH EFFECTS

Symptoms identified with nitrate-induced vasodilation or compensatory vasoconstriction have been observed in studies examining human exposure to Otto Fuel II and its major component, propylene glycol dinitrate. For example, headaches of presumed vascular origin were experienced either frequently or occasionally by 65% of 87 torpedo maintenance workers with l-132 months (average of 47 months) of exposure to Otto Fuel II (Horvath et al. 1981). However, it was not reported whether the incidence of this effect was greater than in controls. Also, workers at an incinerator where Otto Fuel II was burned reported that they were able to identify exposures to Otto Fuel II by the characteristic vasodilatory headache (ATSDR 1990).

Experimental exposure of volunteers to atmospheres of propylene glycol dinitrate generated by volatilizing this chemical from Otto Fuel II, resulted in headaches of presumed vascular origin (Stewart et al. 1974). The headaches began as mild frontal headaches and became progressively worse and throbbing in nature. Headaches were reported by some subjects exposed to concentrations of propylene glycol dinitrate as low as 0.2 ppm for up to 8 hours. With repeated exposures, the severity and frequency of headaches was observed to decrease. By analogy with the effects of other aliphatic nitrates, the headaches are most likely the result of vasodilation of the meningeal blood vessels (Nickerson 1975).

Nasal congestion was also reported by 31% of the torpedo maintenance workers interviewed by Horvath et al. (1981) as an occasional or frequent symptom associated with Otto Fuel II exposure. This effect was considered to be cardiovascular in origin because it was most likely the result of vasodilation of blood vessels in the nasal mucosa and sinuses.

Lowered blood pressures were observed in workers at an incineration facility at which Otto Fuel II comprised approximately 10% of the waste burned (ATSDR 1990). However, this effect cannot be directly attributed to Otto Fuel II exposure because of the number of other materials incinerated at the facility. An increase in diastolic pressure was observed during the last 2-3 hours of exposure in volunteers exposed to 0.5 ppm propylene glycol dinitrate for 8 hours (Stewart et al. 1974) possibly indicating compensatory vasoconstriction.

Based on the observation that nitrated esters cause a compensatory vasospasm that may produce coronary insufficiency upon withdrawal from exposure (Carmichael and Lieben 1963; Morton 1977), a study was conducted to examine the incidence of coronary symptoms among 1,352 Navy torpedoman’s mates with potential exposure to Otto Fuel II (Forman et al. 1987). This study demonstrated a significantly greater incidence of hospitalizations for myocardial infarctions or angina pectoris in the exposed torpedoman's mates than in 14,336 unexposed torpedoman's mates or 29,129 fire control technicians. Palpitations and chest pain were also reported by the workers in the study by Horvath et al. (1981). Of the 87 exposed workers that were interviewed, 10% reported experiencing palpitations and 4% reported experiencing chest pain. However, it was not reported whether the incidence of these symptoms was greater than in the controls. Chest pain and tightness were also reported by several workers at an incinerator where Otto Fuel II was burned (ATSDR 1990). One of these workers was diagnosed with nitrate withdrawal angina when cardiac catheterization failed to reveal any other cause. However, causative agents other than Otto Fuel II cannot be eliminated because of the large number of other hazardous wastes also burned at the facility.

No changes were observed in the electrical activity or mechanical performance of the hearts of 9 subjects exposed to up to 0.5 ppm propylene glycol dinitrate for 8 hours, 1.5 ppm propylene glycol dinitrate for 3.2 hours, or 0.2 ppm propylene glycol dinitrate for 5 days for 7.5-8 hours/day (Stewart et al. 1974). Tests were conducted during exposure, and baseline studies were repeated 16 hours following each exposure.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, limited information was located regarding cardiovascular effects in animals following inhalation exposure to propylene glycol dinitrate.

Relative to a pre-exposure period, anesthetized rats exposed nose-only to up to 94 ppm propylene glycol dinitrate vapors for 30-45 minutes exhibited no changes in mean systolic pressure during exposure (Godin et al. 1993). Exposure of monkeys to 74-103 ppm of propylene glycol dinitrate for 6 hours resulted in pallor and cold extremities of the monkeys during exposure (Jones et al. 1972), suggesting hypotension and compensatory vasoconstriction. The monkeys recovered within 30-45 minutes after termination of the exposure. No other studies reported effects associated with changes in vascular tone. However, two studies found no gross or microscopically apparent damage to the heart following inhalation exposure to propylene glycol dinitrate. In one study, no gross or histopathologic changes in the heart were observed following exposure of rats, guinea pigs, dogs, or monkeys to 35 ppm propylene glycol dinitrate for 24 hours/day, for 90 days (Jones et al. 1972). In the other study, no gross or histopathologic changes in the heart were observed during routine examination of tissues from rats or mice exposed to 35 ppm propylene glycol dinitrate for 6 hours/day, 5 days/week, for 1 year, or from dogs exposed to 0.2 ppm propylene glycol dinitrate for 6 hours/day, 5 days/week, for 14 months (Air Force 1985a). The test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to Otto Fuel II or its components.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine or dibutyl sebacate. However, extremely limited information was located regarding potential gastrointestinal effects resulting from inhalation exposure of animals to propylene glycol dinitrate.

Routine gross and histopathological examination of the esophagus, stomach, duodenum, ileum, colon, and anus of rats and mice exposed to 35 ppm propylene glycol dinitrate for 1 year, 6 hours/day, 5 days/week, and then observed for an additional year post-exposure revealed no treatment-related effects (Air Force 1985a). Similarly, no treatment-related gross or microscopic changes were observed in this study in dogs exposed to 0.2 ppm propylene glycol dinitrate for 14 months, 6 hours/day, 5 days/week.

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, methemoglobin levels were examined in one study in which volunteers were exposed to concentrations of 1.5 ppm propylene glycol dinitrate for 3.2 hours or 0.2 ppm for 7.5-8 hours/day for 5 days (Stewart et al. 1974). Inhalation exposure at these levels was insufficient to elevate methemoglobin levels above control values. Test atmospheres in this study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

No studies were located regarding hematological effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, hematological end points were assessed in several studies following inhalation exposure of animals to propylene glycol dinitrate.

Elevated methemoglobin levels were observed in a number of acute-, intermediate-, and chronic-duration exposure studies in which animals were exposed to propylene glycol dinitrate. Methemoglobin levels of 23.5% were measured in rats immediately following a 4-hour exposure to 200 ppm propylene glycol dinitrate (Jones et al. 1972). Cyanosis and elevated methemoglobin levels (18.2%) were observed in a rabbit exposed to 35 ppm propylene glycol dinitrate for 23 hours/day for 4 days (Jones et al. 1972). This animal died on the 4th day of exposure. At the time of death, the methemoglobin level was 32.8%. Similarly, the methemoglobin level in a squirrel monkey that died following exposure to 61 ppm propylene glycol dinitrate for 23 hours/day for 3 days was 40.2% at the time of death (Jones et al. 1972).

Continuous (24 hours/day) exposure of rats, guinea pigs, dogs, and monkeys to propylene glycol dinitrate for 90 days resulted in elevated methemoglobin levels during exposure and histopathologic evidence of hemolysis in all four species (Jones et al. 1972). At concentrations as low as 10 ppm, hemosiderin deposits (indicating phagocytosis of oxidized hemoglobin released from hemolyzed red cells) were observed in kidneys and livers from dogs and in kidneys from some rats. At 16 ppm, hemosiderin deposits were observed in the liver of dogs and monkeys; at 35 ppm, in addition to the liver and kidneys, heavy hemosiderin deposits were observed in the spleens of these animals. At 35 ppm, all four species exhibited elevated methemoglobin levels. Postexposure values for leukocytes, hemoglobin, and hematocrit were not significantly altered in rats, guinea pigs, or monkeys, but dogs exposed to 35 ppm experienced an average 63% decrease in hemoglobin and a 37% decrease in hematocrit (Jones et al. 1972).

Chronic intermittent (6 hours/day, 5 days/week) exposure of dogs to 0.2 ppm propylene glycol dinitrate for 14 months resulted in a small but statistically significant increase in methemoglobin levels (1-3% above normal levels) (Air Force 1985a). Exposure at this level also caused anemia in the dogs. At the first 2-week blood test, a decreased hematocrit and hemoglobin content was observed, and at 4 weeks, a significant decrease in the number of red blood cells and reticulocytes was also observed. These decreases were maintained throughout the duration of the study. Despite the indication that hematopoiesis was affected (low reticulocyte count in the presence of reduced red cell count), samples of bone marrow taken at necropsy showed no effect on the blood forming cells and no effect was observed on the spleen. Additional tests performed to determine the nature of the anemia revealed neither excessive hemoglobin denaturation nor increase in the fragility of the erythrocyte membrane. No Heinz bodies (precipitates of denatured hemoglobin within the red blood cell) were observed, and the erythrocytes demonstrated only a Slight increase in osmotic fragility at the lowest osmotic strengths tested. Rats exposed to 35 ppm propylene glycol dinitrate for 1 year, 6 hours/day, 5 days/week, also demonstrated a small but statistically significant increase in methemoglobin levels (1-2% above normal) during exposure, but no consistent effects on the hematocrit, hemoglobin, or red blood cell content of the blood were observed (Air Force 1985a), indicating the increased sensitivity of the dog relative to the rat. The test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. However, a “seronegative arthritis” was diagnosed in several workers from an incinerator at which 10% of the material burned was Otto Fuel II (ATSDR 1990). Because of the large number of other wastes handled at the facility, the arthritis cannot be ascribed to Otto Fuel II exposure with any certainty.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, effects on the skeletal system were observed in one animal study following inhalation exposure to propylene glycol dinitrate.

An increased incidence of osteosclerosis of cortical bone (stemebrae, vertebrae and/or femur) was observed in female rats 1 year after they had been exposed to 35 ppm propylene glycol dinitrate for 1 year, 6 hours/day, 5 days/week (Air Force 1985a). This effect was attributed by the study authors to altered estrogen levels in these animals, but no data on estrogen levels were presented to support this assertion. Routine gross and histopathologic examination of the thigh muscle and stemebrae, vertebrae, or femur of mice exposed to 35 ppm propylene glycoi dinitrate for 1 year, 6 hours/day, 5 days/week, and then observed for an additional year, or of dogs exposed to 0.2 ppm propylene glycol dinitrate for 14 months, 6 hours/day, 5 days/week, revealed no abnormalities in these tissues (Air Force 1985a). The test atmospheres in this study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. However, transient elevations were noted in unspecified parameters assessing liver function in several incinerator workers at a facility at which approximately 10% of the waste handled was Otto Fuel II (ATSDR 1990). This effect cannot be definitively attributed to Otto Fuel II because the other wastes incinerated included a number of solvents.

No studies were located regarding hepatic effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, several animal studies provided information regarding hepatic end points following inhalation exposure to propylene glycol dinitrate.

Continuous (24 hours/day) exposure of rats, guinea pigs, dogs, and monkeys to propylene glycol dinitrate for 90 days has been shown to result in degenerative changes in the liver (Jones et al. 1972). Concentrations of propylene glycol dinitrate as low as 10 ppm in rats and guinea pigs, and 16 ppm in dogs and monkeys, have been shown to cause fatty changes in the livers of these animals. Changes observed at 35 ppm included vacuolar changes in the livers of guinea pigs, focal liver necrosis in female rats (male rats were unaffected), and vacuolar change, mononuclear, cell infiltrates, and focal necrosis in the livers of monkeys and dogs (Jones et al. 1972). In addition, bromosulfophthalein retention was increased in one of the two dogs exposed at 35 ppm, indicating depressed hepatic function. In dogs and monkeys, the degenerative changes were commonly associated with heavy deposition of hemosiderin in the liver. It is unclear whether these effects are causally related.

In contrast, routine gross and histopathological examination of livers from animals that were intermittently exposed to propylene glycol dinitrate for intermediate or chronic durations did not reveal any adverse effects. For example, gross and histopathological examination of livers of male rats exposed to 10 ppm propylene glycol dinitrate for 6 weeks, 7 hours/day, 5 days/week (Jones et al. 1972) or 35 ppm propylene glycol dinitrate for I year, 6 hours/day, 5 days/week (Air Force 1985a) showed no treatment-related effects. The 6-week study is limited in that no controls were used. Gross and histopathological examination of livers of mice exposed for I year, 6 hours/day, 5 days/week, to 35 ppm propylene glycol dinitrate or dogs exposed for 14 months, 6 hours/day, 5 days/week, to 0.2 ppm propylene glycol dinitrate revealed no adverse treatment-related effects (Air Force 1985a). The test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to Otto Fuel II or its components.

No studies were located regarding renal effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, several studies have examined the renal toxicity of propylene glycol dinitrate following inhalation exposure.

Continuous (24 hours/day) exposure of rats to 35 ppm of propylene glycol dinitrate for 90 days resulted in an increased incidence of acute tubular necrosis in female, but not male, rats (Jones et al. 1972). In addition, continuous exposure of monkeys to propylene glycol dinitrate at concentrations as low as I6 ppm for 90 days resulted in increased serum urea nitrogen and decreased serum alkaline phosphatase (indicating the possibility of renal dysfunction). However, no gross or histological evidence of degenerative changes in the kidneys was observed in monkeys exposed to concentrations as high as 35 ppm for 90 days (Jones et al. 1972). The renal toxicity observed in these cases may have been caused by hemoglobinuria resulting from massive hemolysis (Cotran et al. 1989). In support of this is the observation that continuous exposure of rats to concentrations as low as 10 ppm and monkeys to concentrations as low as 16 ppm of propylene glycol dinitrate for 90 days resulted in an increase in hemosiderin deposits in the proximal convoluted tubules of the kidneys (Jones et al. 1972). Heavy hemosiderin deposits were observed in the kidneys of monkeys continuously exposed to 35 ppm propylene glycol dinitrate for 90 days. These deposits were attributed to increased destruction of erythrocytes (see also Hematological Effects above). Arguing against the role of hemoglobinuria in the renal toxicity is the observation that dogs exposed to concentrations of propylene glycol dinitrate as low as 10 ppm also had increased hemosiderin deposits in the proximal convoluted tubules of the kidneys but no clinical or microscopic evidence of renal dysfunction at concentrations as high as 35 ppm (Jones et al. 1972). Thus, it is unclear whether the observed renal effects in female rats and monkeys were the result of hemoglobinuria or a direct toxic effect of propylene glycol dinitrate on the kidneys.

Other studies in which intermittent exposures were used have not detected renal toxicity. Routine gross and histopathological examination of kidneys from male rats that have been intermittently (7 hours/day, 5 days/week, for 6 weeks) exposed to 10 ppm of propylene glycol dinitrate by inhalation (Jones et al. 1972) or from rats or mice that have been intermittently (6 hours/day, 5 days/week, for 1 year) exposed by inhalation to 35 ppm propylene glycol dinitrate (Air Force 1985a) did not reveal any adverse effects. The 6-week study by Jones et al. (1972) is limited in that no controls and only male rats were used. The test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Endocrine Effects. Limited information is available regarding endocrine effects after inhalation exposure to Otto Fuel II and its components. No gross or histopathologic alterations were observed in the adrenals of two male dogs continuously exposed to up to 35 ppm propylene glycol dinitrate for 90 days (Jones et al. 1972). In a chronic-duration study, no gross or microscopical alterations were observed in the thyroid, parathyroid, and pituitary glands from mice and rats exposed for a year to 35 ppm of propylene glycol dinitrate vapors 6 hours/day, 5 days/week, or in dogs exposed to 0.2 ppm using a similar protocol (Air Force 1985a).

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to propylene glycol dinitrate, 2-nitrodiphenylamine or dibutyl sebacate. Eczema, dermatitis with macropapular rashes, and sweating with no apparent cause were reported by incinerator workers at a facility at which Otto Fuel II made up approximately 10% of the waste material handled (ATSDR 1990). However, other materials processed at the incinerator could have been responsible for these effects.

No studies were located regarding dermal effects in animals after inhalation exposure to Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate. No adverse effects of inhalation exposure to propylene glycol dinitrate on the skin were reported in rats or mice exposed to 35 ppm for 1 year, 6 hours/day, 5 days/week, or in dogs exposed to 0.2 ppm for 14 months, 6 hours/day, 5 days/week (Air Force 1985a). The test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to 2-nitrodiphenylamine and dibutyl sebacate. However, eye irritation has been reported by workers occupationally exposed to Otto Fuel II and volunteers experimentally exposed to propylene glycol dinitrate. Slight eye irritation was reported by one of twelve volunteers exposed to atmospheres containing 0.2 propylene glycol dinitrate in an exposure chamber for 8 hours (Stewart et al. 1974). An exposure level of 1.5 ppm propylene glycol dinitrate caused frank eye irritation in 8 out of 8 subjects after 40 minutes in the chamber (Stewart et al. 1974). However, the same investigators also reported that none of 9 volunteers exposed to 0.2 ppm propylene glycol dinitrate 8 hours/day for 5 days complained of eye irritation (Stewart et al. 1974). Eye irritation was also reported as an occasional or frequent symptom experienced by 26% of a group of 87 workers occupationally exposed to Otto Fuel II (Horvath et al. 1981). However, the incidence of this effect was not contrasted with the incidence in an unexposed population. Eye irritation was also a common complaint among incinerator workers at a facility at which Otto Fuel II made up approximately 10% of the waste materials handled (ATSDR 1990). However, other materials processed at the incinerator could have been responsible for these effects.

No studies were located regarding ocular effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, limited information on ocular end points was found in one study in which animals were exposed to propylene glycol dinitrate by inhalation.

Pupillary dilation was observed to increase from slight to moderate in monkeys exposed to atmospheres containing 35 ppm propylene glycol dinitrate for 24 hours/day for 90 days (Jones et al. 1972). It was not stated whether this effect was a direct effect on the eyes or whether the effect may have been neurologically mediated (see also Section 2.2.1.4).

Body Weight Effects. Body weight effects after inhalation exposure to Otto Fuel II or its components are limited to studies in animals exposed to propylene glycol dinitrate. No significant alterations in body weight gain were reported in rats, guinea pigs, dogs and monkeys exposed continuously to 35 ppm propylene glycol dinitrate vapors for 90 days (Jones et al. 1972). Similar results were reported in rats and mice exposed to 35 ppm and dogs exposed to 0.2 ppm intermittently for approximately one year (Air Force 1985a).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. However, an immunological end point was observed in a situation where workers were exposed to Otto Fuel II.

A child of a worker at an incinerator at which Otto Fuel II was processed developed asthma (ATSDR 1990). The asthma was linked to materials handled at the incinerator because when the father of the child stopped bringing his work clothing home, the child's condition improved. However, Otto Fuel II comprised only approximately 10% of the wastes handled at the facility; thus, other materials may have triggered the reaction in the child. The possibility also exists that the asthma-like response may have been caused by tetryl particles activating nerve receptors which triggered vagal reflexes inducing bronchoconstriction.

No studies were located regarding immunological effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, limited information was located regarding immunological effects of propylene glycol dinitrate in animals after inhalation exposure.

No studies that directly examined immunological function were located. However, no gross or histopathoiogic alterations were observed in the spleens from rats and guinea pigs exposed continuously to up to 35 ppm propylene glycol dinitrate for 90 days (Jones et al. 1972). Dogs and monkeys exposed in the same fashion showed heavy iron deposits in their spleens at 35 ppm, but not at 16 ppm or less (Jones et al. 1972). Total and differential leukocyte counts and routine gross and histopathological examination of the mandibular and mesenteric lymph nodes, spleen and thymus were normal in rats and mice exposed to 35 ppm propylene glycol dinitrate for 6 hours/day, 5 days/week, for 1 year, and in dogs exposed to 0.2 ppm for 6 hours/day, 5 days/week, for 14 months (Air Force 1985a). Test atmospheres in the Air Force study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

The highest NOAEL values for immunologic effects of propylene glycol in rats, mice, guinea pigs, monkeys, and dogs in intermediate-duration and chronic-duration studies are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to 2-nitrodiphenylamine or dibutyl sebacate. However, neurological effects were reported in studies examining occupational exposure to Otto Fuel II and experimental inhalation exposure to propylene glycol dinitrate.

Studies designed to assess the neurological effects of Otto Fuel II and its component, propylene glycol dinitrate, in humans have indicated that an alteration of central nervous system activity may result from occupational exposures. In one study, workers were given tests of balance and oculomotor performance before and after a torpedo maintenance procedure (Horvath et al. 1981). The maintenance procedures were approximately 30-60 minutes in duration, and propylene glycol dinitrate concentrations measured in the work area ranged from 0 to 0.22 ppm (88% of the concentrations measured were less than 0.1 ppm and 50% were less than 0.05 ppm). Although no statistically significant decrement in balance was observed, some tests of oculomotor performance were significantly altered. Mean saccade velocity was significantly decreased and mean saccade delay was significantly increased in the workers. Saccade accuracy and smooth pursuit were not significantly affected. A decrease in saccade velocity and an increase in saccade delay have been observed in cases of central nervous system depression. Consistent with this effect was the observation that volunteers exposed to various concentrations of propylene glycol dinitrate also exhibited central nervous system effects (Stewart et al. 1974). Exposure to 0.2 ppm propylene glycol dinitrate for 1-8 hours altered the visual evoked responses measured in the subjects. With repeated 7.5-8 hour exposures to 0.2 ppm, the change in the visual evoked response was observed to increase in magnitude indicating a cumulative effect. Exposure to 0.5 ppm for 8 hours resulted in nausea, dizziness, and more markedly altered visual evoked responses. At this concentration, the subjects had significantly altered ability to perform the modified Romberg and heel-to-toe tests. At the highest concentration tested, 1.5 ppm, subjects experienced coordination deficits and altered visual evoked responses although they were exposed for less than 4 hours. The effects on visual evoked responses and coordination were consistent with central nervous system depression. The central nervous system effects noted in these studies are consistent with the reports of dizziness and loss of balance reported by 13% and 1%, respectively, of workers occupationally exposed to Otto Fuel II (Horvath et al. 1981). However, it is unknown whether the incidence of the effects reported by exposed workers was significantly greater than in controls. No significant differences between the results of tests of oculomotor function or coordination and balance were observed when workers occupationally exposed to Otto Fuel II for 1-132 months (47 months average) were compared to clerical and technical personnel with no known exposure to Otto Fuel II (Horvath et al. 198 I).

An unspecified number of workers at an incinerator at which Otto Fuel II comprised approximately 10% of the waste materials processed, were diagnosed with a number of neurological disorders (ATSDR 1990). These included mood disorders, cerebellar dysfunction (ataxia, tremor, nystagmus), cognitive disorders, memory loss, and possible vestibular dysfunction. Magnetic resonance imaging showed that two of these workers had cerebellar and cortical atrophy. However, the effects observed cannot be attributed to Otto Fuel II with certainty because a large number of solvents and other wastes were also handled at the incinerator.

Headaches have frequently been reported both by workers occupationally exposed to Otto Fuel II and volunteers experimentally exposed to propylene glycol dinitrate (ATSDR 1990; Horvath et al. 1981 ; Sfewart et al. 1974). The headaches are most likely associated with meningeal blood vessel dilation (Nickerson 1975) (see also Cardiovascular Effects in Section 2.2.1.2).

No studies were located regarding neurological effects in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, several studies have examined neurological end points following inhalation exposure of animals to propylene glycol dinitrate.

Monkeys exposed to concentrations of propylene glycol dinitrate as low as 2 ppm for 4 hours have demonstrated altered visual evoked responses (Mattsson et al. 1981); however, studies in animals have provided only very limited gross behavioral evidence of neurological effects of propylene glycol dinitrate. For example, exposure of an unspecified number of monkeys to 74-103 ppm propylene glycol dinitrate for 6 hours resulted in semiconsciousness and clonic convulsions (Jones et al. 1972). Recovery from these effects was observed within 30-45 minutes after termination of exposure. Also, monkeys exposed to 39 ppm propylene glycol dinitrate for 24 hours/day, for 90 days, experienced an increase in pupillary dilation from slight to moderate (Jones et al. 1972). No effect on visual discrimination or visual acuity was observed. This study was limited by the small number of animals used.

Other tests have not demonstrated neurological effects of propylene glycol dinitrate in animals. Performance of monkeys in an operant avoidance behavioral test was not affected by inhalation exposure to propylene glycol dinitrate at concentrations as high as 33 ppm for 4 hours or by exposure to concentrations as high as 4.23 ppm for 23 hours/day in an increasing dose paradigm lasting

125 days (Mattsson et al. 1981). This study is limited in that only two monkeys were used. No gross or histopathological effects have been observed in sections from brain and spinal cord or sciatic nerve in dogs and monkeys exposed to 35 ppm, 24 hours/day, for 90 days (Jones et al. 1972), in rats and mice exposed to 35 ppm, 6 hours/day, 5 days/week, for I year, and in dogs exposed to 0.2 ppm, 6 hours/day, 5 days/week, for 14 months (Air Force 1985a).

The highest NOAEL values and all reliable LOAEL values for neurological effects of propylene glycol dinitrate in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to the individual components of Otto Fuel II. However, a study compared the incidence of spontaneous and induced abortions in female Navy enlisted personnel exposed to Otto Fuel II with that in two groups of enlisted female workers nat exposed to Otto Fuel II and found no increase (Forman 1988). The number of female workers exposed to Otto Fuel II in this study was extremely small, limiting the sensitivity of the comparison.

No studies were located that examined the effects of Otto Fuel II or its individual components on reproductive performance in animals after inhalation exposure. Although no information was located regarding reproductive performance, limited data were available regarding effects of propylene glycol dinitrate on the gross and microscopic structure of reproductive organs. Routine gross and histopathological examination of the seminal vesicles, prostate, testes, ovaries, uterus, and mammary glands of mice and rats exposed to 35 ppm propylene glycol dinitrate for 1 year, 6 hours/day, 5 days/week, and dogs exposed to 0.2 ppm for 14 months, 6 hours/day, 5 days/week, revealed no treatment-related effects (Air Force 1985a). Test atmospheres in this study were generated by volatilizing propylene glycol dinitrate from Otto Fuel II.

The highest NOAEL values for reproductive effects in each species following chronic-duration inhalation exposure to propylene glycol dinitrate are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. However, extremely limited information regarding developmental effects in children of workers occupationally exposed to Otto Fuel II was available.

A child with multiple birth defects was born to the wife of a worker at an incineration facility at which Otto Fuel II comprised approximately 10% of the waste processed (ATSDR 1990). The defects included club foot, imperforate anus, renal anomalies and persistence of the cloaca. Chromosomal studies on the child were normal. However, the birth defects cannot be definitively ascribed to Otto Fuel II exposure because other possible causes for the defects existed (i.e., exposure to other developmental toxicants) and the incidence of similar defects in a control population were not adequately characterized.

No studies were located regarding developmental effects in animals after inhalation exposure to Otto Fuel II or its components.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to Otto Fuel II or its components.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to Otto Fuel II or any of its individual components.

No studies were located regarding cancer in animals after inhalation exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate.

Extremely limited information was located regarding cancer in animals after inhalation exposure to propylene glycol dinitrate. One osteoma and one osteosarcoma were observed in rats 1 year following exposure to 0.2 ppm of propylene glycol dinitrate for I year, 5 days/week, 6 hours/day;
2 osteosarcomas were observed in rats I year following exposure at the 35ppm level for the same duration (Air Force 1985a). These tumors are rare and could be indicative of a tumorigenic potential of propylene glycol dinitrate. However, the study authors concluded that the lack of a dose response given the large differences in doses tested suggested that the tumors were not exposure related. Mice exposed to 35 ppm of propylene glycol dinitrate for 6 hours/day, 5 days/week, for 1 year, and then observed for 1 year postexposure, had an increased incidence of lymphoid hyperplasia (considered to be indicative of early lymphoma, a common lesion in older mice) (Air Force 1985a). However, the study authors also concluded that this lesion was incidental and not exposure related. Both of these studies are limited in that they were less than lifetime studies (18 months in the mouse and 2 years in the rat), the controls were not sham exposed, and a chronic ulcerative dermatitis was observed in the control mice, confounding the analysis of the results of the study.

2.2.2 Oral Exposure

With the exception of acute oral LD_{50} data, virtually all of the information on the effects of Otto Fuel II or its components after oral exposure comes from studies examining the oral toxicity of dibutyl sebacate. These studies show that dibutyl sebacate is a relatively nontoxic component of Otto Fuel II. The only toxicity observed with dibutyl sebacate is a slight depression of body weight of offspring from parental animals that had consumed large amounts of dibutyl sebacate prior to conception (Smith 1953).

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to Otto Fuel II or its components.
The only study that was located regarding death in animals after oral exposure to Otto Fuel II was an LD_{50} determination in rats; however, very few experimental details were presented (Navy 1982b). This study reported an LD_{50} value of 2,000 mg/kg.

A number of studies have examined the acute oral toxicity of propylene glycol dinitrate in rats. Oral LD_{50} values ranging from 250 to 1,190 mg/kg have been determined (Andersen and Mehl 1979; Clark and Litchfield 1969; Jones et al. 1972). The reason for the wide range of values obtained is not clear but may have been due to differences in the strain, sex, age, or weight of the rats tested. Different rat strains were used in all three studies: Sprague Dawley (Andersen and Mehl 1979) Alderley Park strain (Clark and Litchfield 1969), and Long Evans (Jones et al. 1972). Also, Andersen and Mehl (1979) and Jones et al. (1972) used only male rats; whereas, Clark and Litchfield (1 969) used only females. All three studies described similar symptoms before death including prostration and anoxia. In addition, mild convulsions were observed in the rats prior to death in the study by Jones et al. (1972).

Dibutyl sebacate has very low toxicity and only very large oral doses were observed to result in death. All rats given a single oral dose of 32,000 mg/kg died; whereas, all rats given 16,000 mg/kg survived (Smith 1953). No gross or histopathologic changes indicating the cause of death were observed in the rats at necropsy. However, extremely large volumes of test material were administered (approximately 2.4 mL at the highest dose tested) to 60-75gram rats; thus, it is possible that death may have resulted from aspiration of the test material. This is supported by the observation of hemorrhaging and edema in the lungs of the rats and mice receiving doses greater than or equal to 10-1 5 g/kg in the oral LD_{50} study by Komarova (1976, 1979). Oral LD_{50} values for dibutyl sebacate in rats and mice in this study were reported to be 17,200 mg/kg/day and 18,100 mg/kg/day, respectively (Komarova 1976, 1979).

The only information located regarding death following ingestion of 2-nitrodiphenylamine indicated that the oral toxicity of 2-nitrodiphenylamine was also very low. The oral LD_{50} value for rats was 6,150 mg/kg. (This information was obtained from a Material Safety Data Sheet on 2-nitrodiphenylamine [American Cyanamid 19821). Because the actual study was unavailable for review, this value could not be verified.)

All reliable LOAEL values for death in rats following acute-duration exposure are recorded for propylene glycol dinitrate in Table 2-2 and for dibutyl sebacate in Table 2-3 and plotted for propylene glycol dinitrate in Figure 2-2 and for dibutyl sebacate in Figure 2-3.

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol Dinitrate - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (G)				250 M (LD50)	Andersen and Mehl 1979
2	Rat (Alderley Park)	once (GO)				1,190 F (LD50)	Clark and Litchfield 1969
3	Rat (Long- Evans)	once (G)				860 (LD50)	Jones et al. 1972

[a]The number corresponds to entries in Figure 2-2.

F = female; (G) = gavage; (GO) = gavage in oil; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

Figure 2-2. Levels of Significant Exposure to Propylene Glycol Dinitrate – Oral

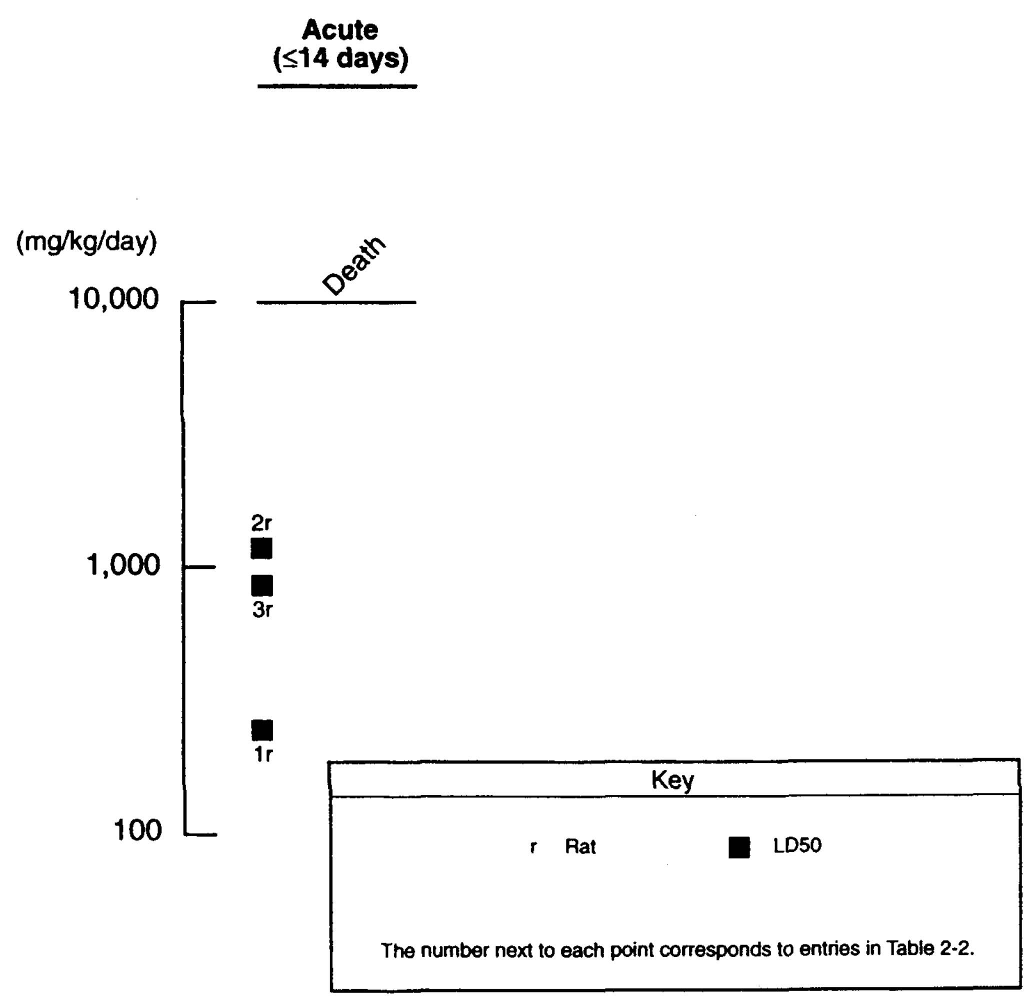


TABLE 2-3. Levels of Significant Exposure to Dibutyl Sebacate - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (NS)	once (G)				17,200 (LD50)	Komarova 1976, 1979
2	Rat (Sprague-Dawley)	once (NS)				32,000 M (6/6 died)	Smith 1953
3	Mouse (NS)	once (G)				18,100 (LD50)	Komarova 1976, 1979
	INTERMEDIATE EXPOSURE						
	Reproductive						
4	Rat (Sprague-Dawley)	10 wk ad lib (F)		3,125			Smith 1953
	Developmental						
5	Rat (Sprague-Dawley)	10 wk ad lib (F)			3,125 (decreased weight gain of litters)		Smith 1953

TABLE 2-3. Levels of Significant Exposure to Dibutyl Sebacate - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	CHRONIC EXPOSURE						
	Systemic						
6	Rat (Sprague-Dawley)	2 yr ad lib (F)	Resp	3,125 M			Smith 1953
			Cardio	3,125 M			
			Gastro	3,125 M			
			Hemato	3,125 M			
			Hepatic	3,125 M			
			Renal	3,125 M			
			Endocr	3,125 M			
	Immuno./Lymphor						
7	Rat (Sprague-Dawley)	2 yr ad lib (F)		3,125 M			Smith 1953
8	Rat (Sprague-Dawley)	1 yr ad lib (F)		625 M			Smith 1953
	Neurological						
9	Rat (Sprague-Dawley)	1 yr ad lib (F)		625 M			Smith 1953

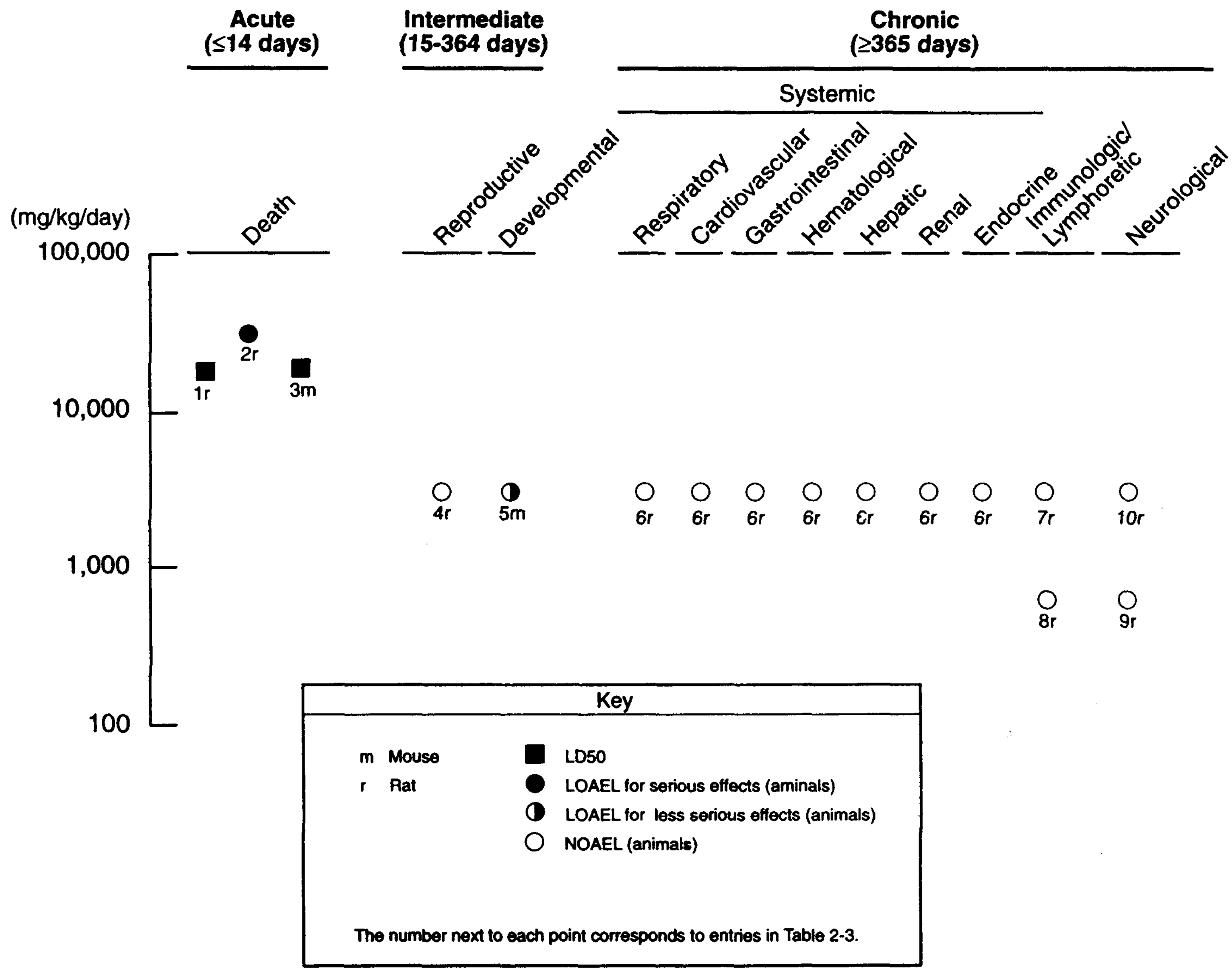
TABLE 2-3. Levels of Significant Exposure to Dibutyl Sebacate - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
10	Rat (Sprague-Dawley)	2 yr ad lib (F)		3,125M			Smith 1953

[a]The number corresponds to entries in Figure 2-3.

ad lib = ad libitum; Cardio = cardiovascular; Endocr = endocrine; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-3. Levels of Significant Exposure to Dibutyl Sebacate – Oral



2.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to Otto Fuel II or its components.

The highest NOAEL values and all reliable LOAEL values for each study for each end point for dibutyl sebacate in rats are recorded in Table 2-3 and plotted in Figure 2-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding respiratory effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine. However, necropsy of rats and mice that died as a result of receiving a single oral dose of dibutyl sebacate greater than or equal to 10,000 and 15,000 mg/kg, respectively, revealed hemorrhaging and edema of the lungs (Komarova 1976, 1979). No information regarding the number of animals per dose with lung pathology or the dose relationship of this response was presented. It is possible that the hemorrhaging and edema in the lungs was the result of aspiration of the gastric contents, considering the relatively large gavage volumes used. In contrast, routine gross and histopathological examination of rats consuming 3,125 mg/kg/day of dibutyl sebacate for 2 years demonstrated no treatment-related gross or histopathological alterations in the lungs (Smith 1953).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding cardiovascular effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine. However, cardiovascular end points were reported in animals following oral exposure to dibutyl sebacate in two studies.

Hypervolemia of the heart muscle was observed at necropsy of rats and mice that died following administration of a single oral dose of dibutyl sebacate greater than or equal to 10,000 and 15,000 mg/kg, respectively (Komarova 1976, 1979). Insufficient information regarding the incidence of this effect or the number of animals exposed limits this study. Also, it is unclear whether this represents a direct toxic effect of the dibutyl sebacate or is a result of the administration of a large volume of test material. Routine gross and histopathological examination of rats consuming 3, 125 mg/kg/day of dibutyl sebacate for 2 years showed no treatment-related gross or histopathological changes in the heart (Smith 1953).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding gastrointestinal effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine. However, gastrointestinal end points were reported in animals following oral exposure to dibutyl sebacate in two studies.

Hypervolemia of the walls of the small intestines and paresis of the stomach were observed in rats and. mice that died following oral administration *of* single doses of dibutyl sebacate greater than or equal to 10,000 and 15,000 mg/kg, respectively (Komarova 1976, 1979). It is unclear whether these effects represented direct toxic effects of the dibutyl sebacate or were the result of administration of a large oral volume of test material. Routine gross and histopathological examination of rats consuming 3,125 mg/kg/day of dibutyl sebacate for 2 years revealed no treatment-related gross or histopathological changes in the stomach or small intestine (Smith 1953).

Hematological Effects. No studies were located regarding hematologicat effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding hematological effects in animals after oral exposure to Otto Fuel II or its component, propylene glycol dinitrate. However, limited information was located regarding the hematological toxicity of 2-nitrodiphenylamine and dibutyl sebacate.

An Army review indicated that oral administration of 3,070 mg/kg of 2-nitrodiphenylamine to rats resulted in elevation of methemoglobin levels to 9.45% (Army 1979). (This information was obtained by the U.S. Army through personal communication with American Cyanamid. Because the actual study was unavailable for review, this information could not be verified.)

Routine hematology performed at 6, 12, 18, and 24 months revealed no effects of consumption of up to 3,125 mg/kg/day of dibutyl sebacate on hemoglobin, total erythrocytes, or total or differential leukocyte counts in rats (Smith 1953). Differential counts taken on bone marrow smears at the time of final sacrifice also revealed no effect on cellular distribution or the myeloid-erythroid ratio.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding hepatic effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine. However, routine gross and histopathological examination of rats consuming 3,125 mg/kg/day of dibutyl sebacate for 2 years revealed no treatment-related gross or histopathological changes in the liver (Smith 1953).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding renal effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine. However, in two studies, renal end points were evaluated in animals following oral exposure to dibutyl sebacate.

Hypervolemia of the kidneys was observed at necropsy of rats and mice that died as a result of oral administration of a single dose of dibutyl sebacate greater than or equal to 10,000 and 15,000 mg/kg, respectively (Komarova 1976, 1979). However, insufficient information regarding the number of animals tested and the incidence of this observation limits the interpretation of this report. In addition, it is unclear whether this effect is a direct toxic effect of the dibutyl sebacate or the result of the administration of a large volume of test material. Routine gross and histopathological examination of rats consuming 3,125 mg/kg/day of dibutyl sebacate for 2 years revealed no treatment-related gross or histopathological changes in the kidneys (Smith 1953).

Endocrine Effects. Information regarding endocrine effects after oral exposure to Otto Fuel II or its components was limited to an early study with dibutyl sebacate in rats. In that study (Smith 1953), rats fed a diet that provided up to 3,125 mg dibutyl sebacate/kg/day for up to 2 years showed no gross or histopathological changes in the thyroid and adrenal glands. No further endocrinological end points were assessed.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to Otto Fuel II or its components propylene glycol dinitrate and 2-nitrophenylamine. However, no gross alterations were observed in the spleens of rats fed a diet that provided 625 mg dibutyl sebacate/kg/day for 1 year or 3,125 mg/kg/day for 2 years (Smith 1953). This information is recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding neurological effects in animals after oral exposure to Otto Fuel II or its component, 2-nitrodiphenylamine. However, information regarding the effects of propylene glycol dinitrate and dibutyl sebacate on neurological parameters was available.

A reduced response to external stimuli, prostration, and mild convulsions were observed in rats given single oral doses of propylene glycol dinitrate (Jones et al. 1972). At concentrations ranging from 1,100 to 3,320 mg/kg/day, the effects were observed within 15 minutes, and at lower doses (76-760 mg/kg/day), the symptoms were not as severe and were delayed in onset. The lowest doses at which specific effects were observed in this study were not specified.

Hypervolemia of the “brain substance” was observed in rats and mice that died following administration of a single oral dose of dibutyl sebacate greater than or equal to 10,000 and 15,000 mg/kg, respectively (Komarova 1976, 1979). However, evaluation of this finding is limited because insufficient information regarding the number of animals tested or the dose-related incidence was provided. In addition, it is unclear whether this effect is a direct toxic effect of the dibutyl sebacate or is related to the volume of the test material that was administered. No gross pathological changes were observed in the brains of rats consuming 625 mg dibutyl sebacate/kg/day for I year or 3,125 mg/kg/day for 2 years (Smith 19.53).

The highest NOAEL values for neurological effects in rats following chronic-duration exposure to dibutyl sebacate are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding reproductive effects in animals after oral exposure to propylene glycol dinitrate or 2-nitrodiphenylamine.

The only study located regarding possible reproductive effects of Otto Fuel II was a dominant lethal study in mice which demonstrated that exposure of males to 200 mg/kg/day of Otto Fuel II for 5 days prior to mating had no effect on fertility, the total number of implants per pregnant female, or the number of dead implants per pregnant female (Navy 1982b). However, this study was limited in that the fertility was low overall in both control and treated animals.

Consumption of 3,125 mg/kg/day of dibutyl sebacate in the diet by parental animals for 10 weeks prior to mating caused no adverse effects on fertility, litter size, or litter survival (Smith 1953).

The highest NOAEL for reproductive effects in rats after intermediate-duration oral exposure to dibutyl sebacate is recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding developmental effects in animals after oral exposure to Otto Fuel II or two of its components, propylene glycol dinitrate and 2-nitrodiphenylamine.

Consumption of 3,125 mg/kg/day of dibutyl sebacate in the diet by male and female rats for 10 weeks prior to mating resulted in a decreased weight gain in litters during the preweaning period (Smith 1953). It is unclear whether the reduced growth was caused by contact with test material in utero or during lactation. Additional exposure of a subset of the pups to the parental diet for 21 days postweaning resulted in continued retarded growth. No gross pathological changes were observed at necropsy of the litters following sacrifice at the end of a 21-day postweaning period.

The NOAEL value for developmental effects in rats after intermediate-duration exposure to dibutyl sebacate is recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding genotoxic effects in animals after oral exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate.

Otto Fuel II was evaluated for the potential to induce chromosome aberrations in mouse bone marrow cells following the acute oral administration of 20, 62, or 200 mg/kg/day (Navy 1982b). Although the results from the acute study suggested a clastogenic response (i.e., slight but dose-related increases in chromosome damage and the presence of rare complex aberrations at two doses), no definite conclusions could be drawn. In that study (Navy 1982b), treatment with Otto Fuel II did not induce any signs of overt toxicity. Negative results were reported for the mouse dominant lethal assay conducted with comparable acute oral doses of Otto Fuel II (Navy 1982b). (The.assay detects mainly chromosome aberrations but may also detect ploidy changes and chromosome nondisjunctions.) The relevance, if any, of the reduced fertility indices in the three treatment groups at the majority of mating intervals (weekly matings for the 7-week test period) could not be determined because similar reduced fertility indices were seen in the historic and concurrent negative controls. Also of concern was the low number of pregnant females (<20/treatment group/mating week) evaluated for critical dominant lethal parameters. Although the dominant lethal indices (i.e., dead implants/total implants) for the majority of treatment groups and mating weeks were within the historical spontaneous range of the reporting laboratory and also within published ranges (Green et al. 1985) the small sample size of pregnant females compromised the overall results. It was, nonetheless, concluded that there was no compelling evidence from this study that Otto Fuel II was clastogenic in male mouse germinal cells.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to Otto Fuel II or its components.

No studies were located regarding cancer in animals after oral exposure to Otto Fuel II or its components, propylene glycol dinitrate and 2-nitrodiphenylamine. Limited information was, however, available regarding the tumorigenic potential of dibutyl sebacate in animals after oral exposure. Consumption of up to 3,125 mg/kg/day dibutyl sebacate by rats for 2 years had no effect on tumor incidence (Smith 1953). However, interpretation of this study is limited by the relatively small number of rats tested (20 males and 20 females per dose).

2.2.3 Dermal Exposure

As indicated in the section on inhalation exposure, it is often difficult to clearly separate dermal from inhalation exposures in many occupational studies. Thus, many of the findings from occupational studies described in Section 2.2.1 regarding inhalation exposure are repeated here.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to Otto Fuel II or its components.

Application of 4,000 mg/kg/day of Otto Fuel II to the skin of pregnant rats during days 6-15 of gestation resulted in the deaths of 25 out of 47 rats at this dose (Cooper et al. 1993). No deaths were reported among pregnant rats at doses as great as 2,000 mg/kg/day or in pregnant rabbits at doses as great as 1,000 mg/kg/day (applied during days 6-18 of gestation) (Cooper et al. 1993).

Application of propylene glycol dinitrate to the skin of rabbits for 20 days for 2 hours/day resulted in death in 1 of 5 rabbits after the sixth application of 2,000 mg/kg and death in 13 of I4 rabbits after the fifth application of 4,000 mg/kg (Jones et al. 1972). Similarly, 6 of 1 I rabbits died as the result of daily application of 3,488 mg/kg for 3 weeks (Andersen and Mehl 1979).

No deaths were reported to result from application of an unspecified amount of 100% dibutyl sebacate to the skin of rabbits for 48 hours (Mallette and Von Haam 1952b). This study is limited by the absence of details regarding the sex of the rabbits and dosage of dibutyl sebacate used.

Application of 2-nitrodiphenylamine to the skin of rabbits resulted in a 24-hour dermal LD_{50} value of >l0,000 mg/kg (American Cyanamid 1982). (This information was obtained from a Material Safety Data Sheet on 2-nitrodiphenylamine. Because the actual study was unavailable for review, this value could not be verified.)

All reliable LOAEL values for death in rats following acute-duration dermal exposure to Otto Fuel II are recorded in Table 2-4 and all reliable LOAEL values for death in rabbits after intermediateduration dermal exposure to propylene glycol dinitrate are recorded in Table 2-5:

2.2.3.2 Systemic Effects

No studies were located regarding gastrointestinal effects in humans or animals after dermal exposure to Otto Fuel II or any of its components.

The highest NOAEL value and all reliable LOAEL values for each end point in rabbits after intermediate-duration dermal exposure to propylene glycol dinitrate are recorded in Table 2-4.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to propylene glycol dinitrate, 2nitrodiphenylamine, or dibutyl sebacate. However, respiratory effects associated with Otto Fuel II exposure have been reported.

Approximately 6% of a group of 87 torpedo maintenance workers with 1-132 months (average 47 months) of occupational exposure to Otto Fuel II reported experiencing dyspnea occasionally during past exposures (Horvath et al. 1981). It is possible that these workers may have been exposed

TABLE 2-4. Levels of Significant Exposure to Otto Fuels II and Components - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rat (Fischer 344)	10 d Gd 6-15				4,000 F (25/47 died)	Cooper et al. 1993
Systemic						
Rat (Fischer 344)	10 d Gd 6-15	Hemato			4,000 F (58% methemoglobinemia)	Cooper et al. 1993
		Derm	2,000 F	4,000 F (moderate erythema)		
		Bd Wt			400 F (25% decrease weight gain in dams)	
Rabbit (New Zealand white)	13 d Gd 6-18	Derm	316 F	1,000 F (marked erythema)		Cooper et al. 1993
		Bd Wt			100 F (38% transient body weight gain decrease in dams)	
Developmental						
Rat (Fischer 344)	10 d Gd 6-15		400 F	2,000 F (decreased fetal weight)	4,000 F (increased resorptions; decreased viable fetuses and number of fetuses per dam)	Cooper et al. 1993
Rabbit (New Zealand white)	13 d Gd 6-18		1,000 F			Cooper et al. 1993

d = day(s); Derm = dermal; Gd = gestation day(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = times

TABLE 2-5. Levels of Significant Exposure to Propylene Glycol Dinitrate - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rabbit (New Zealand white)	20 d 2hr/d				2,000 M (1/5 died)	Jones et al. 1972
Systemic						
Rabbit (New Zealand white)	1-20 d 2hr/d	Resp	1,000 M	2,000 M (rapid, shallow breathing)		Jones et al. 1972
		Cardio		4,000 M (myocardial degeneration)		
		Hemato		1,000 M (transient decrease in hemoglobin)	4,000 M (cyanosis; 35.5% methemoglobin)	
		Hepatic		4,000 M (liver degeneration)		
		Renal		4,000 M (bladder distension; vacuolar change in proximal convoluted tubular epithelium)		
		Bd Wt		4,000 M (11% decrease in final body weight)		
Immuno./Lymphor						
Rabbit (New Zealand white)	1-20 d 2hr/d		4,000 M			Jones et al. 1972
Neurological						
Rabbit (New Zealand white)	20 d 2hr/d		1,000 M	2,000 M (weak appearance)		Jones et al. 1972

TABLE 2-5. Levels of Significant Exposure to Propylene Glycol Dinitrate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE						
Death						
Rabbit (New Zealand white)	3 wk 1x/d				3,488 M (6/11 died)	Andersen and Mehl 1979
Systemic						
Rabbit (New Zealand white)	20 d 2hr/d	Dermal		1,000 M (minor skin irritation)		Jones et al. 1972
		Bd Wt	2,000 M			

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s) dermally as well as by inhalation (see Section 2.2. I .2) to Otto Fuel II during the maintenance procedures. It is unknown whether the incidence of the dyspnea was increased relative to controls or whether other chemical exposures may have contributed to the dyspnea.

Nasal congestion was reported by approximately 31% of the workers in the study by Horvath et al. (1981). However, this symptom is most likely due to a direct vasodilatory effect of the propylene glycol dinitrate found in Otto Fuel II on the blood vessels of the nasal mucosa and not an effect on respiratory function as such. Therefore, nasal congestion is discussed below as a symptom of a cardiovascular response.

No studies were located regarding respiratory effects in animals after dermal exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, application of 2,000 mg/kg/day of propylene glycol dinitrate to the skin of rabbits for 2 hours/day for 20 days resulted in rapid and shallow breathing (Jones et al. 1972). This effect was apparently not associated with pulmonary damage because histopathologic examination of the lungs of the animals at the termination of exposure found no pathologic alterations, but was probably related to development of methemoglobinemia.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. However, cardiovascular effects have been associated with exposure to Otto Fuel II.

Symptoms identified with nitrate-induced vasodilation or compensatory vasoconstriction have been observed in studies examining human exposure to Otto Fuel II. For example, symptoms that were experienced either frequently or occasionally by 87 torpedo maintenance workers with 1-132 months (average of 47 months) of exposure to Otto Fuel II included headache (65%) and nasal congestion (31%) (Horvath et al. 1981). However, it was not reported whether the incidence of these symptoms was greater than in the controls. Workers at an incinerator at which Otto Fuel II was burned reported that they were able to identify exposures to Otto Fuel II by its characteristic vasodilatory headache (ATSDR 1990). Labile blood pressures were also recorded in the incinerator workers. However, this effect cannot be directly attributed to Otto Fuel II exposure because only 10% of the waste handled at the facility was Otto Fuel II.

Ten percent of the torpedo maintenance workers also reported experiencing palpitations and 4% reported experiencing chest pain. Although it was not stated whether the incidence of these symptoms was greater than in controls, a study of 1,352 Naval torpedoman's mates with potential exposure to Otto Fuel II demonstrated a significantly greater incidence of hospitalizations for myocardial infarctions or angina pectoris than 14,336 unexposed torpedoman's mates or 29,129, unexposed fire control technicians (Forman et al. 1987). Chest pain and tightness were also reported by several of the incinerator workers, and one worker was diagnosed with nitrate withdrawal angina (ATSDR 1990). However, because of the large number of wastes handled at the facility, other possible causative agents for these cardiac symptoms cannot be eliminated.

No studies were located regarding cardiovascular effects in animals after dermal exposure to Otto Fuel II or two of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, a single application of 50 mg/kg of propylene glycol dinitrate in corn oil to the skin of rats resulted in a 7-mm Hg fall in blood pressure (Clark and Litchfield 1969). It is unclear whether the decrease in blood pressure is statistically significant. Similar drops in blood pressure were reported in a recent study in which anesthetized rats were applied a wide range of doses (5-450 mg/kg) of propylene glycol dinitrate (Godin et al. 1993). It must be mentioned, however, that the magnitude of the fall in blood pressure was not dose-related. Exposure of rabbits to propylene glycol dinitrate for 2 hours/day for 20 days resulted in the appearance of myocardial degeneration in some rabbits (Jones et al. 1972). It was not specified at which dose (1,000, 2,000, or 4,000 mgkg) this effect was observed, but it is assumed that it was present at 4,000 mg/kg/day.

Hematological Effects. No studies were located regarding hematoiogical effects in humans after dermal exposure to Otto Fuel II or its components.

No studies were located regarding hematological effects in animals after dermal exposure to 2-nitrodiphenylamine and dibutyl sebacate. However, hematotoxicity was observed in animals following derrnal exposure to Otto Fuel II or propylene glycol dinitrate.

A brownish discoloration of the blood was observed at necropsy in pregnant rats that died following application of 4,000 mg/kg/day of Otto Fuel II to the skin during gestation days 6-15 (Cooper et al. 1993). This discoloration was attributed by the authors to be due to methemoglobinemia because a blood sample taken from one of the moribund animals had a methemoglobin level of 56.7%.

Application of 1,000 mg/kg/day propylene glycol dinitrate to the skin of rabbits for 2 hours/day, for 20 days, resulted in a transient decrease in hemoglobin (Jones et al. 1972). A transient decrease in hematocrit was observed in rabbits receiving 2,000 mg/kg/day in this study. At 2,000 mg/kg, rabbits appeared cyanotic and internal organs appeared dark blue-gray in color. At the highest concentration tested, 4,000 mg/kg/day, methemoglobin levels were elevated to 34.5%.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate. “Seronegative arthritis” was diagnosed in several workers from an incinerator at which 10% of the material burned was Otto Fuel II (ATSDR 1990). However, because of the large number of other wastes processed at the facility, the arthritis cannot be ascribed to Otto Fuel II exposure with any certainty.

No studies were located regarding musculoskeletal effects in animals after dermal exposure to Otto Fuel II or its components.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate. However, transient elevations in unspecified parameters assessing liver function were noted in several incinerator workers at a facility at which approximately 10% of the waste handled was Otto Fuel II (ATSDR 1990). However, because the other wastes incinerated included a number of solvents, this effect cannot be definitively attributed to Otto Fuel II.

No studies were located regarding hepatic effects in animals after dermal exposure to Otto Fuel II and its components, 2-nitrodiphenylamine and dibutyl sebacate. However, hepatic effects were noted in studies in which animals received dermal applications of propylene glycol dinitrate.

Degenerative changes were observed in the livers of rabbits that died after six applications of 4,000 mg propylene glycol dinitrateikg (Jones et al. 1972). The investigators also indicated that liver oxygen uptake rates and serum proteins, alkaline phosphatase, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, isocitrate dehydrogenase, and lactate dehydrogenase were not affected by propylene glycol dinitrate application, but the dose levels referred to (1,000, 2,000, or 4,000 mg propylene glycol dinitrate/kg) were unclear.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to Otto Fuel II or its components.

No studies were located regarding renal effects in animals after dermal exposure to Otto Fuel II or twc of its components, 2-nitrodiphenylamine and dibutyl sebacate. However, vacuolar changes were reported in the epithelial cells of the proximal convoluted tubules of the kidneys in a study in which 1,000, 2,000, or 4,000 mg/kg propylene glycol dinitrate was applied to the skin of rabbits for 2 hours/day for 20 days (Jones et al. 1972). However, the doses at which this effect was observed were not reported.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to propylene glycol dinitrate or 2-nitrodiphenylamine.

Eczema, dermatitis with macropapular rashes, and sweating with no apparent cause were also reported among incinerator workers at a facility at which Otto Fuel II made up approximately 10% of the waste material processed (ATSDR 1990). However, other materials processed at the incinerator could have been responsible for these effects.

Application of undiluted dibutyl sebacate (dosage not reported) to abraded skin of volunteers for an unspecified period of time was not irritating (Askarova and Muryseva 1975). Application of dibutyl sebacate (dosage not reported) to the skin of volunteers for 48 hours also resulted in no irritation (Mallette and Von Haam 1952b). No sensitization was observed when the subjects in the latter study were reexposed 2 weeks later.

Animal studies were located regarding dermal effects in animals after dermal exposure to Otto Fuel II and each of its individual components.

Moderate erythema was observed at the application site of pregnant female rats that received a daily dose of 4,000 mg/kg/day of Otto Fuel II for 10 days (Cooper et al. 1993). In addition, marked erythema was observed at the application site of pregnant female rabbits that received a daily dose of 1,000 mg/kg/day of Otto Fuel II for 13 days (Cooper et al. 1993).

No skin irritation was observed 24 or 72 hours after a single application of an unspecified amount of propylene glycol dinitrate to the skin of rabbits (Jones et al. 1972). Repeated application of 1,000 mg/kg/day to the skin of rabbits for 2 hours/day for 20 days resulted in slight erythema and roughening of the skin that cleared up 5 days after the final application (Jones et al. 1972). At 2,000 mg/kg/day, the skin appeared slightly wrinkled and scaly at the end of the exposure period.

Slight irritation was observed following application of an unspecified dose of dibutyl sebacate to the skin of rabbits and guinea pigs (Komarova 1976, 1979). However, no experimental details were provided in this report. No skin irritation was observed in rabbits following application of an unspecified concentration of dibutyl sebacate to the skin for 48 hours (Mallette and Von Haam 1952b). Reexposure 2 weeks later resulted in no sensitization.

Also, no irritation was reported following application of an unspecified amount of 2-nitrodiphenylamine to the skin of rabbits (American Cyanamid 1982). (This information was obtained from a Material Safety Data Sheet on 2-nitrodiphenylamine. Because the actual study was unavailable for review, this lack of irritation could not be verified.)

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to 2-nitrodiphenylamine or dibutyl sebacate.

Occupational exposure to Otto Fuel II resulted in approximately 26% of the 87 workers interviewed complaining of eye irritation as an occasional or frequent exposure-related effect (Horvath et al. 1981). However, the incidence of this effect relative to the control population was not reported. Eye irritation was also a common complaint among incinerator workers at a facility at which Otto Fuel II made up approximately 10% of the waste material processed (ATSDR 1990). However, other materials processed at the incinerator could have been responsible for these effects.

One out of 12 volunteers exposed to 0.2 ppm propylene glycol dinitrate for 8 hours experienced eye irritation, and 8 out of 8 had frank eye irritation after 40 minutes of exposure to 1.5 ppm propylene glycol dinitrate (Stewart et al. 1974). In the same study, no eye irritation was reported in nine subjects exposed to 0.2 ppm propylene glycol dinitrate 8 hours/day for 5 days (Stewart et al. 1974).

Data in animals are limited to propylene glycol dinitrate and 2-nitrodiphenylamine. Conjunctival redness was observed 5 minutes after an unspecified dose of propylene glycol dinitrate was instilled into the eyes of rabbits (Jones et al. 1972). The irritation disappeared within 24 hours. No effects on the cornea or iris were observed.

Also, no irritation was reported following application of an unspecified amount of 2-nitrodiphenylamine to the eyes of rabbits (American Cyanamid 1982). (This information was obtained from a Material Safety Data Sheet on 2-nitrodiphenylamine. Because the actual study as unavailable for review, this value could not be verified.)

Body Weight Effects. The only information regarding body weight effects after dermal exposure to Otto Fuel II or its components is that provided by Cooper et al. (1993) who reported significant decreases in body weight gain in both rats and rabbits after repeated applications of Otto Fuel II to the skin during pregnancy (400 mg/kg/day to rats, 100 mg/kg/day to rabbits). However, food consumption data were not provided.)

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after dermal exposure to propylene glycol dinitrate and 2-nitrodiphenylamine. However, sensitization was tested following dermal exposure to dibutyl sebacate and immunological effects (possibly related to Otto Fuel II exposure) were reported.

No skin sensitization was observed in volunteers exposed to an unspecified amount of 100% dibutyl sebacate 2 weeks following an initial 2-day dermal exposure (Mallette and Von Haam 1952b). However, in workers exposed to lubricants containing dibutyl sebacate, a 3.3% rate of sensitization was observed when nonirritating concentrations of dibutyl sebacate were applied to their skin (Askarova and Muryseva 1975). Nonirritating concentrations were determined in volunteers with no known exposure to the lubricants or their ingredients. This study is limited, however, in that a control group was not used in the sensitization portion of the study.

A child of a worker at an incineration facility at which Otto Fuel II was processed developed asthma (ATSDR 1990). The asthma was linked to materials handled at the incinerator because when the father of the child stopped bringing his work clothing home, the child's condition improved. However, Otto Fuel II comprised only approximately 10% of the wastes handled at the facility; thus, other materials may have triggered the reaction in the child. The possibility also exists that the asthma-like response may have been caused by tetryl particles activating nerve receptors which triggered vagal reflexes inducing bronchoconstriction.

No studies were located regarding immunological effects in animals after dermal exposure to Otto Fuel II or its component, 2-nitrodiphenylamine. However, extremely limited information was located regarding immunological effects of propylene glycol dinitrate and dibutyl sebacate in animals after dermal exposure. No studies that directly examined immunological function were located. However, total and differential leukocyte counts and routine gross and histopathological examination of the spleen were normal in rabbits after application of doses as high as 4,000 mg/kg/day of propylene glycol dinitrate to the skin for 2 hours/day for 20 days (Jones et al. 1972).

No skin sensitization was observed in rabbits reexposed to an unspecified dose of 100% dibutyl. sebacate 2 weeks after a 2-day dermal application (Mallette and Von Haam 1952b).

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate.

The only reliable information regarding neurological effects in humans after dermal exposure to Otto Fuel II was found in a study examining the effects of exposure to Otto Fuel II during torpedo maintenance procedures on tests of balance and oculomotor performance (Horvath et al. 1981). Twenty-nine workers with an unspecified number of months of previous occupational exposure to Otto Fuel II were tested both before and after a typical torpedo maintenance procedure. The duration of the procedure was between 30 and 45 minutes, and both inhalation and dermal exposures were likely. The inhalation exposures ranged from 0 to 0.22 ppm, but the amount of dermal exposure was not monitored. No significant difference in the tests evaluating balance and coordination were observed when comparing pre- and postexposure results. However, a significant decrease in saccade velocity and increase in saccade delay were observed. Although these effects were reported by the authors to be functionally insignificant, they were proposed as evidence of preclinical neurological effects of Otto

Fuel II exposure. Eighty-seven torpedo maintenance workers were also questioned regarding effects experienced during past exposures. Dizziness was reported by 13% of the workers and loss of balance was reported by 1% of the workers; however, the incidence of these effects was not compared to that in an unexposed control group.

Workers at an incinerator where Otto Fuel II comprised approximately 10% of the waste materials processed, were diagnosed with a number of neurological disorders (ATSDR 1990). These included mood disorders, cerebellar dysfunction (ataxia, tremor, nystagmus), cognitive disorders, memory loss, and possible vestibular dysfunction. Magnetic resonance imaging showed that two of the four workers, interviewed in the report had cerebellar and cortical atrophy. However, the effects observed cannot be attributed to Otto Fuel II with certainty because a large number of solvents and other wastes were also handled at the incinerator. It is also unclear from the report whether the individuals that were examined represented a substantial percentage of the workers that were exposed to Otto Fuel II.

Headaches have frequently been reported by workers occupationally exposed to Otto Fuel II (Horvath et al. 1981). However, the headaches are most likely associated with meningeal blood vessel dilation (Nickerson 1975) (see also Cardiovascular Effects in Section 2.2.3.2).
No studies were located regarding neurological effects in animals after dermal exposure to Otto Fuel II or its components, 2-nitrodiphenylamine or dibutyl sebacate. Extremely limited information was obtained regarding possible neurological effects resulting from dermal application of propylene glycol dinitrate. Weakness was observed in rabbits after the third 2-hour/day application of 2,000 mg/kg/day of propylene glycol dinitrate to the skin (Jones et al. 1972). The animals had recovered by the 20th daily application. However, it is not known whether the weakness that was observed was neurological in origin. The gross and histopathological examination of sections of brain and spinal cord showed no adverse structural effects of propylene glycol dinitrate on these tissues.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to Otto Fuel II or any of its individual components.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate. However, a child with multiple birth defects was born to the wife of a worker at an incinerator where Otto Fuel II comprised approximately 10% of the waste processed (ATSDR 1990). The defects included club foot, imperforate anus, renal anomalies, and persistence of the cloaca. Chromosomal studies on the child were normal. The birth defects cannot be definitively ascribed to exposure to Otto Fuel II because other possible causes for the defects exist (i.e., exposure to other developmental toxicants) and the incidence of similar defects in a control population were not adequately characterized.

No studies were located regarding developmental effects in animals after dermal exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate.

Rat pups from dams receiving daily dermal applications of 2,000 mg/kg/day of Otto Fuel II during gestation days 6-15 had decreased body weight when compared to pups from control rats (Cooper et al. 1993). At 4,000 mg/kg/day, an increase in the number of resorptions, decrease in the number of viable pups, and decreases in pup weight were observed. Decreased maternal body weights were observed among dams at 2,000 and 4,000 mg/kg/day indicating maternal toxicity at these doses. Discoloration of the blood, likely due to methemoglobinemia, was observed in dams at the 4,000 mg/kg/day dose. No developmental toxicity was observed in pups from dams at doses where no maternal toxicity was evident. No increase in visceral or skeletal abnormalities was observed at any dose. No developmental toxicity was observed at doses as high as 1,000 mg/kg/day in rabbits that received daily dermal applications of Otto Fuel II during gestation days 6-18 (Cooper et al. 1993).

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to Otto Fuel II or its components.
Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were Located regarding cancer in humans or animals after dermal exposure to Otto Fuels XI or its components.

2.3 TOXICOKINETICS

Otto Fuel II is a mixture of three components. Discussion of the toxicokinetics of Otto Fuel II is directed specifically at the toxicokinetics of the individual components of Otto Fuel II. This has been done because the individual components of Otto Fuel II, and not the mixture itself, are subject to absorption, distribution, metabolism, and excretion by the body based upon their individual physical and chemical characteristics.

Data regarding the toxicokinetics of the components of Otto Fuel II in humans are limited to a single study in volunteers exposed to propylene glycol dinitrate by the inhalation route. These data provide qualitative evidence that propylene glycol dinitrate may be absorbed in humans by this route. There are no data regarding oral or dermal absorption of 2-nitrodiphenylamine or dibutyl sebacate in humans. There is qualitative evidence that animals can absorb propylene glycol dinitrate after inhalation, oral, and dermal exposure, and also, that animals can absorb 2-nitrodiphenylamine and dibutyl sebacate after oral exposure. The mechanisms by which the components of Otto Fuel II are transported to the tissues are unknown. There are no data regarding distribution patterns for the components of Otto Fuel II or their metabolites in humans or animals. No information is available regarding the metabolism of the components of Otto Fuel II in humans. In animal studies, limited data suggest that propylene glycol dinitrate undergoes enzymatic reduction to the mononitrates and nitrite, with the subsequent formation of inorganic nitrate. No data were available for 2-nitrodiphenylamine or dibutyl sebacate. There is no information on how 2-nitrodiphenylamine or dibutyl sebacate or their potential metabolites are excreted in humans or animals. Qualitative information indicates that humans may excrete unchanged propylene glycol dinitrate in expired air after inhalation exposure and that urinary nitrate may represent a major excretion for propylene glycol dinitrate in animals after dermal exposure. The mechanism of 2-nitrodiphenylamine or dibutyl sebacate toxicity is unknown. The toxicity of propylene glycol dinitrate is related to its vasodilating properties and its methemoglobin forming capacity in the red blood cells.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located that examined the absorption of the nonvolatile components of Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate, in humans after inhalation exposure.

Limited information exists regarding absorption of the Otto Fuel II component, propylene glycol dinitrate, in humans as a result of inhalation exposures. Less than 5 ppb (limit of detection of the method) of propylene glycol dinitrate were measured in the blood of volunteers during a 3.2-hour exposure to test atmospheres containing 1.5 ppm propylene glycol dinitrate (Stewart et al. 1974), indicating that absorption occurs during inhalation exposures.

No studies were located that examined the absorption of two of the components of Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate, in animals after inhalation exposure.

Data are also extremely limited regarding absorption of the Otto Fuel II component, propylene glycol dinitrate, in animals as a result of inhalation exposures. Exposure of monkeys to concentrations of 1.6 ppm and 4.2 ppm of propylene glycol dinitrate for 20 and 14 days, respectively, resulted in the detection of small amounts of propylene glycol dinitrate in plasma (Mattsson et al. 1981). During exposures to 1 .6 ppm, 35 ug/mL propylene glycol dinitrate was detected in plasma, and during exposures at 4.2 ppm, 170 ug/mL was detected in plasma.

2.3.1.2 Oral Exposure

No studies were located that examined the absorption of the components of Otto Fuel II, propylene glycol dinitrate, 2-nitrodiphenylamine, dibutyl sebacate, in humans after oral exposure.
No quantitative data regarding oral absorption of the components of Otto Fuel II, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate, were located. However, all three components have been demonstrated to cause some measure of toxicity after ingestion (American Cyanamid 1982; Andersen and Mehl 1979; Clark and Litchfield 1969; Jones et al. 1972; Smith 1953), indicating some gastrointestinal absorption.

2.3.1.3 Dermal Exposure

No studies were located that examined the absorption of the components of Otto Fuel II, propylene glycol dinitrate, 2-nitrodiphenylamine, dibutyl sebacate, in humans after dermal exposure.

Also, no studies were located that either directly or indirectly examined the absorption of two of the components of Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate, in animals after dermal exposure. Information supporting the dermal absorption of propylene glycol dinitrate was obtained from studies demonstrating systemic toxicity after dermal exposure in rats (Clark and Litchfield 1969) and rabbits (Jones et al. 1972) and from a recent study which attempted to quantify absorption in rats (Godin et al. 1993). For example, a transient decrease in hemoglobin was observed following dermal application of doses of propylene glycol dinitrate as low as 1,000 mg/kg/day, 2 hours/day, for 20 days to rabbits (Jones et al. 1972). Also, observation of elevated levels of the metabolite nitrate in the urine of rabbits receiving a dermal dose of 4,000 mg/kg/day supported the absorption of propylene glycol dinitrate after dermal exposure (Jones et al. 1972). In a recent study in rats (Godin et al. 1993), dermal absorption of propylene glycol dinitrate was estimated as the difference between the amount of compound applied and the amount that could be later extracted from the skin. It should be noted, however, that this difference may not necessarily indicate absorption since local metabolism may occur. The authors found that, in general, absorption was inversely related to the amount applied, such that 75% of a 5 mg/kg dose was presumably absorbed, whereas only 20% of a 450 mg/kg dose was absorbed.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Extremely little information is available regarding the distribution of the components of Otto Fuel II following inhalation exposure in humans. No information was located regarding the distribution of 2-nitrodiphenylamine or dibutyl sebacate. The only information located regarding the distribution of propylene glycol dinitrate in humans was the observation that propylene glycol dinitrate could be measured in the blood of volunteers during inhalation exposures to propylene glycol dinitrate volatilized from Otto Fuel II (Stewart et al. 1974).

Similarly, no information was located regarding the distribution of 2-nitrodiphenylamine or dibutyl sebacate in animals after inhalation exposure. Also, no information was located regarding a differential distribution of propylene glycol dinitrate in animals after inhalation exposure. The only information located regarding the distribution of propylene glycol dinitrate in animals was the observation that propylene glycol dinitrate could be measured in plasma of monkeys during inhalation exposures to concentrations of 1.6 and 4.2 ppm (Mattsson et al. 1981). In vitro studies using dog blood have shown that propylene glycol dinitrate preferentially associates with red blood cells in the blood (Air Force 1982b). The ratio of propylene glycol dinitrate in red blood cells versus plasma was 2.12.

2.3.2.2 Oral Exposure

No information was located regarding the distribution of the components of Otto Fuel II in humans or animals after oral exposure.

2.3.2.3 Dermal Exposure

No information was located regarding the distribution of the components of Otto Fuel II in humans or animals after dermal exposure.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

No information was located regarding the metabolism of the components of Otto Fuel II in humans after inhalation exposure.

No studies were located that examined the metabolism of either 2-nitrodiphenylamine or dibutyl sebacate in animals after inhalation exposure. Also, no studies were located that followed the metabolism of propylene glycol dinitrate in animals after inhalation exposure. The only information relating to the metabolism of propylene glycol dinitrate after inhalation exposure was the observation of elevated blood levels of inorganic nitrate, a metabolic product of propylene glycol dinitrate, in dogs and monkeys exposed to 35 ppm for 24 hours/day for 90 days (Jones et al. 1972). Nitrate is not specific to propylene glycol dinitrate, however; thus, an increase in urinary nitrates is not specific for propylene glycol dinitrate exposure.

2.3.3.2 Oral Exposure

No information was located regarding the metabolism of the components of Otto Fuel II in humans or animals after oral exposure.

2.3.3.3 Dermal Exposure

No information was located regarding the metabolism of the components of Otto Fuel II in humans or animals after dermal exposure.

2.3.3.4 Other Routes of Exposure

No information was located on the metabolism of the components of Otto Fuel II in humans exposed by other routes.

Also, no information was located on the metabolism of 2-nitrodiphenylamine in animals exposed by other routes. The metabolism of propylene glycol dinitrate has been studied in animals after parenteral administration (Clark and Litchfield 1969). Subcutaneous injection of 65 mg/kg propylene glycol dinitrate in rats caused a rapid increase in blood levels of propylene glycol dinitrate. Peak blood levels of propylene glycol dinitrate were observed within 1 hour and then were observed to decline to zero by 8-12 hours postinjection. Appearance of metabolites of propylene glycol dinitrate in the blood was maximal 2-4 hours postinjection and had declined to essentially zero by 8-12 hours postinjection. The predominant metabolite observed in the blood was nitrate, with propylene glycol 2-mononitrate observed at approximately one-half the concentration of inorganic nitrate. The levels of propylene glycol 1-mononitrate and inorganic nitrite were less than half that of propylene glycol 2-mononitrate. Similar results have been reported in rats after intravenous injection of 0.1-30 mg propylene glycol dinitrate/kg (Godin et al. 1994). In that study, maximum concentration of metabolites (propylene glycol 2-mononitrate and propylene glycol I-mononitrate) in blood was achieved 10 minutes after the injection. Elimination of the parent compound from blood was monoexponential. For doses of 0.3, 3, and 30 mg/kg, the elimination half-time of propylene glycol dinitrate was 8.8, 13.1, and 17.4 hours, respectively. Rapid metabolism of propylene glycol dinitrate *in vitro* has also been observed. Incubation of propylene glycol dinitrate in rat blood resulted in degradation of approximately half of the propylene glycol dinitrate by 60 minutes and degradation of half of the remainder by 120 minutes (Clark and Litchfield 1969). Levels of inorganic nitrate and the mononitrates increased with time, but only small amounts of inorganic nitrite were observed. The breakdown of propylene glycol dinitrate *in vitro* was shown to occur primarily in the erythrocytes, as no degradation in purified plasma was observed (Clark and Litchfield 1969). In contrast with the *in vivo* situation, however, the mononitrates were stable and did not undergo further degradation. Based on these observations and their study of the metabolism of ethylene glycol dinitrate (Clark and Litchfield 1967) the study authors proposed the following metabolic, scheme (Figure 2-4): A nitrate group of propylene glycol dinitrate could be reduced to give an organic nitrite-nitrate, followed by hydrolysis to yield the mononitrate and inorganic nitrite. The inorganic nitrite in the blood could then be oxidized to inorganic nitrate. The authors suggested that the predominance of the 2-isomer in the blood may have been due to either its more rapid formation or the more rapid degradation of the 1-isomer.

The only information regarding metabolism of dibutyl sebacate was an *in vitro* analysis in which dibutyl sebacate was added to a preparation of pancreatic lipase (Smith 1953). Hydrolysis of dibutyl sebacate in the lipase preparation was reported to occur more rapidly than the hydrolysis of triolein, causing the author to speculate that dibutyl sebacate is metabolized in the body by the same pathways used in normal fat metabolism. No other information on the metabolism of dibutyl sebacate was located.

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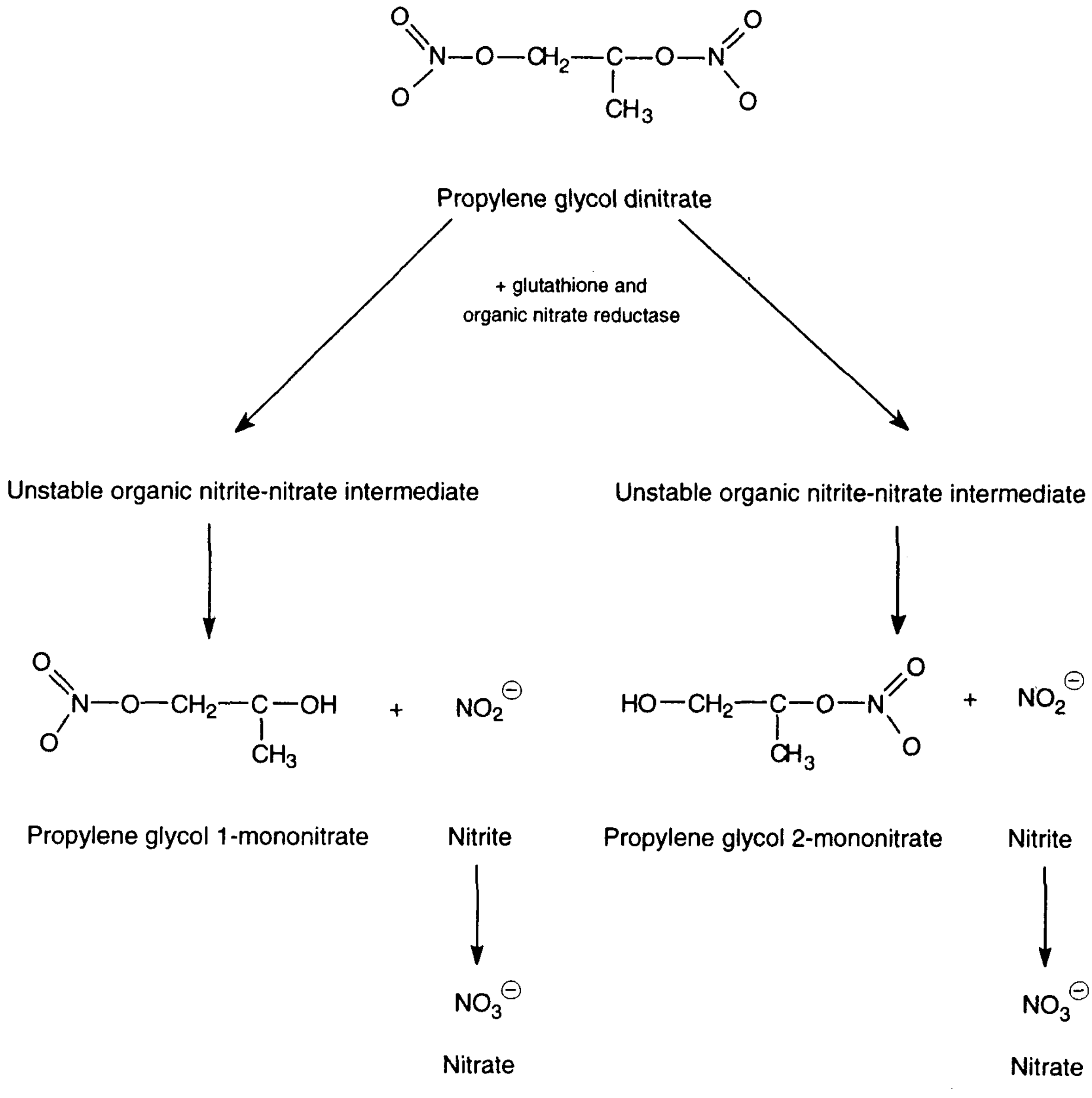
2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located that examined the excretion of 2-nitrodiphenylamine or dibutyl sebacate in humans after inhalation exposure.

Alveolar breath samples taken from volunteers during and after exposure to 1.5 ppm propylene glycol dinitrate demonstrated the short duration of excretion of this chemical in expired air (Stewart et al. 1974). During exposure, alveolar breath samples contained between 20 and 35 ppb propylene glycol dinitrate. By 5 minutes after the termination of exposure, only between 1 and 5 ppb of propylene

FIGURE 2-4. Proposed Metabolic Pathway for Propylene Glycol Dinitrate *



As proposed by Clark and Litchfield 1969 glycol dinitrate were found in expired air. No measurable propylene glycol dinitrate was found in expired air I5 minutes after the termination of exposure. No information on other routes of excretion of propylene glycol dinitrate in humans was located.

No studies were located that examined the excretion of any of the components of Otto Fuel II in animals after inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located that examined the excretion of any of the components of Otto Fuel II in humans or animals after oral exposure.

2.3.4.3 Dermal Exposure

No studies were located that examined the excretion of any of the components of Otto Fuel II in humans after dermal exposure.

No studies were located regarding the excretion of 2-nitrodiphenylamine or dibutyl sebacate in animals after dermal exposure. Only extremely limited informaticq was found regarding excretion of propylene glycol dinitrate in animals after dermal exposure. One study reported that excretion of nitrate in the urine of rabbits exposed to 4,000 mg/kg/day for 2 hours/day for 20 days accounted for approximately 7% of nitrate in the propylene glycol dinitrate that had been applied (Jones et al. 1972). Because excess propylene glycol dinitrate was wiped off each day at the end of the 2-hour exposure period, the excretion of nitrate relative to the applied dose of propylene glycol dinitrate is unknown.

2.3.4.4 Other Routes of Exposure

No information was located on the excretion of the components of Otto Fuel II in humans exposed by other routes.

No information was located on the excretion of 2-nitrodiphenylamine or dibutyl sebacate in animals exposed by other routes. Subcutaneous injection of a dose of 65 mg propylene glycol dinitrate/kg in the rat resulted in rapid excretion of unmetabolized propylene glycol dinitrate and its metabolites in the urine (Clark and Litchfield 1969). Urinary excretion of propylene glycol dinitrate and its metabolites was essentially complete within 24 hours. Inorganic nitrate was the major metabolite excreted in the urine, accounting for approximately 56% of the nitrate in the injected dose. Unmetabolized propylene glycol dinitrate and other metabolites were present in the urine in amounts less than 0.5% of the injected dose. Excretion of unmetabolized propylene glycol dinitrate in the urine accounted for less than 1% of an intravenous dose (Air Force 1982b). In addition, less than 1% of a dose of propylene glycol dinitrate administered intravenously was excreted unchanged in expired air (Air Force 1982b). The major means of elimination of propylene glycol dinitrate from the blood was by metabolism through stepwise removal of nitrate radicals. The rate constant for elimination by metabolism was estimated as 0.895 min-1 (Air Force 1982b).

2.3.5 Mechanisms of Action

No information was located regarding the mechanism by which propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate enter the blood stream from the lungs, skin, or gastrointestinal tract. The mechanism of propylene glycol dinitrate toxicity is related to its vasodilating capacity. Propylene glycol dinitrate is an organic nitrate and shares many of the cardiovascular properties of therapeutic nitrates such as nitroglycerin, which is widely used for the symptomatic treatment of angina pectoris (Nickerson 1975). Organic nitrates induce peripheral vasodilation, decreased ventricular ejection time, relaxation, and a longer period of coronary blood flow. One of the earliest consequences of overexposure to propylene glycol dinitrate (or to Otto Fuel II) is a vasodilation of the cerebral vessels, which is believed to be the major factor in the development of the typical “trinitrotoluene” headache. Should the overexposure be more severe, the relaxation of the vascular smooth muscle can result in a fall in blood pressure followed by a compensatory vasoconstriction (Abrams 1980). However, a decrease in the magnitude of the vasodilating effect has been observed after repeated exposure to organic nitrates. Although the exact mechanism of initiation and maintenance of tolerance to organic nitrates is not known, several possibilities have been suggested, including depletion of sulfhydryl groups at the receptor sites, reduced availability or activity of the active intermediate S-nitrosothiol, and altered pharmacokinetics leading to decreased nitrate concentration in vascular tissues (Parker 1985). Massive overexposure to propylene glycol dinitrate can produce toxic levels of methemoglobin. This property is shared by many organic and inorganic nitrates and also by aromatic amines, 2-nitrodiphenylamine among them (Beard and Noe 1981; Donovan 1990; Ellenhom and Barceloux 1988). Methemoglobinemia is defined as a methemoglobin concentration of greater than 1%, and it results from iron in the normal ferrous state being oxidized to the ferric state at a rate that exceeds the erythrocyte's reducing capacity. Methemoglobin is unable to combine reversibly with oxygen and carbon dioxide and also causes a shift in the oxygen dissociation curve toward increased oxygen affinity, preventing the transfer of oxygen from the blood to the tissues. The possible mechanism of dibutyl sebacate toxicity is not known.

2.4 RELEVANCE TO PUBLIC HEALTH

Exposure to Otto Fuel II may occur by the inhalation, oral, or dermal routes. The only component of Otto Fuel II with significant volatility is propylene glycol dinitrate. Thus, inhalation exposures to Otto Fuel II would consist primarily of inhalation exposure to propylene glycol dinitrate. Oral exposures to all three components as well as the mixture, Otto Fuel II, are possible through consumption of contaminated water. Information was located that indicated that propylene glycol dinitrate and 2-nitrodiphenylamine are released into waste water effluent streams from plants manufacturing and/or using these substances as a military propellant. It is unknown whether oral exposure to propylene glycol dinitrate and 2-nitrodiphenylamine may occur through consumption of contaminated food products because extremely limited data are available on their presence in food products or their bioaccumulation, biomagnification, or biodegradation. It is likely that significant ingestion of dibutyl sebacate may occur as a result of its civilian use in food packaging materials and as a flavor enhancer in ice cream, candy, baked goods, and non-alcoholic beverages. It is unknown to what extent dermal exposure to Otto Fuel II and its components is likely through contact with contaminated soils because information on the extent of soil contamination, leaching, and/or soil adsorption of these substances was not located. Limited information was also located regarding the degradation of the components in the environment, but the available data indicate that degradation would occur fairly rapidly (i.e., within days), It is likely that dermal contact with dibutyl sebacate may be significant as a result of the civilian use of this substance (as a lubricant in shaving lotions).

The group with the greatest likelihood of exposure to Otto Fuel II consists of persons with occupational exposure to torpedo propellants as this is the predominant use of Otto Fuel II. Information on the effects that occur in humans comes from studies of workers occupationally exposed to Otto Fuel II and from experimental exposures of humans to propylene glycol dinitrate and dibutyl sebacate. These studies indicate that short-term exposure to Otto Fuel II may result in headache, loss of balance, poor eye-hand coordination, eye irritation, and dizziness, and that propylene glycol dinitrate is probably the component of Otto Fuel II responsible for these effects. Studies of longer-term exposure suggest that humans may experience an increased incidence of angina and myocardial infarctions.

For the most part, studies in animals support the observation of these toxic effects. In addition, animal studies indicate that methemoglobinemia, degenerative hepatic and renal effects, and developmental toxicity (at maternally toxic doses) may occur.

Minimal Risk Levels for Otto Fuel II and Its Components.

Inhalation MRLs.

- An MRL of 0.003 ppm has been derived for acute inhalation exposure (14 days or less) to propylene glycol dinitrate.

The acute inhalation MRL was based on a NOAEL for altered visual evoked responses in volunteers exposed to concentrations ranging from 0.03 to 1.5 ppm for 1-8 hours (Stewart et al. 1974). At 0.2 ppm 7 of 9 subjects reported headaches. The change in visual evoked response was duration-related indicating a cumulative effect. Exposure to 0.5 ppm for 8 hours resulted in nausea, dizziness, and more markedly altered visual evoked responses. These results are supported by other studies in humans (Horvath et al. 198 1) and studies in monkeys (Mattsson et al. 1981).

- An MRL of 0.00004 ppm has been derived for intermediate inhalation exposure (15-364 days) to propylene glycol dinitrate.

The intermediate inhalation MRL was based on a LOAEL for hematological changes in dogs exposed to 0.2 ppm propylene glycol dinitrate intermittently for 14 months (Air Force 1985a). As early as 4 weeks into the study, significantly decreased hematocrit, hemoglobin, red blood cells, and reticulocytes were observed, and by exposure day 44, significantly increased methemoglobin levels were observed. No other exposure level was tested. These results are supported by human data (Donovan 1990), and also by studies in other animal species, such as guinea pigs, rats, and monkeys (Jones et al. 1972).

- An MRL of 0.00004 ppm has been derived for chronic inhalation (365 days or more) to propylene glycol dinitrate.

The chronic inhalation MRL was based on a LOAEL for hematological changes in dogs exposed to 0.2 ppm propylene glycol dinitrate intermittently for 14 months (Air Force 1985a). Significant hematological changes, such as decreased hematocrit, hemoglobin, red blood cells, and reticulocytes, and increased in methemoglobin concentration were observed before the seventh week of exposure. These effects persisted at the termination of the study at 14 months. Methemoglobinemia was also reported in rats exposed to propylene glycol dinitrate for 1 year (Air Force 1985a).

Inhalation MRLs were not derived for Otto Fuel II due to lack of proper exposure characterization in the human studies and lack of animal data. Inhalation MRLs were not derived for 2-nitrodiphenylamine, or dibutyl sebacate due to both lack of human and animal data.

Oral MRLs.
No oral MRLs were derived for Otto Fuel II or its components due to lack of adequate human and animal data. An intermediate and a chronic duration study were identified for oral exposure to dibutyl sebacate (Smith 1953); however, the fact that this early study represents the only existing information on dibutyl sebacate precludes its use as the basis for MRLs.

Dermal MRLs were not derived because of the lack of an appropriate methodology for doing so.

Death. No studies were located that reported deaths in humans attributable to exposure to Otto Fuel II or any of its components. Studies in animals indicate that there are species differences in lethality of propylene glycol dinitrate by the inhalation route. Rabbits appear most sensitive with deaths reported after continuous exposure to concentrations as low as 35 ppm (Jones et al. 1972). Animal studies also indicate that propylene glycol dinitrate is the most toxic component of Otto Fuel II following exposure by the oral route. Oral LD,, values in rats for propylene glycol dinitrate ranged from 250 to I, 190 mg/kg (Andersen and Mehl 1979; Clark and Litchfield 1969; Jones et al. 1972), whereas the oral LD,, values in rats for 2-nitrodiphenylamine and dibutyl sebacate were 6,150 (Army 1979) and 17,200 mg/kg (Komarova 1976, 1979), respectively. Comparison of the dermal lethality of the individual components of Otto Fuel II in rabbits is not as straightforward because of differing durations of exposure and incomplete information on the doses applied; however, the same hierarchy of toxicity appears to hold (Army 1979; Jones et al. 1972; Mallette and Von Haam 1952b). Very limited information is available on the cause of death in these studies, but symptoms observed in propylene glycol dinitrate-treated animals prior to death are consistent with methemoglobin-induced anoxia (Jones et al. 1972).

Although environmental data are limited, based on the potentially rapid degradation of the components of Otto Fuel II and the high doses necessary to cause death, it is unlikely that propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate levels near hazardous waste sites are sufficient to cause death in exposed populations.

Systemic Effects.

Respiratory Effects. A small percentage of workers with occupational exposure to Otto Fuel II have reported experiencing dyspnea during occupational exposure to this substance (Horvath et al. 1981); however, the majority of animal studies have not reported similar effects, and those that have, do not clearly demonstrate the cause for this symptom. Application of a large concentration of propylene glycol dinitrate to the ‘skin of rabbits (2,000 mg/kg/day) has been reported to cause rapid and shallow breathing (Jones et al. 1972), but examination of the respiratory system at necropsy did not reveal any abnormalities that might account for the change in breathing pattern. Chronic inhalation exposure of rats to 35 ppm propylene glycol dinitrate resulted in microscopic evidence of slight respiratory irritation (mild degeneration of the nasal epithelium and very slight pulmonary inflammation) (Air Force 1985a); however, it is unlikely that these findings are associated with the dyspnea reported by exposed workers. Dyspnea has been reported to be a common finding in patients with clinically significant methemoglobinemia (see Hematological Effects below) (Bronstein and Currance 1988); thus, the dyspnea described in the above reports may have been associated with methemoglobinemia. The combined results of these studies indicate that sensitive members of exposed populations near hazardous waste sites may experience difficulty breathing when exposed to sufficiently high concentrations, but the cause of this effect remains unknown.

Cardiovascular Effects. The major component of Otto Fuel II, propylene glycol dinitrate, is an organic nitrate and shares many of the cardiovascular properties of therapeutic nitrates such as amyl nitrate and nitroglycerin. The primary cardiovascular action of the therapeutic nitrates is to relax vascular smooth muscle resulting in a fall in blood pressure. Under normal conditions, this decrease in blood pressure is counteracted by a reflex vasoconstriction and increase in heart rate (Nicker-son 1975). Effects associated with both nitrate-induced vasodilation and compensatory vasoconstriction have been reported in studies evaluating the human response to Otto Fuel II and/or propylene glycol dinitrate exposure.

Headaches (of likely vasodilatory origin) were reported as a frequent symptom by workers exposed to Otto Fuel II (ATSDR 1990; Horvath et al. 1981) and by subjects experimentally exposed to propylene glycol dinitrate (Stewart et al. 1974). These reports *are* consistent with the reported ability of aliphatic nitrates to cause meningeal blood vessel dilation which results in a characteristic type of headache (Nickerson 1975). The earliest and most commonly encountered symptom of overexposure to propylene glycol dinitrate (or Otto Fuel II) is headache. In the study by Stewart et al. (1974), the severity and frequency of the headaches decreased with repeated exposures, indicating adaptation to the vasodilatory effects.

In studies of other aliphatic nitrates, continued adaptive vasoconstriction after removal from the source of exposure has been reported to be the cause of coronary insufficiency (Carmichael and Lieben 1963; Morton 1977). The increased incidence of angina pectoris and myocardial infarction among workers exposed to Otto Fuel II (Forman et al. 1987) indicates that compensatory vasoconstriction of the blood vessels of the heart may lead to coronary insufficiency in these workers.

Studies in animals have assessed the vasodilatory activity of propylene glycol dinitrate following exposure by the dermal route (Clark and Litchfield 1969) and following parenteral administration (Air Force 1982b; Clark and Litchfield 1969; Pharmackon 1988). These studies demonstrate that propylene glycol dinitrate causes a decrease in blood pressure that is rapidly corrected. An increase in heart rate also occurs as part of the compensatory response. Comparison of the time-course of the vasodilation with the blood levels of propylene glycol dinitrate and its metabolites indicated that propylene glycol dinitrate levels correlated most closely with the decrease in blood pressure (Clark and Litchfield 1969). Animal studies also suggest that the heart may be adversely affected by exposure to propylene glycol dinitrate. Evidence of myocardial degeneration was observed in rabbits receiving a large dermal dose of propylene glycol dinitrate (Jones et al. 1972).

These results suggest that persons exposed to sufficient concentrations of Otto Fuel II or propylene glycol dinitrate at hazardous waste sites may experience transitory vasodilation and headaches. The development of a compensatory level of vasoconstriction may also lead to coronary vasospasm in susceptible individuals.

Hematological Effects. In addition to their effects on the cardiovascular system, nitrates are also known to oxidize the heme iron molecule of hemoglobin, resulting in the formation of methemoglobin (Donovan 1990). Experimental acute-duration exposure of humans to low levels of propylene glycol dinitrate did not result in elevation of methemoglobin levels (Stewart et al. 1974). However, studies in animals demonstrated that exposure to high levels of Otto Fuel II or propylene glycol dinitrate for short periods or exposure to low levels for longer periods resulted in elevation of blood methemoglobin levels (Air Force 1982b, 1985a; Cooper et al. 1993; Jones et al. 1972).

Nitrates have also been reported to oxidize the sulfhydryl groups of the globin portion of the hemoglobin molecule resulting in hemoglobin denaturation and hemolysis (ATSDR 1991; Cotran et al. 1989). Evidence of hemolysis and phagocytosis of hemoglobin has been observed in animal studies (Air Force 1985a; Jones et al. 1972). Heavy increases in hemosiderin deposits in the spleen, liver, and kidneys were observed in rats, dogs, and monkeys following continuous inhalation exposure to moderate levels of propylene glycol dinitrate (Jones et al. 1972). Also, decreased red cell count, hemoglobin, and/or hematocrit were observed in rabbits after short-term, high-level dermal exposure (Jones et al. 1972) and dogs after long-term, low-level exposure (Air Force 1985a) to propylene glycol dinitrate.

Comparison of the susceptibility of hemoglobin from various species to oxidation by propylene glycol dinitrate revealed that human hemoglobin is relatively resistant to oxidation (Wyman et al. 1985). Therefore, it is unlikely that exposure to low levels of propylene glycol dinitrate at hazardous waste sites would result in clinically significant methemoglobinemia in most persons. However, some persons are highly susceptible to agents that oxidize hemoglobin (see also Section 2.7), and such persons may experience elevated methemoglobin levels when exposed to Otto Fuel II or propylene glycol dinitrate at hazardous waste sites. Intermediate- and chronic-duration inhalation MRLs were derived based on a study in which dogs exhibited increased methemoglobin levels and decreased red blood cells, hematocrit, and hemoglobin during intermediate-to-chronic inhalation exposures (Air Force 1985a).

Musculoskeletal Effects. Although no adverse effects on the musculoskeletal system have been identified in humans exposed to Otto Fuel II or its components, a study in rats demonstrated an increase in osteosclerosis in females chronically exposed to propylene glycol dinitrate (Air Force 1985a). No studies were available that corroborated this effect; thus, it is unknown whether it may have been incidental or exposure related. Insufficient information is available to assess the relevance of this finding to persons exposed to Otto Fuel II or propylene glycol dinitrate at hazardous waste sites.

Hepatic Effects. Studies in humans have not demonstrated adverse effects of Otto Fuel II or its components on the liver. However, studies in animals continuously exposed to moderate levels of propylene glycol dinitrate by inhalation (16-35 ppm) have demonstrated degenerative hepatocellular changes (Jones et al. 1972). Intermittent exposures to similar levels did not, however, cause such changes (Air Force 1985a). Thus, it is possible that persons continuously exposed to Otto Fuel II or propylene glycol dinitrate by virtue of their living and/or working in close proximity to a hazardous waste site may also experience some degree of hepatocellular damage.

Renal Effects. No adverse renal effects have been observed in studies of persons exposed to Otto Fuel II or its components. However, a number of animal studies have shown renal toxicity resulting from propylene glycol dinitrate exposure. Evidence of renal toxicity in these studies includes acute tubular necrosis in rats and elevated serum urea nitrogen and decreased serum alkaline phosphatase in monkeys continuously exposed to moderate levels of propylene glycol dinitrate (Jones et al. 1972); vacuolar changes in the proximal convoluted tubules of kidneys of rabbits to which a large dermal dose of propylene glycol dinitrate had been applied (Jones et al. 1972); and decreased urine production and increased red blood dells in the urine of dogs receiving an intravenous dose of 2 mg/kg of propylene glycol dinitrate (Air Force 1982b). The renal toxicity observed in these studies may be the result either one or a combination of the following causes: a direct toxic effect of propylene glycol dinitrate on the kidneys or renal toxicity resulting from the urinary excretion of massive amounts of hemoglobin resulting from hemolysis (Cotran et al. 1989) (see also Hematological Effects above). Based on the observation of renal toxicity in animals, it may be concluded that it is possible that persons exposed to sufficiently high levels of Otto Fuel II or propylene glycol dinitrate at hazardous waste sites may experience renal toxicity.

Dermal Effects. Animal studies indicate that Otto Fuel II and its components are only very slightly to moderately irritating when applied to rabbit skin (Army 1979; Cooper et al. 1993; Jones et al. 1972; Komarova 1976, 1979; Mallette and Von Haam 1952b), and dibutyl sebacate has been demonstrated to be nonirritating to the skin in humans (Askarova and Muryseva 1975; Mallette and Von Haam 1952b). Thus, it is unlikely that skin contact with Otto Fuel II or its components at hazardous waste sites would result in a severe skin reaction.

Ocular Effects. Slight eye irritation has been reported by subjects experimentally exposed to propylene glycol dinitrate by inhalation (Stewart et al. 1974). This finding has been corroborated in an eye irritation study in which propylene glycol dinitrate was instilled into the eyes of rabbits (Jones et al. 1972). Thus, persons exposed to Otto Fuel II or propylene glycol dinitrate at hazardous waste sites may experience mild eye irritation.

Body Weight Effects. No significant effects on body weight were observed in rats mice, guinea pigs, dogs, and monkeys after intermediate- or chronic-duration exposure to propylene glycol dinitrate (Air Force 1985a; Jones et al. 1972). However, a significant reduction in body weight gain was reported in rats and rabbits exposed to propylene glycol dinitrate dermally during pregnancy (Cooper et al. 1993). The relevance of these results to human health is unknown.

Immunological and Lymphoreticular Effects. Very little information was located regarding immunological effects of Otto Fuel II or its components in humans or animals. Dibutyl sebacate was not shown to cause dermal sensitization when applied to the skin of human volunteers or rabbits (Mallette and Von Haam 1952b). However, 3.3% of workers occupationally exposed to lubricants containing dibutyl sebacate reacted to application of this material in a skin test (Askarova and Muryseva 1975). Hemosiderin deposits were observed in the spleens of dogs and monkeys, but not rats or guinea pigs, exposed continuously for 90 days to atmospheres containing 35 ppm propylene glycol dinitrate (Jones et al. 1972). This response probably reflects increased destruction of erythrocytes. Insufficient information exists to conclude whether exposure to dibutyl sebacate at hazardous waste sites might result in sensitization or whether the other components of Otto Fuel II at hazardous waste sites may cause other adverse immunological effects.

Neurological Effects. Studies in humans have demonstrated adverse effects of acute-duration exposure to low levels of propylene glycol dinitrate (0.5 ppm) on coordination (Stewart et al. 1974) and effects of acute-duration exposure to 0.2 ppm on subclinical indicators of neuronal function (Horvath et al. 1981; Stewart et al. 1974). An acute-duration inhalation MRL was derived for propylene glycol dinitrate based on altered visual responses in human subjects voluntarily exposed to propylene glycol dinitrate (Stewart et al. 1974). Animal studies have also demonstrated effects of propylene glycol dinitrate exposure on neuronal function, although most effects (ataxia, decreased consciousness, convulsions) have been observed following inhalation and parenteral exposure to high levels of this chemical (Andersen and Mehl 1979; Bogo et al. 1987; Jones et al. 1972). Behavioral paradigms designed to detect performance decrements caused by low-level exposure to propylene glycol dinitrate have given negative results (Mattsson et al. 1981). Thus, humans may be more sensitive than any of the other species that have been tested to the neurological effects of propylene glycol dinitrate. Based on the effects reported in the studies by Stewart et al. (1974) and Horvath et al. (1981), it is possible that persons exposed to sufficient levels of Otto Fuel II or propylene glycol dinitrate at hazardous waste sites may experience adverse neurological effects.

In vitro studies have demonstrated the ability of propylene glycol dinitrate to disrupt neuromuscular activity (Andersen and Mehl 1979) and to inhibit monoamine oxidase activity (Kalin and Kylin 1969); however, it is unknown what possible role the effects observed *in vitro* might play in the neurotoxicity observed in human subjects.

Headaches have frequently been reported both by workers occupationally exposed to Otto Fuel II and volunteers experimentally exposed to propylene glycol dinitrate (ATSDR 1990; Horvath et al. 1981; Stewart et al. 1974). However, the headaches are most likely associated with meningeal blood vessel dilation (Nickerson 1975) (see also Cardiovascular Effects above).

Reproductive Effects. Studies in humans have begun to address the reproductive toxicity of exposure to Otto Fuel II (Forman 1988). However, for purposes of epidemiological evaluation, the exposed population is still too small to allow meaningful analysis of the data. Animal studies examining reproductive function are limited to a single study that examined the reproductive effects of consumption of large amounts of dibutyl sebacate in rats (Smith 1953) and a dominant lethal study in mice that examined the effects of oral exposure to Otto Fuel II (Navy 1982b). These studies demonstrated no adverse effects of consumption of large amounts of dibutyl sebacate on fertility, litter size, or litter survival or of Otto Fuel II on male.fertility. Routine examination of the reproductive organs of animals chronically exposed to propylene glycol dinitrate did not reveal any abnormalities

(Air Force 1985a); however, the effects of propylene glycol dinitrate and 2-nitrodiphenylamine on reproductive function are unknown. Thus, although dibutyi sebacate does not appear to have any adverse reproductive effects in either sex and Otto Fuel II does not appear to cause adverse effects on male reproductive function, insufficient information exists on propylene glycol dinitrate or 2-nitrodiphenylamine to conclude whether populations exposed to these chemicals or to Otto Fuel II at hazardous waste sites are at risk of significant reproductive toxicity.

Developmental Effects. Developmental toxicity consisting of increased resorptions and decreased fetal viability, weight, and length has been observed following dermal exposure of rats to Otto Fuel II during mid-gestation (Cooper et al. 1993). However, the developmental effects were observed only at maternally toxic doses. Reduced growth of litters of parental rats given very large amounts of dibutyl sebacate in their diets prior to conception has also been reported (Smith 1953). It is unlikely that persons exposed to dibutyl sebacate at hazardous waste sites could be exposed to sufficiently high concentrations of this material to adversely affect development. The absence of information on developmental effects of propylene glycol dinitrate or 2-nitrodiphenylamine precludes estimation of the developmental effects of these components of Otto Fuel II on exposed populations.

Genotoxic Effects. No studies were located regarding the genotoxicity of Otto Fuel II or its components in humans. Two *in vivo* experiments were performed using the oral route of exposure to assess potential genotoxic activity of Otto Fuel II in somatic cells (bone marrow) or germinal cells (dominant lethal mutations in sperm) (Navy 1982b). Slight increases in the frequency of chromosome aberrations were seen in the bone marrow cytogenetic assay, but the finding was not definitive. Similarly, there was no evidence that Otto Fuel II was clastogenic in the dominant lethal assay; however, the number of pregnant females available for analysis did not constitute a reliable sample size. The only *in vivo* assays performed on a fuel component were two assays done with dibutyl sebacate (Wild et al. 1983). Both assays obtained negative results, but were incomplete. *Drosophila melanogaster* allowed to consume a 5% saccharose solution containing 19 mmol/L dibutyl sebacate showed no evidence of sex-linked recessive lethal mutations. Doses of dibutyl sebacate ranging from 943 to 2,829 mg/kg did not increase the frequency of micronuclei induction in bone marrow cells harvested from mice receiving the test compound by intraperitoneal injection (Wild et al. 1983). However, less than the recommended number of animals was used, and there was no indication that the test material was toxic to the animals or cytotoxic to the target organ. Based on the above considerations, no conclusions can be reached from the available *in vivo* genetic toxicology assays; the genotoxic activity, if any, of Otto Fuel II and its constituents in whole animals remains uncharacterized.

In vitro genotoxicity studies have been performed with Otto Fuel II and its constituents (propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate). The U.S. Navy (1982b) concluded that Otto Fuel II assayed at toxic levels did not cause a significant increase in the frequency of sister chromatid exchange in mouse lymphoma cells in the presence or absence of rat liver microsomes (S9). There was also no evidence of mitotic delay at any dose. Exposure to severely cytotoxic levels (<=10% survival) of Otto Fuel II in the nonactivated phase of the mouse lymphoma cell forward mutation assay increased the mutation frequencies and the number of mutant colonies. This evidence suggesting mutagenesis was confirmed under S9-activated conditions. Levels ranging from 0.025% to 0.075% with microsomal activation induced significant and dose-related increases in the mutation frequency at the thymidine kinase locus. Therefore, the U.S. Navy (1982b) concluded that Otto Fuel II was mutagenic in this mammalian cell line. Otto Fuel II was also evaluated for mutagenesis in *Saccharomyces cerevisiae* D4 and several histidine-requiring mutant strains of *Salmonella typhimurium* (Navy 1982b). In both of these test systems, Otto Fuel II, both with and without S9 activation, was assayed over an appropriate range of doses (0.005-10 uL/mL) but failed to induce a mutagenic effect.

Several authors (Kleindienst et al. 1985; McGregor et al. 1980; Shepson et al. 1985; Wild et al. 1983) have reported that the components of Otto Fuel II are not mutagenic in microbial systems, but none of their results were conclusive. Propylene glycol dinitrate was negative in the Ames test with or without activation at unspecified concentrations (Kleindienst et al. 1985; Shepson et al. 1985). McGregor et al. (1980) stated that 2-nitrodiphenylamine with or without activation did not cause mitotic recombination in *Saccharomyces cerevisiae,* gene mutation in *S. typhimurium,* or preferential inhibition of a polA^{-} *Escherichia coli* strain: no data were presented to support their claims. Kononova et al. (1972) concluded that propylene glycol dinitrate produced mutations in the r gene of phage T4B without activation. However, the only dose tested inactivated over 95% of the phage, casting doubts on the validity of the conclusion. Finally, a report that dibutyl sebacate with and without activation was negative in the Ames test presented no study results (Wild et al. 1983). Key *in vivo* genotoxicity studies are presented in Table 2-6 and *in vitro* genotoxicity studies are presented in Table 2-7.

TABLE 2-6. Genotoxicity of Otto Fuel II and Its Components *In Vivo*

Species (test system)	End point	Results	Reference
OTTO FUEL II			
Mice (per os, acute dosing)	Chromosome aberrations	(+)[a]	Navy 1982b
Mice (per os, intermediate dosing)	Chromosome aberrations	–[a]	Navy 1982b
Mice (oral gavage)	Chromosome aberrations in male germ cells	–[a]	Navy 1982b
DIBUTYL SEBACATE			
Drosophila melanogaster (sex linked recessive lethal)	Gene mutation in male germ cells	–[a]	Wild et al. 1983
Mice (intraperitoneal exposure)	Micronuclei formation	–[a]	Wild et al. 1983

[a]Data presented are insufficient to support authors' conclusions.

– = negative result; (+) = weakly positive result

TABLE 2-7. Genotoxicity of Otto Fuel II and Its Components *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	References
OTTO FUEL II				
Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	Navy 1982b
Saccharomyces cerevisiae (D4)	Gene mutation	–	–	Navy 1982b
Mouse lymphoma (L5187Y cells/TK test)	Forward gene mutation	+	(+)	Navy 1982b
Mouse lymphoma L5178Y cells	Sister chromatid exchange	–	–[a]	Navy 1982b
PROPYLENE GLYCOL DINITRATE				
S. typhimurium TA100	Gene mutation	–[a]	–[a]	Kleindienst et al. 1985
S. typhimurium TA100	Gene mutation	No data	–[a]	Shepson et al. 1985
Bacteriophage T4B (liquid preincubation test)	Gene mutation	No data	+[a]	Kononova et al. 1972
2-NITRODIPHENYLAMINE				
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–[a]	–[a]	McGregor et al. 1980
Escherichia coli (W3110 DNA polymerase I repair test)	Cell death	–[a]	–[a]	McGregor et al. 1980
S. cerevisiae (D5)	Mitotic recombination	–[a]	–[a]	McGregor et al. 1980
DIBUTYL SEBACATE				
S. typhimurium TA100	Gene mutation	–[a]	–[a]	Wild et al. 1983

[a] Data presented are insufficient to support authors' conclusions

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; TK = thymidine kinase

Cancer. Studies in humans have not evaluated the carcinogenic potential of Otto Fuel II or its components. Studies in animals have examined the carcinogenic potential of inhalation exposure to propylene glycol dinitrate in rats and mice and have not found strong evidence of a carcinogenic potential (Air Force 1985a). However, the appearance of osteosarcoma and osteoma (rare tumors) in rats, and possibly the increase in the incidence of a common preneoplastic observation (lymphoid hyperplasia) in mice, precludes concluding that exposure to propylene glycol dinitrate is without a carcinogenic risk. No increase in the incidence of neoplasms was noted in a study examining the effects of chronic-duration consumption of large amounts of dibutyl sebacate in rats (Smith 1953); however, the number of rats used in this study was somewhat small for an adequate test of oncogenicity. Thus, insufficient information is available to conclude whether the potential for carcinogenicity exists from exposure to Otto Fuel II or its components at hazardous waste sites.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to Otto Fuel II and its components are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by Otto Fuel II and its components are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Otto Fuel II and Its Components

Extremely limited information was located regarding biomarkers that may be used to estimate exposures to Otto Fuel II. No standard procedures exist for identifying or quantifying exposure to Otto Fuel II. Furthermore, no standard procedures were identified for estimating exposure to the components of Otto Fuel II, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate. However, based on information on the toxicokinetics of one of the components, propylene glycol dinitrate (Air Force 1982b; Clark and Litchfield 1969; Jones et al. 1972; Mattsson et al. 1981; Stewart et al. 1974), biomarkers for exposure to this component may be proposed.

Propylene glycol dinitrate is rapidly metabolized in the blood (Air Force 1982b; Clark and Litchfield 1969; Kylin et al. 1966). Therefore, measurement of blood levels of this substance or the propylene glycol mononitrates is limited to exposures of a very large magnitude and that occur within a very few hours of the time at which the blood sample is obtained. Also, because propylene glycol dinitrate may be metabolized in isolated blood samples (Clark and Litchfield 1969), steps must be taken to prevent the continued metabolism of this substance. Measurement of propylene glycol dinitrate in the urine or in expired air is of limited value since only a very small fraction of propylene glycol dinitrate is excreted by these routes (Air Force I982b; Clark and Litchfield 1969; Stewart et al. 1974). Measurement of inorganic nitrate, a metabolic product of propylene glycol dinitrate, in the blood may give some indication of whether exposure levels were high. However, this biomarker may increase following exposure to a large number of other nitrate-containing substances.

Urinary nitrate is the major metabolic marker for propylene glycol dinitrate (Clark and Litchfield 1969). However, measurement of urinary nitrate as a biomarker for exposure to propylene glycol dinitrate is limited by the rapid excretion of nitrate in the urine following exposure (Clark and Litchfield 1969). Within 24 hours of exposure, excretion of nitrate in the urine may be complete. Measurement of urinary nitrate as a biomarker for exposure to propylene glycol dinitrate is also limited by the fact that a large number of inorganic and organic nitrite and nitrate compounds used commercially or therapeutically may produce increased urinary nitrate that is indistinguishable from that caused by propylene glycol dinitrate (Donovan 1990). Such nitrites and nitrates include sodium, potassium, and calcium nitrate (used as fertilizers and food preservatives), bismuth subnitrate (antidiarrheal), ammonium nitrate (diuretic, fertilizer), silver nitrate (topical burn therapy), isosorbide dinitrate or tetranitrate (vasodilator), amyl nitrite (cyanide therapy, vasodilator, abused substance), butyl and isobutyl nitrite (room odorizer, abused inhalant), sodium nitrite (cyanide therapy, food preservative, anticorrosive), and nitroglycerin (vasodilator, explosives).

Methods for detecting 2-nitrodiphenylamine and dibutyl sebacate in body tissues or in excretory products were not located in the literature. In addition, metabolites for these chemicals have not been identified. Thus, measurement of these substances in bodily tissues or excretory products cannot be proposed as useful biomarkers of exposure.

The physiological effects caused by exposure to propylene glycol dinitrate (vasodilation, headache, loss of balance, poor eye-hand coordination, eye irritation, congested nose, nausea, dizziness, and methemoglobin formation) either individually or in combination are not unique to propylene glycol dinitrate exposure. Thus, observation of any one or a combination of these effects does not contribute to the identification or quantification of exposure to propylene glycol dinitrate. For example, eye irritation may be produced by a wide range of substances. Also, a number of other chemicals are known to cause methemoglobinemia (e.g., aniline, benzocaine, chlorate salts, chloroquine, copper sulfate, dapsone, lidocaine, metoclopramide, methylene blue (high doses), monolinuron, naphthalene, nitrates, nitrites, nitrobenzene, nitrogen oxide, nitroglycerin, permanganate salts, phenacetin, phenazopyridine, phenols, prilocaine, primaquine, sulfonamides, toluidine) (Donovan 1990). Finally, the combination of symptoms, vasodilation, headache, methemoglobin formation, dizziness, and nausea, may be caused by any of a number of inorganic or organic nitrites or nitrates (Donovan 1990). However, if there is a known exposure event (e.g., accidental release) and a potentially exposed individual experiences vasodilation, headache, eye irritation, nausea, dizziness, and methemoglobinemia, these symptoms may be confirmatory that significant exposure has occurred. It must be mentioned, however, that the absence of headache almost always rules out significant physiological overexposure to propylene glycol dinitrate (or Otto Fuel II) in otherwise healthy individuals.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.5.2 Biomarkers Used to Characterize Effects Caused by Otto Fuel II and Its Components

Very limited information was located regarding effects caused by Otto Fuel II. Also, limited information was located regarding effects caused by two of the components of Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate. The effects caused by propylene glycol dinitrate have, however, been described sufficiently to discuss possible biomarkers for these effects. Such effects include the characteristic type of headache, vasodilation, methemoglobin formation, and dizziness. In experimental exposures in humans, headache due to meningeal blood vessel dilation appears to be the most sensitive effect caused by propylene glycol dinitrate (Stewart et al. 1974). No studies were located that discussed methods for measuring meningeal vessel dilation or the resulting headaches in humans. However, individuals learn to differentiate this type of headache from ordinary headaches. Magnetic resonance imaging and positron emission tomography are noninvasive techniques that may be used to measure cerebral blood flow. Laser-Doppler flowmetry has been used to measure cerebral blood flow; however, in this method, the skull must be opened to allow the probe to be placed in direct contact with the *duru mater* (Dimagl et al. 1989; Saeki et al. 1989).

Measurement of vasodilation outside of the brain region may be accomplished by monitoring blood pressure (Air Force I982b; Stewart et al. 1974); however, in normal healthy individuals, a rapid vasoconstriction and increase in heart rate may limit the observation of a fall in blood pressure caused by exposure to low concentrations of propylene glycol dinitrate. In fact, in the study by Stewart et al. (1974), a reflex increase in vascular tone may have obscured any fall in blood pressure and may have accounted for the increase in diastolic pressure that was observed.

Experimental exposures in humans indicate that alterations in visual evoked responses may be used to identify subclinical changes in central nervous system activity (Stewart et al. 1974). However, the type of alterations in visual evoked responses produced by propylene glycol dinitrate (increases in the peak-to-peak voltage amplitude) were characterized as being typical of the type of changes produced by central nervous system depressants. Thus, this type of change in the visual evoked responses may be produced by a number of central nervous system depressants. Changes in saccade velocity and delay have been observed in workers acutely exposed to Otto Fuel II in the absence of an effect on coordination or balance (Horvath et al. 1981). The authors of this study suggest that changes in oculomotor responses may be used to detect subclinical changes in central nervous system activity caused by Otto Fuel II. However, similar changes are produced by brain lesions such as those caused by Huntington's chorea, brain stem degeneration, and multiple sclerosis, and from the actions of tranquilizers or alcohol. Thus, these changes are also not specific to the effects of Otto Fuel II. However, in light of a suspected exposure, these tests could be used to assess central nervous system involvement.

A slate-gray cyanosis, appearing first on the mucous membranes, is produced by exposure to relatively high concentrations of propylene glycol dinitrate as a result of the reduced oxygen-carrying capacity of methemoglobin (Donovan 1990; Jones et al. 1972). Cyanosis is not, however, a specific indicator of methemoglobin formation. Cyanosis may also result from increased levels of deoxyhemoglobin in pulmonary or cardiac disease. Cyanosis may also result from agents causing sulfhemoglobin formation. Distinction between cyanosis due to methemoglobinemia and cyanosis due to increased levels of deoxyhemoglobin may be accomplished by shaking a blood sample in the air. In the case of elevated levels of deoxyhemoglobin, the blood should turn bright red, whereas, in the case of methemoglobinemia, the color of the blood (brown or grayish) should be unaffected. Distinction between the cyanosis caused by methemoglobin and that caused by sulfhemoglobin may be achieved by diluting blood in deionized water (1 : 100) with a crystal of potassium cyanide. Blood containing methemoglobin should turn pink because of the formation of cyanomethemoglobin. Indicators of methemoglobinemia include a lactate metabolic acidosis and a normal blood oxygen content with low oxygen saturation. Methemoglobin concentrations in the blood may also be quantified spectrophotometrically. These biomarkers are not, however, specific for the methemoglobinemia produced by propylene glycol dinitrate. Heinz bodies in peripheral blood smears may also suggest methemoglobinemia (ATSDR 1991). However, Heinz bodies are not specific for methemoglobinemia.

No information was located regarding possible biomarkers of exposure or effect for 2-nitrodiphenylamine or dibutyl sebacate.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding the influence of other chemicals on the toxicity of Otto Fuel II or its components, propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. Intraperitoneal administration of propylene glycol dinitrate was, however, observed to decrease ethanol consumption in ethanol-addicted rats (Komura 1974). This decrease in ethanol drinking behavior was suggested by Komura (1974) to be related to increased tissue levels of acetaldehyde and ethanol caused by propylene glycol dinitrate-induced depression of alcohol dehydrogenase and acetaldehyde dehydrogenase activities.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to Otto Fuel II and its components than will most persons exposed to the same level of Otto Fuel II and its components in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Review of the literature regarding toxic effects of Otto Fuel II or its components, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate, did not reveal any populations that are known to be unusually sensitive to these chemicals. However, based on the knowledge of the primary toxic effects of propylene glycol dinitrate, vasodilation and methemoglobin formation, a number of groups may be proposed as being potentially highly sensitive to this chemical.

Groups that may be especially sensitive to the vasodilatory effects of propylene glycol dinitrate include those with arteriosclerotic or cardiac disease (Donovan 1990). In normal individuals, the vasodilation produced by propylene glycol dinitrate is compensated for by a reflex increase in arteriolar constriction and heart rate. Persons with arteriosclerosis have blood vessels with a limited ability to constrict reflexively. Persons with cardiac disease have a limited ability to enhance the mechanical performance of the heart. These groups may experience a greater degree of hypotension than normal individuals exposed to propylene glycol dinitrate.

Individuals with asymptomatic, subclinical coronary heart disease (the majority of the U.S. adult population over age 50) who are chronically exposed to propylene glycol dinitrate vapor concentrations that exceed the industrial time-weighted average-threshold limit value (TWA-TLV) standards, and who develop a tolerance to this exposure, are at risk of experiencing angina pectoris and possible heart injury when the exposure is suddenly terminated, as could occur during a long weekend or vacation away from the job site.

A number of populations may also experience greater sensitivity to the methemoglobinemia produced by propylene glycol dinitrate. For example, some groups may develop greater-than-normal levels of methemoglobin when exposed to propylene glycol dinitrate either as the result of the possession of a type of hemoglobin that is especially easily oxidized or resistant to reduction or as the result of decreased levels of enzymes or cofactors necessary for reduction of methemoglobin. Such persons include infants, persons with the hemoglobin variant, hemoglobin M, and those with congenital deficiencies in NADH-dependent methemoglobin reductase, the enzyme responsible for approximately 95% of the reduction of methemoglobin to hemoglobin. Infants are at increased risk because (1) they possess fetal hemoglobin, which has a greater susceptibility to oxidation than adult hemoglobin, (2) they are deficient in methemoglobin reductase, and (3) they have low levels of erythrocyte NADH (Donovan 1990). Persons with hemoglobin M may have enhanced methemoglobin production because this type of hemoglobin is especially easily oxidized and is resistant to the reductive process (Donovan 1990).

The increase in methemoglobin produced by propylene glycol dinitrate may be compounded by the concurrent exposure of some groups to other chemicals that cause methemoglobin formation. For example, munitions workers may also be exposed to the methemoglobin-producing substances: ammonium nitrate, pentaerythritol tetranitrate, and erythrityl tetranitrate because of their use in explosives and pyrotechnics. Also, ingestion of inorganic nitrates (primarily in well water contaminated with nitrogenous fertilizers, animal waste, or seepage from septic tanks) has been shown to cause methemoglobin production. Also, several therapeutic agents such as bismuth subnitrate (antidiarrheal); ammonium nitrate (diuretic); nitroglycerin, isosorbide dinitrate,. sodium nitroprusside, pentaerythritol, and erythrityl tetranitrate (vasodilators); metoclopramide (antiemetic); prilocaine, benzocaine, and lidocaine (anesthetics); phenazopyridine (urinary tract analgesic); and dapsone, chloroquine, and primaquine (antimalarials) have been shown to increase methemoglobin levels. Abuse of organic nitrites (snappers, poppers) for their enhancement of erections and relaxation of the anal sphincter has also been associated with increased methemoglobin production. Also, accidental or intentional overdose of chlorate salts (found in toothpastes and throat soothants) may cause methemoglobinemia. Finally, exposure to aniline in inks, dyes, shoe polish, paints, varnishes, and gasoline additives has also been reported to induce elevated levels of methemoglobin (Donovan 1990).

The increase in methemoglobin produced by propylene glycol dinitrate may .also be compounded by preexisting elevations of methemoglobin due to a medical condition. For example, pregnant women experience an elevation of methemoglobin during pregnancy. The level of methemoglobin peaks at approximately 10.5% at the 30th week of pregnancy and then declines to normal after delivery. Thus, women in the third trimester of pregnancy may be especially sensitive to the increases in methemoglobin produced by propylene glycol dinitrate
Some groups may experience a greater level of tissue anoxia as the result of methemoglobin formation. These include persons with an impaired ability either to oxygenate blood (seen in those with compromised pulmonary function) or to deliver blood to the tissues (seen in those with impaired circulation). In addition, persons suffering from anemia have depressed numbers of red blood cells available to carry oxygen to the tissues (Donovan 1990).

Finally, some groups are resistant to the methemoglobin antidote, methylene blue (see also Section 2.8). These include persons with congenitally low levels of NADPH-dependent methemoglobin reductase (the enzyme utilized for the reduction of methylene blue) and those with low glucose-6-phosphate dehydrogenase activities (an enzyme necessary for NADPH production in red blood cells) (Donovan 1990).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to Otto Fuel II and its components. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to Otto Fuel II and its components. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Based on currently available information, the constituent of Otto Fuel II that presents the major health concern is propylene glycol dinitrate. Exposure to propylene glycol dinitrate occurs primarily by inhalation or through dermal absorption. In an acute exposure situation, general recommendations include removing the exposed person from the source of exposure. Dermal absorption may be reduced by removing contaminated clothing, blotting any excess liquid material on the skin with an absorbent material, and washing the skin with copious amounts of water and mild soap (Bronstein and Currance 1988; Donovan 1990; Ellenhom and Barceloux 1988; Stutz and Janusz 1988). If the eyes have been contaminated, they may be flushed with water or normal saline (Bronstein and Currance 1988; Stutz and Janusz 1988). If ingestion of Otto Fuel II or propylene glycol dinitrate has occurred, absorption from the gastrointestinal tract may be limited by administering water or milk for dilution and activated charcoal to adsorb the material (Bronstein and Currance 1988; Donovan 1990; Ellenhom and Barceloux 1988; Stutz and Janusz 1988). The efficacy of gastric decontamination is optimal within 2-4 hours after ingestion (Donovan 1990).

2.8.2 Reducing Body Burden

There are no known specific methods for reducing Otto Fuel II or its components body burden.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The most commonly encountered symptom of overexposure to propylene glycol dinitrate (and Otto Fuel II) is headache due primarily to the vasodilation of cerebral vessels. Controlled human studies have demonstrated that the administration of 100% oxygen by mask, which produces a compensatory constriction of cerebral vessels, is efficacious (Stewart et al. 1974). Strong, black coffee with a high caffeine content, as well as aspirin, have proven helpful in alleviating head pain when there are no contraindications for the administration of either (Stewart et al. 1974).

No agents are known to interfere with the ability of propylene glycol dinitrate to cause vasodilation or cyanosis (resulting from methemoglobin production), but procedures are available and have been recommended to counteract these effects. Hypotension may respond to intravenous fluids and Trendelenburg's position, but vasopressors may be required (Donovan 1990; Ellenhorn and Barceloux 1988). Cyanosis may be treated with high flow (100%) oxygen administration to saturate all remaining normal hemoglobin with, oxygen (ATSDR 1991; Donovan 1990; Ellenhom and Barceloux 1988). Elevated levels of methemoglobin may be decreased by enhancing the rate of conversion of methemoglobin to hemoglobin. Methylene blue is the antidote of choice in this situation. Ascorbate has been suggested as an alternative reducing agent, but it is believed to have limited efficacy (Donovan 1990; Ellenhorn and Barceloux 1988). Methylene blue is administered intravenously. It is first reduced to leukomethylene blue by NADPH-dependent methemoglobin reductase in the red blood cell. The leukomethylene blue then acts as an electron donor to reduce methemoglobin to hemoglobin nonenzymatically. Use of methylene blue is generally indicated when methemoglobin levels exceed 30% but may be used at lower methemoglobin levels in persons with pulmonary or cardiovascular disease or with preexisting anemia (Donovan 1990; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990). Methylene blue is ineffective in persons with glucose-6-phosphate dehydrogenase deficiency and of limited effectiveness in persons with NADPH-dependent methemoglobin reductase deficiencies (Donovan 1990; Ellenhom and Barceloux 1988; Goldfrank et al. 1990). Severe hemolytic anemia may develop if given to persons with glucose-6-phosphate dehydrogenase deficiency (ATSDR 1991). Caution should be also used when administering methylene blue to others because high doses (>7 mg/kg) may increase methemoglobin levels and cause hemolysis (Donovan 1990; Ellenhorn and Barceloux 1988). In cases of failure of methylene blue therapy, exchange transfusions have been used to replace hemoglobin and remove the absorbed toxin (Donovan 1990; Ellenhorn and Barceloux 1988).

Information on the effects of low-level chronic exposure to Otto Fuel II or its components is limited. No treatment strategies were located for minimizing the effects of chronic low-level exposures.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of Otto Fuel II and its components is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of Otto Fuel II and its components.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

2.9.1 Existing Information on Health Effects of Otto Fuel and Its Components

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to Otto Fuel II and its components are summarized in Figures 2-5 through 2-8. The purpose of these figures is to illustrate the existing information concerning the health effects of Otto Fuel II and its components. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs.” A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

FIGURE 2-5. Existing Information on Health Effects *of Otto Fuel II*

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●		●		●	●			
Oral										
Dermal		●		●		●	●			

Human

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral									●	
Dermal	●	●						●		

Animal

● Existing Studies

FIGURE 2-6. Existing Information on Health Effects of Propylene Glycol Dinitrate

Human

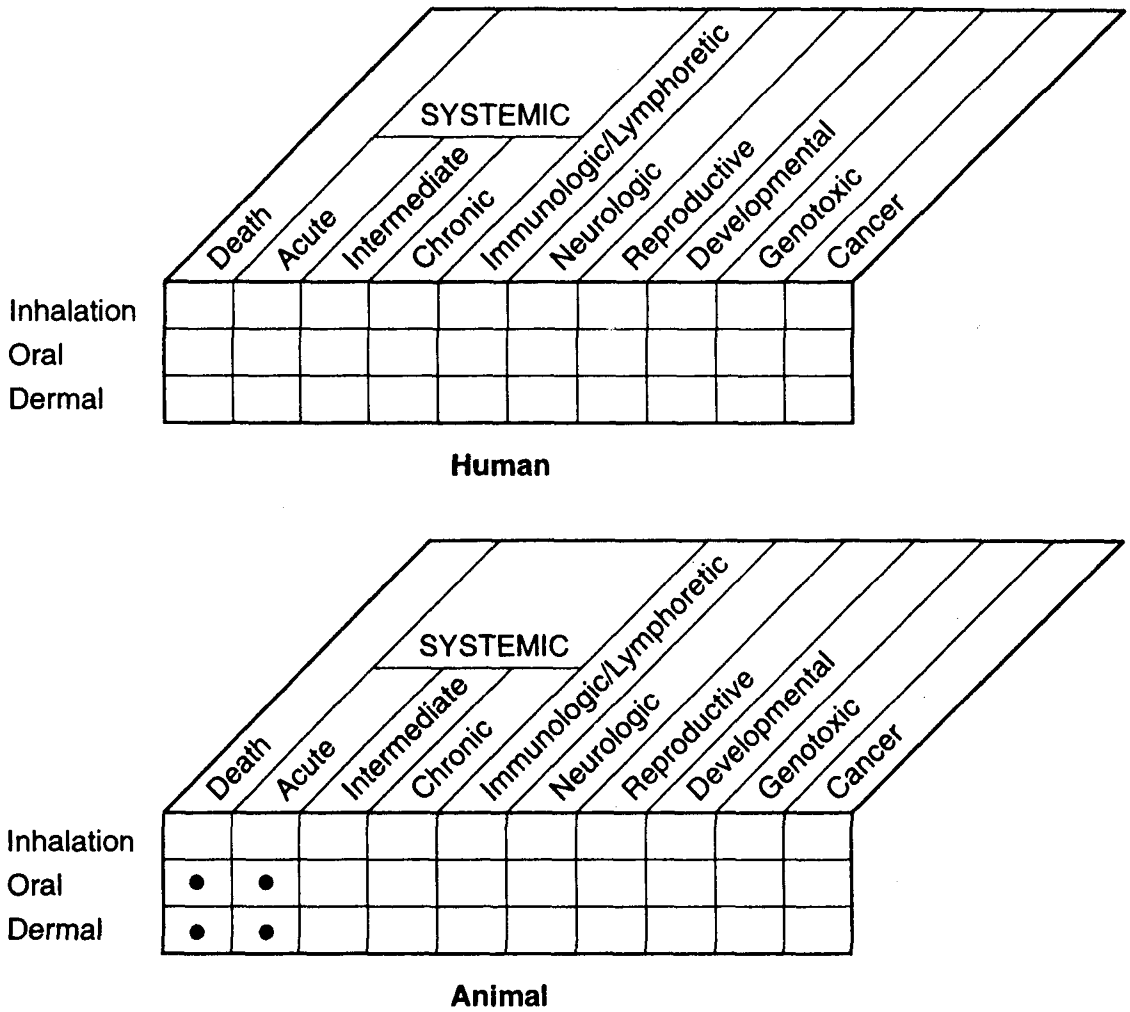
		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●				●				
Oral										
Dermal										

Animal

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●			●
Oral	●	●				●				
Dermal		●	●		●	●				

● Existing Studies

FIGURE 2-7. Existing Information on Health Effects of 2-Nitrodiphenylamine



● Existing Studies

FIGURE 2-8. Existing Information on Health Effects of Dibutyl Sebacate

Human

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral										
Dermal		●			●					

Animal

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral	●	●	●	●	●	●	●	●		
Dermal		●			●					

● Existing Studies

As can be seen in Figures 2-5 through 2-8, the information available on the health effects of Otto Fuel II and its individual components, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate, varies greatly depending on the specific substance under consideration.

The only information available on the human health effects of Otto Fuel II comes from studies of torpedo maintenance workers and incinerator workers occupationally exposed to Otto Fuel II (ATSDR 1990; Forman 1988; Forman et al. 1987; Horvath et al. 1981). Because occupational exposure could occur either as the result of inhalation of fumes arising from Otto Fuel II or as the result of dermal contact with Otto Fuel II, the information obtained in these studies is indicated as resulting from both inhalation and dermal exposures. One study in rats and rabbits has examined the developmental and maternal toxicity of dermal exposure to Otto Fuel II (Cooper et al. 1993).

The information available on the health effects of propylene glycol dinitrate, the major component of Otto Fuel II, is the most comprehensive of all of the components reviewed. However, the information on this component is not complete. The human data are limited to a study in which volunteers were briefly exposed to propylene glycol dinitrate vapors volatilized from samples of Otto Fuel II (Stewart et al. 1974). The bulk of the animal data on propylene glycol dinitrate is from inhalation studies (Air Force 1985a; Jones et al. 1972; Mattsson et al. 1981). The only animal data resulting from oral exposure are the results of three acute oral toxicity (LD_{50}) studies (Andersen and Mehl 1979; Clark and Litchfield 1969; Jones et al. 1972), and the only dermal data are from two single-dose toxicity studies (Clark and Litchfield 1969; Jones et al. 1972) and two 3-week studies (Andersen and Mehl 1979; Jones et al. 1972).

Very limited information is available on the toxicity of 2-nitrodiphenylamine. The only data located on this component of Otto Fuel II were obtained from a review article (Army 1979) and consisted of a summary of the results of an oral LD_{50} study, a dermal LD_{50} study, and eye and skin irritation studies in animals. (These results are included in the profile because they represent the only information located on 2-nitrodiphenylamine. Attempts are underway to try to obtain the studies upon which the reported results are based.)

The information on the health effects of dibutyl sebacate is somewhat less comprehensive than the information on propylene glycol dinitrate. The human ,data are limited to two dermal irritation and skin sensitization studies (Askarova and Muryseva 1975; Mallette and Von Haam 1952b). The animal data come almost exclusively from oral studies (Komarova 1976, 1979; Smith 1953). The dermal data from animals consist of information obtained in two skin irritation and sensitization studies (Komarova 1976, 1979; Mallette and Von Haam 1952b). Although the information available on dibutyl sebacate is limited, it indicates that this chemical is not very toxic by the oral or dermal routes and not expected to be toxic via other routes.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Populations in areas where Otto Fuel II is disposed of may be exposed to this substance for brief periods. Because of the limited volatility of two of the components of Otto Fuel II, 2-nitrodiphenylamine and dibutyl sebacate, inhalation exposures will be primarily to propylene glycol dinitrate. Insufficient information is available to eliminate any of the components of Otto Fuel II as possible water or soil contaminants, and thus, oral and dermal exposures to Otto Fuel II and its components must be considered. There are acute-duration inhalation exposure data in humans on Otto Fuel II and propylene glycol dinitrate from experimental exposure situations that indicate that the cardiovascular and nervous systems are target organs of these substances by the inhalation route (Horvath et al. 1981; Stewart et al. 1974). Headaches (most likely of cardiovascular origin) and impairment of coordination have been observed (Stewart et al. 1974). An acute-duration inhalation MRL for propylene glycol dinitrate was derived based on the NOAEL for visual evoked responses defined in this study. In addition, subclinical measures of nervous system activity and oculomotor function, have shown effects of low-level inhalation exposure to Otto Fuel II and propylene glycol dinitrate (Horvath et al. 1981; Stewart et al. 1974). No information was available regarding inhalation effects of 2-nitrodiphenylamine or dibutyl sebacate, but the chances for inhalation exposure to these substances is minimal due to their low volatility. No information was available on acute-duration oral exposure of humans to Otto Fuel II or any of its components. Acute-duration dermal exposure of humans to dibutyl sebacate indicated that this substance was not irritating to the skin (Mallette and Von Haam 1952b). Acute-duration occupational exposure to Otto Fuel II, consisting of mixed inhalation and dermal exposures, caused changes in subclinical neurologic parameters (Horvath et al. 1981). However, no information was located on dermal exposure to propylene glycol dinitrate or 2-nitrodiphenylamine.

Acute-duration studies of animals (rats, dogs, and, monkeys) exposed to propylene glycol dinitrate by inhalation support the identification of the neurological and cardiovascular systems as target organs of this substance by the inhalation route and indicate that the hematological system is also a target of propylene glycol dinitrate-induced toxicity (Air Force 1985a; Jones et al. 1972; Mattsson et al. 1981). In addition to causing altered neuronal activity and convulsions (Jones et al. 1972; Mattsson et al. 198 1) and effects attributable to vasodilation (Jones et al. 1972), increased levels of methemoglobin and decreased hemoglobin and hematocrit were observed after acute-duration inhalation exposure to propylene glycol dinitrate (Air Force 1985a; Jones et al. 1972). Acute-duration studies in rats exposed to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate by the oral route are limited to those with death as the end point (Andersen and Mehl 1979; Army 1979; Clark and Litchfield 1969; Jones et al. 1972; Smith 1953). Because death was the only end point examined in these studies, insufficient information was available to calculate an acute-duration oral MRL. An acute-duration study in rats and rabbits showed that high concentrations of this substance may produce moderate-to-marked skin irritation, methemoglobinemia, and fetal toxicity (Cooper et al. 1993). Acute-duration studies in rats or rabbits exposed to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate by the dermal route indicate that these substances are practically nonirritating to the skin and cause limited eye irritation (Army 1979; Jones et al. 1972; Komarova 1976, 1979; Mallette and Von Haam 1952b). Acute-duration dermal exposure of rats or rabbits to propylene glycol dinitrate also demonstrates the susceptibility of the cardiovascular system to this chemical (Clark and Litchfield 1969; Jones et al. 1972). There are limited pharmacokinetics data regarding propylene glycol dinitrate; however, the data that were obtained do not indicate that route-specific target organs exist. Pharmacokinetics dka were extremely limited regarding dibutyl sebacate and 2-nitrodiphenylamine. Thus, it is difficult to speculate on whether similar target organs would be affected across the various potential routes of exposure.

The physical properties of 2-nitrodiphenylamine and dibutyl sebacate do not indicate that inhalation exposure to these substances in the environment is likely. Thus, additional studies examining the effects of acute-duration inhalation exposure to these chemicals are not necessary. Also, lethality studies in rats indicate that oral exposure to 2-nitrodiphenylamine and dibutyl sebacate at levels likely to be encountered in the environment are relatively innocuous. Thus, additional acute-duration studies designed to evaluate the target organs affected by these chemicals do not appear to be necessary. However, additional studies examining the effects of acute-duration oral exposure to propylene glycol dinitrate may be valuable for defining levels of exposure associated with toxicity thresholds. In addition, a study examining the oral and dermal toxicity of the mixture Otto Fuel II would be helpful in eliminating the possibility of synergistic toxic effects of the components. Although the components of Otto Fuel II do not appear to cause appreciable dermal or ocular toxicity, additional studies examining the acute-duration dermal toxicity of Otto Fuel II and its components on other target organs would provide valuable information.

Intermediate-Duration Exposure. No studies were located regarding the effects of intermediate-duration exposure to Otto Fuel II or its components in humans by the inhalation, oral, or dermal routes. No studies were located regarding the effects of intermediate-duration exposure to Otto Fuel II in animals by the inhalation, oral, or dermal routes. Intermediate-duration inhalation exposure studies are limited to studies examining the effects of propylene glycol dinitrate in rats, dogs, monkeys, and guinea pigs (Air Force 1985a; Jones et al. 1972; Mattsson et al. 1981). These studies indicate that the blood, liver, and kidneys are target organs of such exposures. In these studies, effects on the blood (elevated methemoglobin and hemolysis of red blood cells) were observed at lower concentrations than effects on the liver or kidneys. An intermediate-duration inhalation MRL was derived for propylene glycol dinitrate based on the observation of elevated methemoglobin and decreased hematocrit, hemoglobin, red blood cells, and reticulocytes in dogs (Air Force 1985a). No intermediate-duration oral studies were located in which animals were exposed to propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate. Therefore, no intermediate-duration oral MRL was derived. Additional animal studies examining the effects of intermediate-duration exposure to dibutyl sebacate do not seem warranted at this time since chronic-duration studies showed the substance to be relatively nontoxic (Smith 1953). However, additional studies examining the effects of intermediate-duration oral exposure to propylene glycol dinitrate, 2-nitrodiphenylamine, and Otto Fuel II would be helpful because of the possibility of oral exposures to these substances. The only intermediate-duration dermal exposure study that was located examined the effects of propylene glycol dinitrate in the rabbit (Jones et al. 1972). This study showed the adverse effects of this chemical on the blood, liver, heart, skin, urinary tract, and possibly the respiratory system. These effects, however, were evident after only a few applications of the chemical; therefore, the study is better categorized as an acute-duration study. Although the effects were produced at relatively high doses, an additional study more clearly delineating the doses associated with the histopathological changes would be helpful. In view of the relatively low chronic-duration toxicity of dibutyl sebacate by the oral route (Smith 1953), additional intermediate-duration studies examining the dermal toxicity of this chemical would not appear to be valuable. However, very little is known regarding the effects of 2-nitrodiphenylamine by the inhalation, oral, and dermal routes of exposure, so studies examining its intermediate-duration toxicity would be helpful.

Chronic-Duration Exposure and Cancer. Only a few studies have examined the effects of chronic-duration occupational exposure to Otto Fuel II in humans (ATSDR 1990; Forman et al. 1987; Horvath et al. 1981). In these studies, exposures were not quantified and may have been by the inhalation, dermal, or combined inhalation and dermal routes. These studies have examined the effects of such exposures on the likelihood of angina and myocardial infarctions (Forman et al. 1987), the incidence of abortions among exposed female personnel (Forman 1988), and performance on tests of coordination and balance and oculomotor function (Horvath et al. 1981). The study examining myocardial parameters was the only study demonstrating an exposure-related effect (Forman et al. 1987). However, the other two studies were limited by the small numbers of subjects examined, and in the ATSDR study, workers were exposed to other hazardous substances. No studies were located regarding chronic-duration exposures of humans to any of the individual components of Otto Fuel II. Chronic-duration studies in animals are likewise limited in number. The only chronic-duration studies in animals that were located were an inhalation exposure study of the effects of propylene glycol dinitrate in rats, mice, and dogs (Air Force 1985a) and an oral exposure study of the effects of dibutyl sebacate in rats (Smith 1953). Propylene glycol dinitrate exposure resulted in an increase in methemoglobin and decrease in hematocrit, hemoglobin, red blood cells, and reticulocytes in dogs and possibly an increase in mild degeneration of the nasal epithehum of rats at the lowest dose tested (Air Force 1985a). A chronic-duration inhalation MRL for propylene glycol dinitrate was derived from this study based on hematological effects which were observed within several weeks in dogs and continued through 14 months of exposure. No studies were available regarding the effects of chronic-duration oral or dermal exposure to propylene glycol dinitrate in animals. No chronic-duration oral MRL value was derived because of the absence of information on the effects of propylene glycol dinitrate after oral exposure. Studies examining the chronic oral and dermal effects of propylene glycol dinitrate may provide valuable information regarding toxicity thresholds for persons exposed to propylene glycol dinitrate by these routes over an extended period. The absence of toxicokinetic data limits cross-route extrapolation of exposure levels and effects. In addition, a study examining the incidence of anemia or methemoglobin concentration in human populations exposed to propylene glycol dinitrate occupationally may also provide useful information. Long-term consumption of high levels of dibutyl sebacate resulted in no adverse effects in rats (Smith 1953). The absence of toxic effects in animals after oral exposure indicates that chronic dermal exposure studies and epidemiological studies in exposed human populations may not be needed. Based on the absence of information on the effects of chronic-duration oral or dermal exposure to 2-nitrodiphenylamine in humans or animals, studies examining the effects of such exposures in animals would be valuable. Pending the results of the animal study, an investigation of the effects of chronic exposure of humans to 2-nitrodiphenylamine may be desirable.

No information was located regarding the carcinogenic potential of Otto Fuel II or its components in humans. The only animal study that examined the oncogenicity of any of the components of Otto Fuel II was a chronic-duration inhalation study of propylene glycol dinitrate exposure in rats and mice (Air Force 1985a). While this study did not demonstrate a marked carcinogenic response in rats or mice to propylene glycol dinitrate, rare tumors (osteoma and osteosarcoma) were observed in the rats, and an increased incidence of a preneoplastic lesion (lymphoid hyperplasia) was observed in the mice. These results are suggestive of a carcinogenic effect, and additional studies examining the carcinogenic potential following inhalation exposure to propylene glycol dinitrate may be necessary to resolve the issue. The duration of the additional studies should be extended to cover the entire lifetime of the species selected, since the Air Force study (1985a) examined the effects of 1-year exposures. True lifetime exposures may reveal more subtle effects. A chronic-duration oral study in rats reported no increase in tumors among animals consuming large amounts of dibutyl sebacate, but the number of animals tested may have been too small to adequately test the carcinogenic potential of this compound. Additional studies examining cancer incidence in human populations chronically exposed to Otto Fuel II or its components and animal studies examining the carcinogenic potential of Otto Fuel II and all three of its components by the oral and dermal routes may provide additional valuable information.

Genotoxicity. Negative results were obtained from well-conducted microbial gene mutation assays (in *Salmonella typhimurium* and *Saccharomyces cerevisiae)* (Navy 1982b). Findings from mammalian cell assays indicated that Otto Fuel II increased the frequency of forward mutations but not sister chromatid exchange in mouse lymphoma cells (Navy 1982b). No *in vitro* cytogenetic studies were found. It is doubtful, however, that a clastogenic response would be uncovered in cultured mammalian cells since Otto Fuel II up to cytotoxic doses did not induce a genotoxic response or cause cell cycle delay on the sister chromatid exchange assay. Because sister chromatid exchange induction frequently occurs at much lower doses than are required to produce chromosome aberrations, it is reasonable to assume that the cytotoxic activity of Otto Fuel II would preclude the assessment of higher concentrations for potential adverse effects on chromosome morphology. Nevertheless, well-conducted *in vivo* studies assessing potential clastogenic activity are needed to complete the genetic toxicology profile for Otto Fuel II. The single positive mammalian cell gene mutation assay should be confirmed either in the same or a different cell line. Since no valid data were found for the constituents of Otto

Fuel II, a full battery of *in vitro* and in viva tests evaluating the major genetic end points is required. These include gene mutation in microbial and mammalian cells, chromosome aberrations in *vitro* and *in vivo,* and other mutagenic mechanisms, such as sister chromatid exchange induction in mammalian cells and unscheduled DNA synthesis in primary hepatocytes.

Reproductive Toxicity. One study compared the incidence of spontaneous and induced abortions among female Navy personnel who had occupational exposure to Otto Fuel II with two groups of enlisted females who were not exposed to Otto Fuel II (Forman 1988). Although no increase in the incidence of abortions was observed, the number of women in the exposed group was only five. This severely limits the sensitivity of the comparison. No other studies were located that examined the reproductive effects in humans of exposure to Otto Fuel II or any of its components by the inhalation, oral, or dermal routes of exposure. A single study in laboratory animals has directly examined the reproductive effects of oral exposure to dibutyl sebacate (Smith 1953). This study showed no effect on fertility, litter size, or litter survival of exposed rats. A single dominant lethal study in mice was conducted examining the effects of oral exposure to Otto Fuel II (Navy 1982b); however, no conclusions could be drawn from the fertility phase of the assay because the lower than expected fertility indices in the historic and concurrent negative controls limited the evaluation of reduced fertility in the treatment groups at the majority of mating intervals. No other study has directly examined reproductive function following exposure to Otto Fuel II or any of its components by the inhalation, oral, or dermal route. Routine gross and histopathological examination of reproductive organs (seminal vesicles, prostate, testes, ovaries, uterus, and mammary glands) of mice, rats, and dogs revealed no adverse effects on these tissues following chronic inhalation exposure to propylene glycol dinitrate (Air Force 1985a). Although the oral study using dibutyl sebacate (Smith 1953) indicates that this component of Otto Fuel II has limited reproductive toxicity, other studies examining reproductive function would be helpful. A continuation of the epidemiological study described by Forman (1988) in which the number of exposed female personnel is increased would be useful because this population is expected to have the greatest exposure to Otto Fuel II. In addition, studies in animals examining the reproductive function of inhalation, oral, and dermal exposures to Otto Fuel II or its component propylene glycol dinitrate and of oral and dermal exposure to 2-nitrodiphenylamine are needed to provide information on the possible reproductive effects experienced by persons with these types of exposure to Otto Fuel II at hazardous waste sites.

Developmental Toxicity. No studies in humans have examined the developmental effects of exposure to Otto Fuel II or any of its components. The only information from studies in animals regarding developmental effects has come from a study examining the developmental toxicity of dermal exposure to Otto Fuel II in rats and rabbits (Cooper et al. 1993) and the reproductive toxicity of oral exposure to dibutyl sebacate in rats (Smith 1953). The dermal Otto Fuel II study suggested that, at maternally toxic doses, developmental toxicity may occur. The study on dibutyl sebacate indicated that this component of Otto Fuel II had only minor adverse effects on the weight gain of offspring of parents that had been fed diets containing dibutyl sebacate. Thus, it is likely that dibutyl sebacate did not account for the developmental toxicity of Otto Fuel II. Studies examining the developmental effects of inhalation and oral exposure of animals to Otto Fuel II, inhalation, oral, and dermal exposure to its component propylene glycol dinitrate, and of oral and dermal exposure of animals to 2-nitrodiphenylamine could provide information on the possible developmental effects experienced by persons with these types of exposure to Otto Fuel II at hazardous waste sites. In addition, as the number of women in the military increases and occupational exposure to Otto Fuel II among females becomes more widespread, studies examining the development of their children could provide information on such effects in a population with known exposure.

Immunotoxicity. Extremely limited information is available on immune function in humans and animals after inhalation, oral, or dermal exposure to Otto Fuel II or any of its components. A skin sensitization, study in humans and rabbits examined the dermal sensitization potential of dibutyl sebacate and found no sensitization 2 weeks following a 2-day dermal exposure (Mallette and Von Haam 1952b). In addition, infrequent observation of sensitization to dibutyl sebacate was reported in a study examining the responses of occupationally exposed workers to dibutyl sebacate challenges (Askarova and Muryseva 1975). No other studies examined immune function in humans or animals after inhalation, oral, or dermal exposure to Otto Fuel II or any of its components. Only indirect information regarding the status of the immune system was obtained in animal studies. Results of hematological tests indicated no effect of chronic-duration inhalation or intermediate-duration dermal exposure to propylene glycol dinitrate on total or differential leukocyte counts in rats, dogs, and rabbits (Air Force 1985a; Jones et al. 1972). In addition, the lymph nodes, thymuses and/or spleens of animals in these studies were normal at necropsy. Similarly, no histopathologic alterations were observed in the spleen of rats and guinea pigs in an intermediate-duration inhalation study (Jones et al. 1972) or in the spleen of rats in a chronic-duration oral study (Smith 1953). Because little is known about the effects of Otto Fuel II or its components on the immune system, studies in animals examining immune function following inhalation, oral, and dermal exposures to Otto Fuel II or its component propylene glycol dinitrate and following oral or dermal exposure to the components 2-nitrodiphenylamine and dibutyl sebacate would be informative.

Neurotoxicity. Short-term exposure of humans to Otto Fuel II during torpedo maintenance procedures (30-45 minutes per turnaround) and brief experimental inhalation exposures (1-8 hours) to propylene glycol dinitrate at low levels have been shown to cause subclinical alterations in central nervous system activity (Horvath et al. 1981; Stewart et al. 1974). At higher concentrations, tests of coordination were affected, and subjects reported feeling dizzy (Stewart et al. 1974). No studies were located that examined the neurological effects of either 2-nitrodiphenylamine or dibutyl sebacate in humans after exposure by the inhalation, oral, or dermal route. Studies in monkeys have demonstrated central nervous system effects of propylene glycol dinitrate following inhalation exposure only at concentrations higher than those used in the human studies (Jones et al. 1972; Mattsson et al. 1981). In oral and dermal exposure studies, nervous system effects have also been observed in rats and rabbits following administration of large doses of propylene glycol dinitrate (Jones et al. 1972). No information was located on the nervous system effects of 2-nitrodiphenylamine in animals following exposure by the inhalation, oral, or dermal route. The only data located on the possible effects of dibutyl sebacate on the nervous system come from a chronic-duration oral study in rats in which gross and histopathological examination of selected nervous system tissues revealed no abnormalities (Smith 1953). Although humans appear to be more sensitive to the neurological effects of propylene glycol dinitrate than animals, continued studies in animals directed toward elucidating a possible mechanism of action for the effects of propylene glycol dinitrate would be useful. In addition, studies in animals directly examining the effects of 2-nitrodiphenylamine and dibutyl sebacate on neuronal function following oral and dermal exposures could provide information on the potential for effects of these components on the nervous system from exposures at hazardous waste sites.

Epidemiological and Human Dosimetry Studies. Very few epidemiological studies examining the effects of Otto Fuel II were located (Forman 1988; Forman et al. 1987; Horvath et al. 1981). Exposure to Otto Fuel II is known to occur in only a very small segment of the population, namely those persons with exposure to torpedo engines and propellants. Thus, collecting sufficient numbers of exposed persons for meaningful epidemiological studies is difficult. However, because the population most likely to be exposed consists mainly of enlisted personnel, follow-up studies may be more easily performed. Thus, additional studies examining immunological, developmental, reproductive, oncogenic, and long-term neurological effects would be valuable if a sufficient number of exposed persons are identified.

Biomarkers of Exposure and Effect.

Exposure. Methods are available for the analysis of propylene glycol dinitrate or its metabolites in expired air, blood, and urine (see Table 6-1). Although measurement of urinary nitrates has been used to indicate exposure to propylene glycol dinitrate, this method is limited by the rapid formation of nitrates in the blood, their rapid excretion, and the large number of other chemicals causing elevated urinary nitrates (Clark and Litchfield 1969; Donovan 1990). A method is available for the analysis of 2-nitrodiphenylamine in hand swabs (Bratin et al. 1981). Procedures for measuring dibutyl sebacate in body tissues or excreta were not found. The rapid hydrolysis of dibutyl sebacate to common organic molecules limits the utilization of measurement of either the parent compound or its metabolites as biomarkers of exposure. Studies delineating the metabolism and excretion of 2-nitrodiphenylamine may suggest potential biomarkers for exposure to this chemical and to Otto Fuel II.

Effect. The effects produced by Otto Fuel II and its components include vasodilation, headache (most likely the result of meningeal vessel dilation), dizziness, and methemoglobin formation. No biomarkers were identified for meningeal vessel dilation or the resulting headaches. Also, monitoring blood pressure as a method for detecting vasodilation may be of limited usefulness because of the ability of normal healthy individuals to compensate for venous dilation with an increase in arteriolar constriction and elevation of heart rate (Air Force 1982b). Methods for spectrophotometrically measuring methemoglobin content of the blood are well defined, and methods for distinguishing cyanosis caused by events other than methemoglobinemia have been identified (Donovan 1990). Neurophysiological parameters such as those assessed by Stewart et al. (1974) and Horvath et al. (1981) are commonly used to monitor for subclinical neurological effects; however, neither of these methods can distinguish propylene glycol dinitrate-induced changes from changes in brain activity due to several other causes. As understanding grows regarding the fundamental mechanism by which Otto Fuel II and propylene glycol dinitrate affect neuronal function, tests may be developed to monitor for the underlying neurological changes caused by these substances.

Absorption, Distribution, Metabolism, and Excretion. The only information regarding the absorption of Otto Fuel II or its individual components in humans comes from an inhalation exposure study in which detectable levels of propylene glycol dinitrate were found in the blood of exposed subjects (Stewart et al. 1974). Inhalation exposure of animals to propylene glycol dinitrate has also been demonstrated to result in detectable levels of this substance in the blood (Mattsson et al. 1981). Absorption of all three of the components of Otto Fuel II by the oral route has been indicated by the ability of each of these substances to cause death or systemic toxicity when administered by this route (Andersen and Mehl 1979; Army 1979; Clark and Litchfield 1969; Jones et al. 1972; Smith 1953). Also, dermal absorption of propylene glycol dinitrate has been inferred by the observation of effects on blood pressure after dermal application of this substance (Clark and Litchfield 1969; Godin et al. 1993). True quantitative data on the absorption of propylene glycol dinitrate and dibutyl sebacate following administration by the various routes of exposure may be difficult to obtain because of the rapid metabolism of these substances (Clark and Litchfield 1969; Kylin et al. 1966; Smith 1953). However, information on the relative absorption by the three routes of exposure for propylene glycol dinitrate and by oral and dermal absorption of dibutyl sebacate would be helpful for estimating absorption in humans and clarifying dose limits, and would relate to the practical use of protective clothing. In addition, studies in animals examining absorption of 2-nitrodiphenylamine by the oral and dermal routes of exposure could serve as a basis for estimates of the absorption of this substance by humans.

No information was available on the distribution of 2-nitrodiphenylamine or dibutyl sebacate in either humans or animals following exposure by the inhalation, oral, or dermal route. The only information located on the distribution of propylene glycol dinitrate consists of the observation of this substance in the blood of humans and monkeys that were been exposed by inhalation (Mattsson et al. 1981; Stewart et al. 1974). Therefore, inhalation studies examining the distribution of propylene glycol dinitrate and oral and dermal studies examining the distribution of all three components of Otto Fuel II could provide useful information.

The metabolism of propylene glycol dinitrate and dibutyl sebacate has been studied almost exclusively in *in vitro* studies and/or after parenteral administration (Clark and Litchfield 1969; Godin et al. 1994; Smith 1953). However, the metabolic products of propylene glycol dinitrate have been identified only through the initial steps of metabolism, and the metabolic products of dibutyl sebacate have not been reported. Thus, studies providing the missing information on metabolic products of these chemicals would be useful. No studies were located regarding the metabolism of 2-nitrodiphenylamine. Therefore, studies designed to identify the metabolic products of 2-nitrodiphenylamine would be valuable. Also, studies examining the metabolism of the three components of Otto Fuel II after exposure by the three routes might provide information on the effects of the route of exposure on the relative metabolic rates. Studies designed to identify sex- and species-related differences in metabolism would also be valuable.

The excretion of propylene glycol dinitrate in expired air following inhalation exposure has been examined in humans (Stewart et al. 1974). However, outdated methods were used in this study, and no other information on the excretion of propylene glycol dinitrate by humans was located. In addition, urinary excretion of metabolic products of propylene glycol dinitrate after dermal and parenteral administration has been studied in animals (Air Force 1982b; Clark and Litchfield 1969; Jones et al. 1972). However, no study has examined combined expired air, urine, and fecal excretion of propylene glycol dinitrate following exposure by the inhalation, oral, or dermal route. Also, no information exists on excretion of dibutyl sebacate or 2-nitrodiphenylamine from humans or animals after exposure by the inhalation, oral, or dermal route. Thus, studies examining excretion of these substances and their metabolic products following exposure by at least one route would provide useful information on excretory patterns. Studies examining excretion following exposure by more than one route could provide information on possible differences in excretion with varying routes of exposure. Studies on sex- and species-related differences in excretion would also be useful.

Comparative Toxicokinetics. Data are available that suggest that species differences exist with regard to the doses of propylene glycol dinitrate necessary to cause hematological effects (e.g., dogs versus rats) (Air Force 1985a) and neurological effects (e.g., monkeys versus humans) (Mattsson et al. 1981; Stewart et al. 1974). However, the information available on the toxicokinetics of propylene glycol dinitrate in various species is insufficient to speculate on whether the differences are due to variations in toxicokinetic parameters or differences in target organ sensitivities (Wyman et al. 1985). Additional studies examining the absorption, distribution, metabolism, and excretion of propylene glycol dinitrate in the affected species (i.e., following inhalation exposure) may be necessary before such conclusions can be reached.

No data are available on the toxicokinetics of 2-nitrodiphenylamine, and virtually no data are available on the toxicokinetics of dibutyl sebacate. Studies examining the absorption, distribution, metabolism, and excretion of these chemicals in several species are necessary before comparative evaluations based on toxicokinetic differences can be performed.

Methods for Reducing Toxic Effects. There are good data regarding steps that may be taken to reduce methemoglobin levels and therapeutic measures that may counteract the effects resulting from vasodilation produced by propylene glycol dinitrate. However, additional studies on methods to enhance the breakdown of propylene glycol dinitrate in the blood or to block its effects on vascular smooth muscle would be valuable. No information was located for dealing with toxic effects associated with long-term low-level exposures to Otto Fuel II or its components. Studies examining possible means of preventing coronary vasospasm upon termination of long-term exposures to Otto Fuel II or its major component propylene glycol dinitrate would be helpful. Also, studies assessing appropriate protective equipment (i.e., clothing) and safe methods for handling Otto Fuel II and its components would be helpful.

2.9.3 Ongoing Studies

No ongoing studies evaluating either the health effects or toxicokinetics of propylene glycol dinitrate, 2-nitrodiphenylamine, or dibutyl sebacate, were located. However, ATSDR is conducting a study in Lenoir, North Carolina to evaluate the prevalence of specific diseases and symptoms of a population living within a IS-mile radius of a hazardous waste incinerator where Otto Fuel II was being burned (ATSDR 1992).

3. CHEMICAL AND PHYSICAL INFORMATION

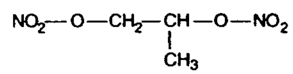
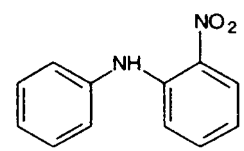
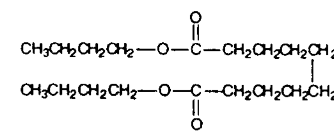
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of Otto Fuel II and its components is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of Otto Fuel II and its components is located in Table 3-2.

TABLE 3-1. Chemical Identity of Otto Fuel II and Its Components[a]

Characteristic	Otto fuel II	Propylene glycol dinitrate[b]	2-Nitrodiphenylamine[c]	Dibutyl sebacate
Synonym(s)	No data	PGDN; 1,2-propylene glycol dinitrate; 1,2-propanediol, dinitrate; propylene dinitrate; isopropylene nitrate; methylnitroglycol; propylene	2-nitrobenzenamine, 2-nitro-N-phenyl; o-nitro-N-phenylaniline; o-nitro-diphenylamine[b]	Bis (n-butyl) sebacate; butyl sebacate; decanedioic acid, dibutyl ester; sebacic acid, dibutyl ester; dibutyl decanedioate; di-n-butylsebacate[a]; dibutylester kyseliny
Registered trade name(s)	No data	No data	Sudan yellow 1339; C.I. 10335[b]	Kodaflex DBS; Staflex DBS; PX 404; Monoplex DBS; Polycizer DBS[f]
Chemical formula	Not applicable	$C_3H_6N_2O_6$[g]	$C_{12}H_{10}N_2O_2$[b]	$C_{18}H_{34}O_4$[f]
Chemical structure	Not applicable	 c	 b	 h
Identification numbers:				
CAS registry	106602-80-6	6423-43-4[i]	119-75-5[b]	109-43-3
NIOSH RTECS	No data	TY 6300000[h]	No data	VS 1150000
EPA hazardous waste	No data	No data	No data	878212204; 878221572; 878221503[j]
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	309
NCI	No data	No data	No data	No data

[a]All information obtained from HSDB 1994 except where noted
[b]Forman 1988
[c]Army 1979
[d]NRC 1982
[e]RTECS 1994
[f]Sax and Lewis 1989a
[g]ACGIH 1986
[h]SANSS 1994
[i]Sax and Lewis 1989b
[j]Chemlist 1991

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Otto Fuel II and Its Components[a]

Property	Otto fuel II	Propylene glycol dinitrate	2-Nitrodiphenylamine	Dibutyl sebacate
Molecular weight	No data	166.1[b]	214.23[c]	314.52[d]
Color	Reddish-orange[e]	Colorless[f]	Orange[g]	Clear[d]
Physical state	Oily liquid[e]	Liquid[f]	Solid (orthorhombic crystals)[c]	Liquid[d]
Melting point	–27.7 °C[h]	-27.7° C[f]	75–76 °C[c]	-10 °C
Boiling point	Decomposes at 121 °C[h]	Decomposes at 121 °C[f]; 92 °C (10 mmHg)[f]	223 °C (20 mmHg)[c]	180 °C (3 mmHg)[d]; 344–345 °C (pressure unspecified)
Density	1.232 g/mL (25 °C)[h]	1.232 g/mL (25 °C)[f]	1.366 g/mL[c]	0.936 g/mL (20 °C)[d]
Odor	Distinctive[h]	Disagreeable[f]	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble[h]	0.13 g/100 mL[f]	Insoluble[i]	Insoluble
Organic solvent(s)	Alcohols; benzene carbon tetrachloride; hexane; chloroform; toluene; dibutyl phthalate; acetone; trichloroethylene[h]	No data	Ethanol, 2 g/100 mL (25 °C)[c]; Methanol, 2.4 g/100 mL (20 °C)[c]; Acetone, 43.6 g/100 mL (20 °C)[c]; Benzene, 51.7 g/100 mL (20 °C)[c]	Ether
Partition coefficients:				
Log K_{ow}	No data	No data	0.49[c]	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	0.0877 mm Hg (25 °C)[h]	0.09844 mm Hg (25 °C)[j]	0.00001 mm Hg (25 °C)[k]	3 mm Hg (180 °C)
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	121 °C[l]	No data	No data	No data
Flashpoint	130 °C[hg]	No data	No data	178 °C
Flammability limits	Monopropellant[l]	No data	No data	Slight potential when exposed to heat or flame
Conversion factors	No data	1 ppm = 7.14 mg/m^3 [m]	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information obtained from HSDB 1994 unless otherwise noted
[b]Sax and Lewis 1989b
[c]Army 1979
[d]Sax and Lewis 1989a
[e]Forman 1988
[f]ACGIH 1986
[g]Dean 1974
[h]Air Force 1985a
[i]American Cyanamid 1982
[j]Crater 1929
[k]Baughman and Perenich 1988
[l]Rivera 1974

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Named after its inventor, Otto Reitlinger (Forman 1988), Otto Fuel II consists of the nitrated ester explosive propellant propylene glycol dinitrate (PGDN), to which a desensitizer (dibutyl sebacate) and a stabilizer (2-nitrodiphenylamine) have been added (Kessick et al. 1978; Rivera 1974). The chief component, propylene glycol dinitrate, accounts for approximately 75% of the mixture, while dibutyl sebacate and 2-nitrodiphenylamine account for approximately 23% and 2%, respectively (Air Force 1985a; Kessick et al. 1978). Wilshire Chemical Co., Inc., of Gardena, California, is the only manufacturer or distributor of propylene glycol dinitrate that was located, and production volumes for this facility were not available (Van and Deyrup 1991). Information on the manufacture of Otto Fuel II was not located. Since Otto Fuel II releases are not required to be reported under SARA Section 313, there are no data on Otto Fuel II in the 1994 Toxic Release Inventory.

2-Nitrodiphenylamine is produced by the reaction of 2-chloronitrobenzene and aniline in the presence of sodium carbonate (Army 1979). A yield of 96% is obtained by removing water in the form of its aniline azeotrope. As of 1978, the only U.S. manufacturer was American Cyanamid Company. There were at least four foreign manufacturers, including Bayer AG in Germany, as well as Hickson & Welch Ltd., Hopkin & Williams, and Koch-Light Laboratories Ltd. in the United Kingdom. Radford Army Ammunition Plant was the only Army ammunition plant employing 2-nitrodiphenylamine at that time. Current domestic producers of 2nitrodiphenylamine include the Aceto Corporation of Lake Success, New York, and Schweizerhall, Inc., of Piscataway, New Jersey (Van and Deyrup 1991). Production volume data, including data on the amounts used by the US. Navy in Otto Fuel II, were not located.

Dibutyl sebacate can be synthesized by at least three methods: (1) reaction of sebacic acid and butanol in the presence of an appropriate esterification catalyst; (2) distillation of sebacic acid with butyl alcohol in the presence of concentrated hydrochloric acid in a benzene solution; and (3) reaction of butyl alcohol with sebacyl chloride (HSDB 1994). Current manufacturers of dibutyl sebacate and their production sites include Eastech Chemical Inc., Philadelphia, Pennsylvania; Merrand International Corporation, Stow, Ohio; Ivanhoe Industries, Inc., Pennington, New Jersey; Bayer USA Inc., Carteret, New Jersey; Union Camp Corp., Chicago, Illinois; The C.P. Hall Company, Dover, Ohio; and Hatco

Chemical Corporation, Fords, New Jersey (SRI 1991; Thomas Publishing 1990a; Van and Deyrup 1991). U.S. production volumes in 1972 totaled 2.04 million kilograms. The volume increased slightly to 2.54 million kilograms by 1975, although this included 2-ethylhexyl sebacate as well (HSDB 1994). More current production data could not be located.

4.2 IMPORT/EXPORT

Import and export data for Otto Fuel II and its three components could not be located.

4.3 USE

Otto Fuel II is a liquid monopropellant (it does not require an atmosphere containing oxygen to support combustion) used by the U.S. Navy in MK-46 and MK-48 torpedoes (Rivera 1974) and other weapons systems (Air Force 1985a).

The principal current use of propylene glycol dinitrate is as a propellant in Otto Fuel II (Forman 1988). Nitrates of polyhydric alcohols, of which propylene glycol dinitrate is an example, have been used in medicine for the treatment of angina pectoris, and as explosives since the mid-nineteenth century (Litchfield 1971).

In addition to its use by the U.S. Navy as a stabilizer in the manufacture of Otto Fuel II, 2-nitrodiphenylamine is employed for similar purposes by the U.S. Army in the manufacture of double base solid propellants (Army 1979). It also has civilian applications as a solvent dye (Army 1979; Baughman and Perenich 1988).

Dibutyl sebacate is a desensitizer in Otto Fuel II. However, its major use is as a plasticizer for cellulose acetate butyrate plastics, cellulose acetate propionate plastics, polyvinyl butyral plastics, polystyrene, and many synthetic rubbers (HSDB 1994). Many of the plastic products containing dibutyl sebacate are used in the food packaging industry. Dibutyl sebacate is also used as a lubricating ingredient in shaving lotions, and as a synthetic flavoring additive in non-alcoholic beverages, ice cream, ices, candy, and baked goods.

4.4 DISPOSAL

The available information on the disposal of Otto Fuel II and propylene glycol dinitrate is limited. Most of the available information comes from laboratory-scale and pilot pl,ant studies of potential treatment methods conducted in the 1970s and early 1980s. Biodegradation studies have provided conflicting evidence of the biodegradability of propylene glycol dinitrate (the major component of Otto Fuel II) by conventional sewage treatment methods (Army l98la, 1981b: Kessick et al. 1978; Wyman et al. 1984). Suggested alternative treatment methods have included carbon absorption techniques combined with base hydrolysis of propylene glycol dinitrate to the biodegradable propylene glycol (Kessick et al. 1978), and decomposition of propylene glycol dinitrate using sodium sulfide (Smith et al. 1983). Bench-scale wet air oxidation screening tests conducted at 280 °C for 60 minutes indicate excellent removal of propylene glycol dinitrate from waste streams that are too dilute to incinerate and too toxic to biotreat (Dietrich et al. 1985).

2-Nitrodiphenylamine is only sparingly soluble in water, and thus it can be recovered as a solid in effluent stream filters (Army 1979). At the Radford Army Ammunition Plant in Radford, Virginia, it was estimated that one-half to two-thirds of the 2-nitrodiphenylamine that is lost during preparation and processing operations is recovered in this manner.

No information on the disposal or treatment of dibutyl sebacate was located.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Otto Fuel II is a mixture of three component chemicals, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate. Otto Fuel II enters the environment as these three components, which partition to the different environmental media according to their individual chemical and physical properties. Otto Fuel II is primarily released to water in waste streams from Navy facilities that produce it or are involved in torpedo rework operations. There is also a possibility that it could be spilled on soil during transfer operations. The limited data located on the environmental fate of Otto Fuel II components indicate that propylene glycol dinitrate is removed from water primarily by volatilization. Propylene glycol dinitrate is the most water soluble of the three components, although its solubility is low and it is not expected to persist in water for more than a few days. Neither 2-nitrodiphenylamine nor dibutyl sebacate is volatile or soluble enough for the partitioning to air or water to be important fate processes. 2-Nitrodiphenylamine has been found in river sediment receiving waste water runoff from an army ammunition plant; this is considered the most likely fate for this chemical. The information on dibutyl sebacate is too limited to determine its transport and partitioning in the environment. However, it is known to be rapidly biodegraded by a wide range of microorganisms. Both propylene glycol dinitrate and 2-nitrodiphenylamine are photolyzed and photooxidized in water. It is likely that these substances are similarly broken down in the air. The data on biodegradation of propylene glycol dinitrate and 2-nitrodiphenylamine are mixed. Some experiments indicate these compounds are readily degraded and others indicate limited biodegradation. A bioconcentration factor has been calculated only for 2-nitrodiphenylamine. It indicates that this chemical does not bioconcentrate in aquatic organisms or biomagnify in the food chain. People working in occupations in which Otto Fuel II is manufactured or used, such as personnel involved in clean up operations or waste treatment facilities handling Otto Fuel II, are most likely to be exposed to the chemical and its components. Incomplete data on disposal practices and levels in the environment prevented a determination of the likelihood of exposure of people !iving or working near hazardous waste sites. General population exposure to Otto Fuel II is not expected to occur because of the limited manufacture and use of the compound, and the suggested low mobility of Otto Fuel II and its components in the environment. However, the general population may be significantly exposed to 2-nitrodiphenylamine or dibutyl sebacate as a result of their manufacture and use in a number of civilian products.

5. POTENTIAL FOR HUMAN EXPOSURE

Otto Fuel II has been detected at 2 of the 1,397 NPL sites that have been proposed for inclusion on the NPL (HazDat 1994). The frequency of these sites within the United States can be seen in Figure 5- 1.

5.2 RELEASES TO THE ENVIRONMENT

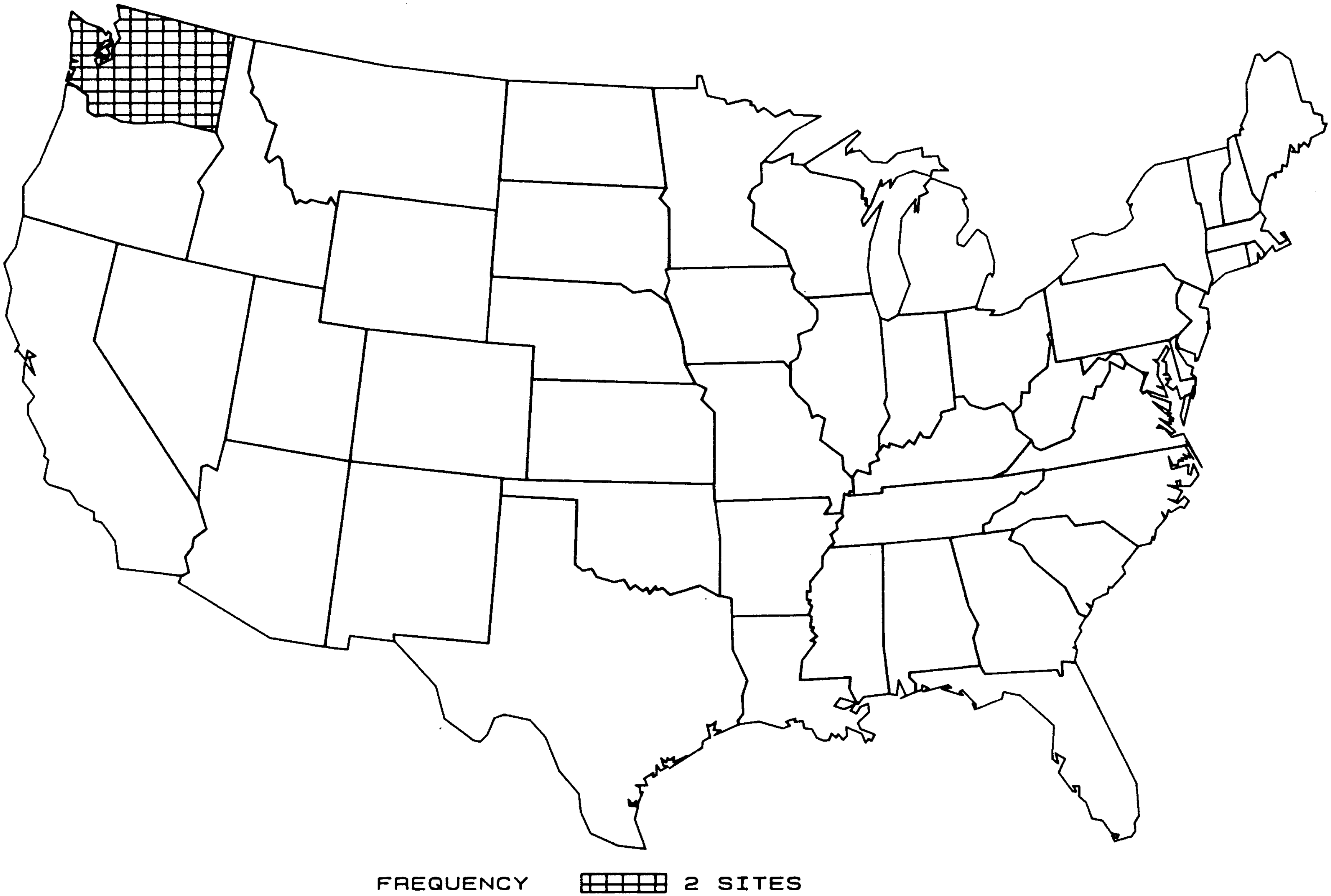
5.2.1 Air

There is no information on the release of Otto Fuel II, 2-nitrodiphenylamine, or dibutyl sebacate to air. Propylene glycol dinitrate could be released to air during torpedo maintenance procedures, manufacturing, transport, etc. However, since the vapor pressure of propylene glycol dinitrate is very low, these releases are not expected to be substantial. Azeotropic evaporation of propylene glycol dinitrate from Otto Fuel II manufacturing waste water may also release propylene glycol dinitrate into the air (Wyman et al. 1984). Experiments conducted using a photochemical smog chamber to simulate reactions that might occur in polluted atmospheres indicate that low levels of propylene glycol dinitrate (approximately 0.1 ppm or less) are generated when air containing 3 ppm propylene and 1.5 ppm nitrogen oxide compounds (NO or NO_2) are irradiated with high pressure xenon lamps (Akimoto et al. 1978, 1980). Further investigation showed that the production of propylene glycol dinitrate was a result of the reaction of photochemically generated nitrogen pentoxide (N_20_5) (Akimoto et al. 1978, 1980) with atmospheric propylene (Akimoto et al. 1978; Hoshino et al. 1978). This suggests that photooxidation of atmospheres containing propylene and nitrogen oxide compounds may result in release of propylene glycol dinitrate to the atmosphere. However, the applicability of these laboratory experiments to actual events taking place in the atmosphere is uncertain since multiple factors that could affect such a reaction (e.g., presence of other compounds, concentrations of reactants, turbulence affecting the chance of collisions between potential reactants) are not present in the smog chamber.

5.2.2 Water

Propylene glycol dinitrate and 2-nitrodiphenylamine are released in waste water effluent streams from plants manufacturing and/or using the compounds to formulate special military propellants including Otto Fuel II (Army 1979, 1981 a). In 1979, only one facility, Radford Army Ammunition Plant in Radford, Virginia, was engaged in the manufacture of propellants containing 2-nitrodiphenylamine

FIGURE 5-1. FREQUENCY OF NPL SITES WITH OTTO FUEL II CONTAMINATION *



*Derived from HazDat 1994

(Army 1979). At that time, the level of 2nitrodiphenylamine released in the waste stream from this plant was estimated to be 240-670 lbs/per month. Of this amount, about one-half to two-thirds was expected to be recovered as particulates from the effluent filters. Approximately 80-200 lbs/per month was estimated to be released to the New River, which receives the waste water effluent from the Radford Army Ammunition Plant. No information on current releases was located.

5.2.3 Soil

Otto Fuel II has been detected in soils (data on levels not available) from two of the 1,397 hazardous waste sites that have been proposed for inclusion on the NPL (HazDat 1994). Otto Fuel II accidentally spilled on soil during transfer operations could result in additional sites contaminated with this monopropellant.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Otto Fuel II has a relatively low vapor pressure (8.8×10^{-2} mm Hg at 25 °C) (Air Force 1985a). Its primary component, propylene glycol dinitrate, also has a low vapor pressure ($9.8\text{x}10^{-2}$ mm Hg at 25 °C) (Crater 1929), which suggests that little evaporation of the compound occurs. In a biodegradation study, 80% loss of propylene glycol dinitrate was observed over a 30-day period. Since growth curves showed essentially static growth of the microbial culture and no breakdown products of biodegradation were detected, the loss could not be attributed to biodegradation. In subsequent experiments employing the commercial culture and including a trap to catch released gases, 61% of the propylene glycol dinitrate added to the culture media was recovered in the exhaust gas trap. As in the previous experiments, no metabolites of biodegradation were detected. It was concluded that the loss of propylene glycol dinitrate was due to formation of an azeotrope with water. The Henry's law constant for the azeotrope was estimated to be $3.3\text{x}10^{2}$ mm Hg($\approx$1 $\text{x}10^{-2}$ atm m^3/mole) (Wyman et al. 1984). This value of Henry's law constant would account for the volatilization loss of propylene glycol dinitrate from water and indicates that volatilization may be an important fate process in water. The vapor pressures of the remaining two components of Otto Fuel II, 2-nitrodiphenylamine (1×10^{-5}mm Hg at 25 °C) and dibutyl sebacate (3 mm Hg at 180 °C) indicate that evaporation is not a significant fate process ,for these chemicals (Baughman and Perenich

1988). However, no values for Henry's law constants were located that might corroborate the volatility characteristic predicted from the vapor pressure data alone.
Otto Fuel II and its component, dibutyl sebacate are insoluble in water (Air Force 1985a; HSDB 1994), and 2-Nitrodiphenylamine is insoluble to only slightly soluble (American Cyanamid 1982; Army 1979). Therefore, these two compounds are not expected to partition substantially to water and these compounds are unlikely to leach from soil to groundwater (Lyman et al. 1982). Propylene glycol dinitrate has a solubility of 1.3 g/L (ACGIH 1986) and is expected to partition substantially into water, However, since this chemical forms an azeotrope with water that readily volatilizes, it is not expected to persist in water for more than a few days.

2-Nitrodiphenylamine is sparingly soluble in water and was found to precipitate out of waste water effluent and sorb to sediment (Army 1979). The chemical has been detected in sediment in a river receiving runoff water from an army ammunition plant (Army 1979). An octanol-water partition coefficient of 3.07 has been calculated for 2-nitrodiphenylamine (Army 1979). The estimated value of octanol-water partition coefficient from EPA's Graphic Exposure and Modelling System (GEMS) (EPA 1986) is 21.7. Both of these values indicate that 2nitrodiphenylamine does not bioaccumulate in aquatic organisms and is not likely to biomagnify in the environment. No information on sorption to particles, sediments, or soils or on bioaccumulation for Otto Fuel II was located.

5.3.2 Transformation and Degradation

5.3.2.1 Air

No information on the transformation and degradation of Otto Fuel II or its components in air was located. However, experiments in aqueous media indicate that both propylene glycol dinitrate and 2-nitrodiphenylamine are subject to photolysis and photooxidation and that these processes are expected to occur in the air as well (Wyman et al. 1984).

5.3.2.2 Water

Decomposition of both the propylene glycol dinitrate and 2-nitrodiphenylamine components of Otto Fuel II was observed when a solution of the mixture was exposed to ultraviolet (UV) radiation

(Wyman et al. 1984) under air and under nitrogen. When the tests were conducted in air, >96% of the propylene glycol dinitrate was decomposed in 42 hours compared to 57% in the dark controls. Decomposition of propylene glycol dinitrate was >89% in 72 hours under nitrogen compared to 9.5% in controls. Under both sets of test conditions, 2-nitrodiphenylamine was removed from the solution as determined by disappearance of its characteristic peak at 442 nm. However, no quantitative rate data on its decomposition were presented. ^{13}C-Nuclear magnetic resonance (^{13}C-NMR) detected lactic and pyruvic acids in the water-soluble portion of the photolyzed Otto Fuel II. It was concluded that UV photolysis of propylene glycol dinitrate produces aldehydes, nitrite esters, nitrogen dioxide, nitric oxide and nitrous acid. In the presence of oxidants (oxygen, ozone produced during photolysis), the aldehydes possibly oxidize to lactic acid and pyruvic acid (Wyman et al. 1984). The importance of photolysis of propylene glycol dinitrate by sunlight can not be ascertained from the study of Wyman et al. (1984) since short wavelength UV lights (wavelengths <290 nm) were not filtered out from the light source. The observed photolysis may have occurred as a result of interaction with these short wavelength UV light that are not available in sunlight (available wavelengths in sunlight are >290 nm).

Limited data suggest that Otto Fuel II may hydrolyze under basic conditions. Incubation of an Otto Fuel II-water mixture with calcium hydroxide and with sodium hydroxide resulted in a loss of propylene glycol dinitrate from the solution (Kessick et al. 1978). Sixty percent of the propylene glycol dinitrate was lost within 4 hours when calcium oxide was added, and no propylene glycol dinitrate could be measured following 15 minutes of incubation with sodium hydroxide. The significance of this for the actual environmental fate of propylene glycol dinitrate is not known since the high pH involved (10.8 or higher) is rarely found in the environment. In addition, work of other investigators suggests that the loss of the propylene glycol dinitrate in these experiments could have been due to volatilization of the propylene glycol dinitrate-water azeotrope (Wyman et al. 1984).

There is conflicting evidence for the microbial breakdown of propylene glycol dinitrate. Experiments using batch and continuous culture methods with an inoculum of fresh activated sewage sludge from a domestic sewage treatment plant revealed evidence of biodegradation of the compound (Army 1981a). Loss of propylene glycol dinitrate from the cultures was observed and propylene giycol mononitrate was identified as a metabolite of the compound. Loss of propylene glycol mononitrate was also observed in this series of experiments. These data indicate that biodegradation occurs by sequential cleavage of the nitrate groups resulting in formation of propylene glycol. A companion study showed that propylene glycol was also rapidly biodegraded (Army 1981b). In contrast, studies performed with pure cultures of *Pseudomonas* aeruginosa, microorganisms from sewage sludge, and a commercial culture of mixed microorganisms specifically designed to degrade recalcitrant substances in waste water from treatment plants indicated that propylene glycol dinitrate was not readily biodegraded by microorganisms (Wyman et al. 1984). On addition of an inoculum of the culture into the Otto Fuel II solution, an initial increase in cells of 1-2 logs was observed over the first 24 hours followed by constant cell counts for the remainder of the 30-day study period. The initial increase in cells was likely due to degradation of the dibutyl sebacate plasticizer since this chemical has been shown to be readily degraded by environmental bacteria and fungi (Klausmeier 1986; Klausmeier and Jones 1960; Klausmeier and Osmon 1976; Osmon et al. 1972; Stahl and Pessen 1953). However, since this component of Otto Fuel II was not specifically monitored, the increased growth cannot be unequivocally attributed to degradation of the dibutyl sebacate. Propylene glycol dinitrate and 2-nitrodiphenylamine were not considered to be biodegraded as no metabolites were detected. Experiments with mixed bacterial cultures from municipal sewage, acclimated to Otto Fuel II by preexposure to the compound, did not degrade propylene glycol dinitrate (Kessick et al. 1978). In addition, biochemical oxygen demand (BOD) over a 5-day period did not change substantially when Otto Fuel II was used as the sole carbon source. These data indicate that Otto Fuel II is not readily degraded by microorganisms. Experiments monitoring BOD in the presence of glucose (as the carbon source) and increasing concentrations of Otto Fuel II (as measured by propylene glycol dinitrate) showed decreased BOD with increasing Otto Fuel II concentration, suggesting that Otto Fuel II was toxic to the microbial culture. The authors considered propylene glycol dinitrate to be the toxic component, although no data were presented to support this assumption. 2-Nitrodiphenylamine and dibutyl sebacate were not monitored in this study.

5.3.2.3 Sediment and Soil

No data on the biotransformation and degradation of Otto Fuel II and two of its components, propylene glycol dinitrate and dibutyl sebacate, were located. 2-Nitrodiphenylamine has been reported to be degraded by mixed cultures of microorganisms when it is available as the sole carbon source (Kessick et al. 1978). However, no data were located to support this or to indicate the importance of biodegradation on the environmental fate of 2-nitrodiphenylamine.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Grab samples of air in four U.S. Navy torpedo facilities (Naval Weapons Station, Charleston, South Carolina; Naval Weapons Station, Yorktown, Virginia; Naval Submarine Support Facility, New London, Connecticut; and Naval Torpedo Station, Keyport, Washington) had levels ranging from 0 to 0.22 ppm propylene glycol dinitrate (detection limit not reported) (Horvath et al. 1981). No data on levels of 2-nitrodiphenylamine or dibutyl sebacate were located.

5.4.2 Water

Dibutyl sebacate was detected in one sample of finished water from an advanced waste treatment plant in Lake Tahoe, California. The concentration of the dibutyl sebacate was not reported. Since dibutyl sebacate is a commonly used plasticizer, it is likely that the dibutyl sebacate found in the water was not due to Otto Fuel II contamination (EPA 1984a, 1984b).

Levels of 2-nitrodiphenylamine ranging from 1 to 14 ppm (mean of 3.5 ppm) have been found in the New River, which receives effluent water from the Radford Army Ammunition Plant in Radford, Virginia (Army 1979).

No data on concentrations of propylene glycol dinitrate in water were located.

5.4.3 Sediment and Soil

Levels of 0.5-12.2 ppm (mean of 1.5 ppm) 2-nitrodiphenylamine were found in the sediments of the New River (Army 1976). The New River receives effluent waste water from the Radford Army Ammunition Plant.

5.4.4 Other Environmental Media

Limited data were located regarding levels of dibutyl sebacate in food. Samples of hard and processed cheese, liver pate, and black pudding purchased from supermarkets in the United Kingdom contained levels of dibutyl sebacate ranging from 2.3 to 137 mg/kg (Castle et al. 1988). The lowest levels were found in the hard cheese, and the highest levels were in the processed cheese and meat products packaged in plastic tubs. The diethyl sebacate in these samples was assumed to have migrated from the plastic wrap used to store the foods and known to contain dibutyl sebacate as a plasticizer. The plastic containers contained from 3.5% to 4.1% diethyl sebacate that had been added as a plasticizer when the containers were manufactured. A sample of leaf lettuce taken from a private garden in Finland contained 0.5 ug 2-nitrodiphenylamine/kg fresh weight of lettuce (Wickstrom et al. 1986). However, the source of the 2-nitrodiphenylamine was probably reaction of polyaromatic hydrocarbons with nitro compounds in the air and not Otto Fuel II contamination. These possible sources of dibutyl sebacate and 2-nitrodiphenylamine contamination should be considered when looking for evidence of Otto Fuel II contamination in environmental samples. No information on the concentrations of propylene glycol dinitrate in other environmental media were located.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

There were insufficient data to reliably assess the potential for general population exposure to Otto Fuel II and its components. However, given the limited manufacture and use of the compound, general population exposure is expected to be limited to persons in the immediate vicinity of waste water effluents containing Otto Fuel II or its components.

Workers employed in occupations in which Otto Fuel II is used (e.g., torpedo maintenance workers) may be exposed to airborne propylene glycol dinitrate. A survey of four Navy torpedo facilities suggested that, in some instances, the air concentrations might exceed the threshold limit value (TLV) of 0.2 ppm in effect at the time the measurements were taken (Horvath et al. 1981). Concentrations ranged from 0.0 to 0.22 ppm (one sample exceeded the TLV). However, 88% of the air samples taken from the facilities had levels of 0.1 ppm or less, and 50% were ≤.05 ppm. Alveolar breath analysis was conducted on two workers employed in Navy torpedo facilities (Horvath et al. 1981). Propylene glycol dinitrate was monitored as an indicator of exposure to Otto Fuel II. A level of 0.001 ppm was measured in the breath of one of the workers 5 minutes after exposure to air concentrations ranging from 0.01 to 0.026 ppm ceased. No propylene glycol dinitrate was detected 15 minutes after exposure ceased. In the second worker, concentrations of 0.0008 and 0.0004 ppm were measured in the expired air 5 and 15 minutes, respectively, after exposure to 0.015-0.222 ppm.

The National Occupational Exposure Survey (NOES) conducted by NIOSH during 1981-1983 to estimate worker exposure to chemicals in different professions did not include any estimate for Otto Fuel II or propylene glycol dinitrate (NOES 1991). However, this survey estimated that 4,856 workers employed in special contracted trades, miscellaneous manufacturing industries, and personal services were potentially exposed to dibutyl sebacate (NOES 1991). Professions included roofers, laundering and dry cleaning machine operators, assemblers, construction laborers, and hand packers and packagers. None of the exposed persons appeared to be employed in facilities or professions in which Otto Fuel II was manufactured or used. These data are not considered relevant to an assessment of occupational exposure to Otto Fuel II.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The only populations that appear to be potentially exposed to higher levels of Otto Fuel II and its components are people who manufacture Otto Fuel II and/or are involved in torpedo refueling and maintenance operations.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of Otto Fuel II and its components is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of Otto Fuel II and its components.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Several important physical properties of Otto Fuel II and its three components, propylene glycol dinitrate, 2-nitrodiphenylamine, and dibutyl sebacate, have yet to be characterized. These include their octanol-water and organic carbon partition coefficients and Henry's law constants. These data are important in estimating the fate of released Otto Fuel II in the environment and determining the potential for human exposure.

Production, Import/Export, Use, and Release and Disposal. Data were located that described the production of 2-nitrodiphenylamine and dibutyl sebacate (Army 1979; HSDB 1994). Dibutyl sebacate is currently manufactured in the United States (HSDB 1994; SRI 1991; Thomas Publishing 1990a), but no information on the current production of 2-nitrodiphenylamine was located. No information was located discussing the production of either Otto Fuel II or its major component, propylene glycol dinitrate. Import/export data on Otto Fuel II and its components were also missing. Only proposed methods of disposal were found (Army 1979; Dietrich et al. 1985; Kessick et al. 1978; Smith et al. 1983), and no information was located on methods of disposal commonly and/or currently used. These data are necessary to determine the likelihood of human exposure to Otto Fuel II and its components.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of Otto Fuel II and its components is largely unknown. Otto Fuel II and its components are not extremely volatile or soluble; however, propylene glycol dinitrate does form a volatile azeotrope with water (Wyman et al. 1984). This makes evaporation of propylene glycol dinitrate an important fate process. 2-Nitrodiphenylamine may precipitate from water or sorb to particulates (Army 1979). Dibutyl sebacate is rapidly biodegraded, but the data on biodegradation of propylene glycol dinitrate and 2-nitrodiphenylamine are equivocal. Both of these chemicals are photolyzed by UV light (Wyman et al. 1984). However, the importance of photolysis of propylene glycol dinitrate as a result of interaction with sunlight has not been ascertained. More information on the environmental fate of the mixture and its components is needed to fully assess the risk of exposure to populations living near facilities where they may be released.

Bioavailability from Environmental Media. Experiments in animals have shown that propylene glycol dinitrate is absorbed by inhalation, oral, and dermal routes (Andersen and Mehl 1979; Army 1979; Clark and Litchfield 1969; Jones et al. 1972; Mattsson et al. 1981; Smith 1953; Stewart et al. 1974). 2-Nitrodiphenylamine and dibutyl sebacate are also absorbed following ingestion (Andersen and Mehl 1979; Army 1979; Clark and Litchfield 1969; Jones et al. 1972; Smith 1953). The potential for absorption of 2-nitrodiphenylamine and dibutyl sebacate following inhalation or dermal contact could not be determined from the data located. No further information on bioavailability is needed for dibutyl sebacate because the compound is not toxic. However, propylene glycol dinitrate is toxic, and the potential toxicity of 2-nitrodiphenylamine is undetermined. Therefore, more data on the bioavailability of these compounds from air, water, soil, and food are needed to assess fully the risk posed by these Otto Fuel II components.

Food Chain Bioaccumulation. An estimated bioaccumulation factor for 2-nitrodiphenylamine based on calculations indicates that this chemical does not bioconcentrate (Army 1979). No data were located for the remaining two components of Otto Fuel II. More information on the bioconcentration potential of these chemicals, including experimental data, is needed to determine the risk of biomagnification in the food chain.

Exposure Levels in Environmental Media. Very little information was located on the levels of Otto Fuel II and its components in environmental media (Army 1976, 1979; Castle et al. 1988; EPA 1984a, 1984b; Horvath et al. 1981; Wickstrom et al. 1986). Most of the data that were located did not concern levels of components originating from Otto Fuel II contamination (Castle et al. 1988; EPA 1984a, 1984b; Wickstrom et al. 1986). This information would be useful in determining the risk to populations living or working in the vicinity of facilities releasing Otto Fuel II to water and soil. Reliable monitoring data for the levels of Otto Fuel II in contaminated media at hazardous waste sites are needed so that the information obtained can be used in combination with the known body burden of Otto Fuel II to assess the potential risk of adverse health effects in populations living the vicinity of hazardous waste sites.

Exposure Levels in Humans. Limited data were located on exposure levels in humans working in facilities where Otto Fuel II is used. These data indicate that workers employed in occupations where Otto Fuel II is used are exposed to sub-ppm levels of Otto Fuel II (Horvath et al. 1981). Alveolar breath samples of two exposed workers had levels of propylene glycol dinitrate of less than 1 ppb. Additional monitoring studies in occupationally exposed workers would be useful for better defining human exposure to Otto Fuel II. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for Otto Fuel II or its components were located. This substance is not currently one of the substances for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 Ongoing Studies

No ongoing studies were located regarding the potential for human exposure to Otto Fuel II and its components.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring Otto Fuel II and its components in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify Otto Fuel II and its components. Rather, the intention is to identify wellestablished methods that are used as the standard methods of analysis. Many of the analytical methods used to detect Otto Fuel II and its components in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter may be those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods may be included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

The chief component (75%) of Otto Fuel II is propylene glycol dinitrate. The balance of Otto Fuel II is composed of 2-nitrodiphenylamine (2%) and dibutyl sebacate (23%). The constituent of Otto Fuel II that presents the major health concern is propylene glycol dinitrate. Therefore, exposure levels to Otto II fuels have been based on measured propylene glycol dinitrate levels and/or its metabolites 1-propylene glycol mononitrate and 2-propylene glycol mononitrate. Methods were located for the analysis of propylene glycol dinitrate or its metabolites in expired air, blood, urine, and hand swabs. However, no methods of detecting the chemical or its metabolites in tissues were found. No information was located concerning the detection or quantification of dibutyl sebacate or 2-nitrodiphenylamine in biological materials. Details of commonly used analytical methods for several types of biological media are presented in Table 6-l.

Two analytical methods exist for detecting propylene glycol dinitrate in expired air. These are gas chromatography (GC) with electron capture detector (ECD) (Horvath et al. 1981; Stewart et al. 1974) and GC with mass spectrometry (MS) (Air Force 1982b). Very little information on these two methods was given. The lower detection limit of the MS method was less than 1 mg/m^3 propylene glycol dinitrate in air, but no information on accuracy and precision was reported. Levels of propylene glycol dinitrate as low as 0.003 mg/m^3 were reported using the ECD method (Horvath et al.

TABLE 6-1. Analytical Methods for Determining Otto Fuel II and Its Components in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Breath (propylene glycol dinitrate)	Direct injection	GC/ECD	NR	NR	Stewart et al. 1974
Breath and blood gas (propylene glycol dinitrate)	Direct injection	MS	<1 mg/m^3 breath; 1 µg/mL blood	NR	Air Force 1982b
Blood and urine (propylene glycol dinitrate, propylene glycol mononitrate)	Extract with diethyl ether; add anhydrous sodium sulphate; wash with ether	GC/ECD	0.2 µg/mL (blood propylene glycol mononitrate)	83–97% (blood propylene glycol mononitrate)	Litchfield 1968
Blood and urine (propylene glycol dinitrate)	Extract with diethyl ether	Spectrophoto metry	0.2 µg/mL (blood)	89–110% (blood)	Litchfield 1968
Blood and urine (propylene glycol dinitrate, propylene glycol mononitrate)	Extract with ether	GC/ECD	10 ng/mL	NR	Erk et al. 1982
Handswab (2-nitrodiphenyl-amine)	Wipe hand with swab; moistened with methyl *tert*-butyl ether; extract swab in methyl *tert*-butyl ether; centrifuge; decant supernatant and evaporate; redissolve in methyl *tert*-butyl ether in pentane; clean up on Amberlite XAD-7® column, eluting with ethyl acetate; concentrate	HRGC/TEA; HRGC/ECD	pg-low ng	NR	Douse 1985
Explosives and gunshot residues; handswabs (2-nitrodiphenyl-amine)	Dissolve explosives in acetone; wipe hand with swab moistened with acetone; wash swab with 20% ethanol; filter; inject	HPLC/ECD	4.1 µg/L	NR	Bratin et al. 1981

ECD = electron capture detection; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; NR = not reported; TEA = thermal energy analyzer

1981). These limited data suggest that GC/ECD may offer better sensitivity than GC/MS. However, GC/MS generally provides better selectivity.

Methods exist for detecting propylene glycol dinitrate and its metabolites in blood and urine. The primary method of analysis for propylene glycol dinitrate and its metabolites in blood and urine is gas chromatography with electron capture detection (Litchfield 1968). A disadvantage of this method is that sample preparation is time consuming, taking 2-3 hours. However, a more rapid GC method enables sample preparation to be completed within 5 minutes (Erk et al. 1982). This rapid method reliably detects propylene glycol dinitrate in blood at concentrations ranging from 0.01 μg/mL to 25 μg/mL. Because propylene glycol dinitrate is rapidly broken down in blood to the corresponding mononitrates and inorganic nitrates, extraction from the blood should be carried out immediately after the sample is drawn (Litchfield 1968). An outdated but simple method for determining propylene glycol dinitrate in blood and urine is calorimetric analysis (Litchfield 1968). Propylene glycol dinitrate is determined spectrophotometrically following alkaline hydrolysis and a diazotization and coupling reaction. This procedure has several drawbacks; it is time consuming, nonspecific, and relatively insensitive. The lower detection limit is only 0.2 μg/mL, more than an order of magnitude greater than GCYECD. In addition, the method does not distinguish between individual nitrates in a mixture of esters. The use of GC with ECD overcomes this difficulty, and the identification of nitrate esters can be achieved. MS with a blood gas catheter was used to detect propylene glycol dinitrate in blood; however, the catheter was not useful and had a high retention rate of propylene glycol dinitrate (Air Force 1982b). The limit of detection was only 1 μg/mL.

6.2 ENVIRONMENTAL SAMPLES

Because of the low threshold limit value (TLV) in the United States of 0.05 ppm for propylene glycol dinitrate (ACGIH 1994), effective means of monitoring very low levels of propylene glycol dinitrate vapors are needed to monitor workers, and prevent exposure to toxic levels. Various methods such as polarography, piezoelectric crystals, high-pressure liquid chromatography (HPLC) with flame ionization (FID), electrochemical (EC), or ultraviolet (UV) detector, linear sweep voltammetry (LSV), GC with thermal energy analyzer (TEA), FID, or ECD, and thin-layer chromatography (TLC) have been investigated for detecting propylene glycol dinitrate in environmental samples. Analytical methods were located for monitoring propylene glycol dinitrate in air and water. Details of commonly used analytical methods for air and water are presented in Table 6-2.

TABLE 6-2. Analytical Methods for Determining Otto Fuel II and Its Components in Environmental Samples

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (propylene glycol dinitrate)	Direct measurement	Piezoelectric crystal	<0.05 ppm	NR	Turnham et al. 1985
Air (propylene glycol dinitrate, propylene glycol mononitrate)	Collect sample on Amberlite XAD-2® adsorbent; extract with methanol; concentrate	GC/TEA; HPLC/EC	0.1 µg/mL (propylene glycol dinitrate); 0.5 µg/mL (propylene glycol mononitrate); 0.2 µg/mL (propylene glycol dinitrate); 4 µg/mL (propylene glycol mononitrate)	NR NR	Tomkins et al. 1985
Air (propylene glycol dinitrate)	NR	IR; GC/ECD	NR	NR	Stewart et al. 1974
Air (propylene glycol dinitrate)	NR	FTIR	NR	NR	Akimoto et al. 1980
Water (propylene glycol dinitrate stock solutions)	Prepare standard aqueous solutions	LSV	0.5 mg/L	NR	Fine and Miles 1983
Effluent water (propylene glycol dinitrate)	Extract with benzene	GC	NR	NR	Kessick et al. 1978
Effluent water (propylene glycol dinitrate)	NR	GC/ECD	NR	NR	Navy 1979
Effluent water (propylene glycol dinitrate, propylene glycol mononitrate)	NR	Single sweep polarography	low-ppb	NR	Navy 1979
Effluent water (propylene glycol dinitrate)	Extract with organic solvent; separate on reverse phase HPLC column	HPLC/UV	1 ppm	NR	Hiltz et al. 1986

TABLE 6-2. Analytical Methods for Determining Otto Fuel II and Its Components in Environmental Samples (continued)

Sample Matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, river sediment (2-nitrodiphenylamine)	Extract with solvent; concentrate; clean up on silica gel; elute with ethyl ether/benzene; concentrate; redissolve in benzene	HPLC/UV GC/FID	<10 ppm (water) NR	NR 91 river sediment	Army 1976
Sea water (dibutylsebacate)	Extract with XAD-2® resin; fraction on silica gel column	GC/MS/TDMC	NR	NR	Shishido et al. 1984
Propellants (2-nitrodiphenylamine)	NR	GC/FID	NR	NR	Dykes and Alley 1974
Propellants (2-nitrodiphenylamine)	Macerate and homogenize propellant; dilute with methanol; filter	HPLC/UV reverse phase	NR	NR	Army 1986b
Propellants (2-nitrodiphenylamine)	Extract with methylene chloride; concentrate; redissolve in methanol; filter	HPLC/EC reverse phase	4.3 µg/L	NR	Bergens 1987
Smokeless powders (2-nitrodiphenylamine)	Extract with methylene chloride; clean up on silica gel; concentrate	HPLC/UV/TEA	Low-ng	NR	Bender 1983
Gunshot residues	Swab spent casings with swab moistened with ethanol; extract with ethanol; centrifuge; evaporate; dilute with buffer	MECE/UV	NR	NR	Northrop et al. 1991

EC = electrochemical detection; ECD = electron capture detection; FID = flame ionization detector; FTIR = fourier transform infrared spectrometry; GC = gas chromatography; HPLC = high-performance liquid chromatography; IR = infrared spectrometry; LSV = linear sweep voltammetry; MECE = micellar electrokinetic capillary electrophoresis; MS = mass spectrometry; NR = not reported; TDMC = three-dimensional mass chromatography; TEA = thermal energy analyzer; UV = ultraviolet detection

6. ANALYTICAL METHODS

Various methods have been proposed for detecting propylene glycol dinitrate in air. Coated piezoelectric quartz crystal microbalances have been studied as potential selective and sensitive detectors for the determination of propylene glycol dinitrate vapor levels (Luoma et al. 1987; McCallum 1989; Turnham et al. 1985). A prototype instrument with crystal design containing a trap for propylene glycol dinitrate on the reference crystal eliminated many of the frequency, stability, and selectivity problems associated with these detectors and produced a detection limit of better than 0.05 ppm. Air samples have been analyzed using TLC, GC/TEA, GC/FID, and HPLC/EC in the reductive mode (Tomkins et al. 1985; Wyman et al. 1984). GC/TEA and HPLC/EC have been used to separate and detect mono- and dinitrated propylene glycols, and have been applied to the problem of quantifying trace levels of nitrated propylene glycols (Tomkins et al. 1985). Both GC/TEA and HPLC/EC are capable of rapidly detecting propylene glycol dinitrate at sub-ppm concentrations in a liquid extract. While both methods separated propylene glycol mononitrate from propylene glycol dinitrate, GC/TEA possessed the added advantages of better sensitivity and resolution of the propylene glycol mononitrate isomers. GC/TEA exhibited a linear range of three orders of magnitude and provided detection limits in the μg/mL range or lower for propylene glycol dinitrate and the two propylene glycol mononitrate isomers. IHPLC/EC provided a linear response over two orders of magnitude and was best suited for the determination of propylene glycol dinitrate. GC/FID and TLC could not be compared to other methods because no details on method sensitivity and reliability were reported (Wyman et al. 1984). Infrared spectrometry and GC/ECD have been used in the quantification of propylene glycol dinitrate in an inhalation exposure chamber (Stewart et al. 1974). Propylene glycol dinitrate has also been quantified in a photochemical smog chamber using Fourier transform infrared spectrometry (FTIR), GC/ECD, and GC/MS (Akimoto et al. 1978, 1980; Hoshino et al. 1978). No data on the sensitivity and reliability of these methods were provided.

Analytical methods for detecting propylene glycol dinitrate and its metabolites, propylene glycol 1-mononitrate and propylene glycol 2-mononitrate in effluent water include polarography, GC, and linear sweep voltammetry (LSV). GC has been used to measure the concentration of propylene glycol dinitrate in waste water (Kessick et al. 1978). No information on the detector, or selectivity and sensitivity of this method was provided. GC/ECD has been used to determine propylene glycol dinitrate in effluent water (Navy 1976a, 1976b, 1979). This method detected propylene glycol dinitrate but not propylene glycol mononitrate. Since propylene glycol dinitrate can hydrolyze rapidly to propylene glycol mononitrate in sump water during storage and also during the clean-up operation of the purification system, GC/ECD has limited use in the monitoring of effluent water. Single sweep polarographic equipment has been designed for field use to monitor propylene glycol dinitrate and propylene glycol mononitrate in effluent water (Navy 1976a, 1976b, 1977a, 1979). The effluent water monitored by the polarograph was obtained from a carbon adsorption system designed to remove propylene glycol dinitrate from Otto Fuel II waste water to concentration levels of 1.0 mg/L. Sensitivity was in the low ppb range with very good accuracy. LSV has been proposed for use in quantifying propylene glycol dinitrate in effluent water by examining the reduction of propylene glycol dinitrate at a silver wire electrode (Fine and Miles 1983; Navy 1984a, 1984b). Propylene glycol dinitrate was readily detectable at 0.5 mg/L. A procedure using reverse phase HPLC and UV detection has been described for the detection and quantification of propylene glycol dinitrate in waste water down to 1 mg/L (DREA 1986). Further details, including accuracy, precision, and selectivity of the methods, were not provided. TLC and UV spectrophotometry have been used to semiquantitatively monitor propylene glycol dinitrate in aqueous culture media (Wyman et al. 1984). These methods could also be applied to contaminated waste water. Lactic and pyruvic acids, suspected of being metabolites from the photolysis/photooxidation of propylene glycol dinitrate, have been identified using nuclear magnetic resonance (NMR) spectrometry (Wyman et al. 1984), but no details were reported for this method.

Analytical methods have been developed for the determination of aqueous components of Otto Fuel II other than propylene glycol dinitrate. 2-Nitrodiphenylamine has been measured in effluent water and river sediment samples using HPLC/UV and GC/FID (Army 1976). The HPLC-UV method was suitable for measuring 2-nitrodiphenylamine at a detection limit of <l0 ppm (<10 mg/L) in water, but detection limit for the GC-FID method was not provided. Dibutyl sebacate has been detected in seawater and advanced waste treatment effluent water using GC/MS (EPA 1984a; Shishido et al. 1984). No information was provided on the sensitivity and reliability of the method; however, when GC/MS was combined with three-dimensional mass chromatography (TDMC), dibutyl sebacate was easily identified in a contaminated sample for which identification was not possible using GC/MS alone (Shishido et al. 1984).

Limited data were located on the detection of Otto Fuel II components in foods. 2-Nitrodiphenylamine was measured in lettuce using GC/MS (Wickstrom et al. 1986). The sensitivity was in the sub-ppb range. Dibutyl sebacate was detected in packaged foods wrapped in dibutyl sebacate-containing plastics using high-resolution gas chromatography (HRGC)/FID (Castle et al.

1988). The sensitivity for this method was in the low ppb. No other data on the reliability and usefulness of these methods were reported.

2-Nitrodiphenylamine has also been detected in other environmental samples including propellants, smokeless powders, explosives, and gunshot residues. GC/FID was used to determine the presence of 2-nitrodiphenylamine in nitrocellulose propellants (Dykes and Alley 1974). This method had an estimated relative standard deviation (RSD) of 0.44% which is excellent repeatability for this type of analysis. However, GC methods may not be desirable for the analysis of 2-nitrodiphenylamine as N-nitrosodiphenylamine (aging product of nitrodipheylamine) is denitrosated to diphenylamine in the heated zone of the chromatograph and remains undetected (Via and Taylor 1992). HPLC/UV using reverse phase columns has also been used to determine the presence of 2-nitrodiphenylamine in propellants (Army 1986b). The method accurately identified and quantified 2-nitrodiphenylamine in the complex propellant mixture. 2-Nitrodiphenylamine in propellants has also been detected using reverse phase HPLC/EC (Bergens 1987). The author stated that HPLC/EC is more selective and sensitive than HPLC/UV and that it provides a more uniform response compared with UV detection. The detection limit was 4.3 μg/L, and the RSD was 1.O-2.0%. Methods for detecting 2-nitrodiphenylamine in smokeless powders and in gunshot residues have been proposed. For smokeless powders, use of HPLC/UV/TEA was investigated (Bender 1983). By using UV/TEA detectors in tandem, compounds could be analyzed in the low nanogram range and selectivity was increased. HRGC combined with TEA or ECD has been used for analysis of explosives in spiked hand swabs (Douse 1985). The author stated that TEA was shown to approach the sensitivity of ECD but was more selective, enabling low nanogram levels of explosives in hand swabs to be detected. Methods of analysis that were located for explosives and gunshot residues include HPLC/ECD, HPLC/UV (Bratin et al. 1981; Dahl and Lott 1987), and micellar electrokinetic capillary electrophoresis with UV spectrophotometry (MECE/UV) (Northrop et al. 1991). HPLC/ECD had a lower detection limit (4.1 μg/L) than HPLC/UV (45.5 μg/L) (Bratin et al. 1981). MECE/JV is a proposed qualitative method for providing rapid and efficient separation and detection of organic gunshot and explosive constituents. MECE is an adaptation of capillary electrophoresis where the addition of a charged micellar agent to the electrolyte provides a separation of neutral molecules. Because each component has a characteristic UV absorption profile, analysis at several different wavelengths can provide additional identification of the components. No information on accuracy, sensitivity, or specificity was given so the method cannot be compared to other located methods. Perhaps the best method available for the analysis of Otto Fuel II components in complex solid matrices is supercritical fluid extraction, supercritical fluid chromatography and MS detection and quantification. This method assures sample integrity, affords faster analysis time compared to conventional methods and enhances the sensitivity of detection (Via and Taylor 1992).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of Otto Fuel II and its components is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of Otto Fuel II and its components.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda may be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist for measuring propylene glycol dinitrate in breath, blood, and urine (Air Force 1982b; Erk et al. 1982; Litchfield 1968; Stewart et al. 1974). Most of the studies did not report enough relevant information on sensitivity, accuracy, precision, and selectivity to determine their reliability for monitoring exposure to Otto Fuel II and its components. No methods of measuring 2-nitrodiphenylamine or dibutyl sebacate in biological media were located. More thorough studies of possible methods for monitoring exposure are needed to determine the best biomarkers for monitoring exposure to Otto Fuel II and its components.

The biomarkers of effect for Otto Fuel II and its components are very general and include headache, mild metbemoglobinemia, and dizziness (Horvath et al. 1981). Since these effects are nonspecific and cannot be quantified, they are not useful biomarkers of effect for Otto Fuel II and its components. A specific biomarker of exposure is needed so that monitoring studies of occupationally exposed workers and other potentially exposed populations can be conducted.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist for detecting propylene glycol in air and water (Akimoto et al. 1980; DREA 1986; McCallum 1989; Navy 1979, 1984a, 1984b; Tomkins et al. 1985; Wyman et al. 1984), 2nitrodiphenylamine in water, sediment, lettuce, and munitions compounds (Army 1976, 1986a; Wickstrom et al. 1986; Wyman et al. 1984), and dibutyl sebacate in water and food (Castle et al. 1988; EPA 1984a; Shishido et al. 1984). Very few details on the sensitivity, accuracy, precision, and selectivity of the methods were provided. More detailed analyses of these methods are needed in order to determine their reliability for measuring background and greater levels of Otto Fuel II and its components in environmental media.

6.3.2 Ongoing Studies

No ongoing studies were located regarding analytical methods for Otto Fuel II or its components,

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding Otto Fuel II and its major components in air, water, and other media are summarized in Table 7-l.

ATSDR has derived three MRL values for propylene glycol dinitrate, the major component of Otto Fuel II. An acute inhalation MRL of 0.003 ppm was derived for propylene glycol dinitrate based on altered visual evoked responses in humans (Stewart et al. 1974). An intermediate and chronic inhalation MRL of 0.00004 ppm was derived for propylene glycol dinitrate based on decreased levels of hematocrit, hemoglobin, red blood cells, and reticulocytes and increased levels of methemoglobin in dogs (Air Force 1985a). There is no EPA reference dose (RfD) or reference concentration (RfC) for Otto Fuel II or its major components.

Under the Hazardous Materials Transportation Act, Otto Fuel II is designated as a hazardous substance subject to special requirements for packaging, labeling, and transportation (DOT 1989a, 1989b).

Table 7-1. Regulations and Guidelines Applicable to Otto Fuel II and Its Components

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Other:			
DOT	Hazardous Material Transportation Act: Class A explosive (high explosive); designated as a hazardous substance subject to special requirements for packaging, labeling, and transportation (explosive torpedo)	Yes	DOT 1989a (49 CFR 172.101); DOT 1989b
Guidelines:			
a. Air			
ACGIH	TLV TWA (skin designation)		ACGIH 1994
	Propylene glycol dinitrate	0.05 ppm (0.34 mg/m^3)	
NIOSH	REL - TWA (skin designation)		NIOSH 1992
	Propylene glycol dinitrate	0.05 ppm (0.3 mg/m^3)	
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentrations		NATICH 1992
	Propylene glycol dinitrate		
CT	8 hr avg. time	6.00 µg/m^3	
FL- Pinellas	8 hr avg. time	3.0 µg/m^3	
FL-Pinellas	24 hr avg. time	7.20x10^{-1} µg/m^3	
ND	8 hr avg. time	3.40x10^{-3} mg/m^3	
NV	8 hr avg. time	7.0x10^{-3} mg/m^3	
TX	30 min avg. time	3.00 µg/m^3	
TX	Annual avg. time	3.00x10^{-1} µg/m^3	
VA	24 hr avg. time	57.0 µg/m^3	
WA/SW	24 hr avg. time	1.00 µg/m^3	

ACGIH = American Conference of Governmental and Industrial Hygienists; DOT = Department of Transportation; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; REL = Recommended Exposure Level; TLV = Threshold Limit Value; TWA = Time Weighted Average

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical. introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

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q1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit STEL) -- The maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the

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uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A
USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0006 ppm (see footnote "c").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0006 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0006 ppm (see footnote "c" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
3 → Systemic							
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11 ↓	
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

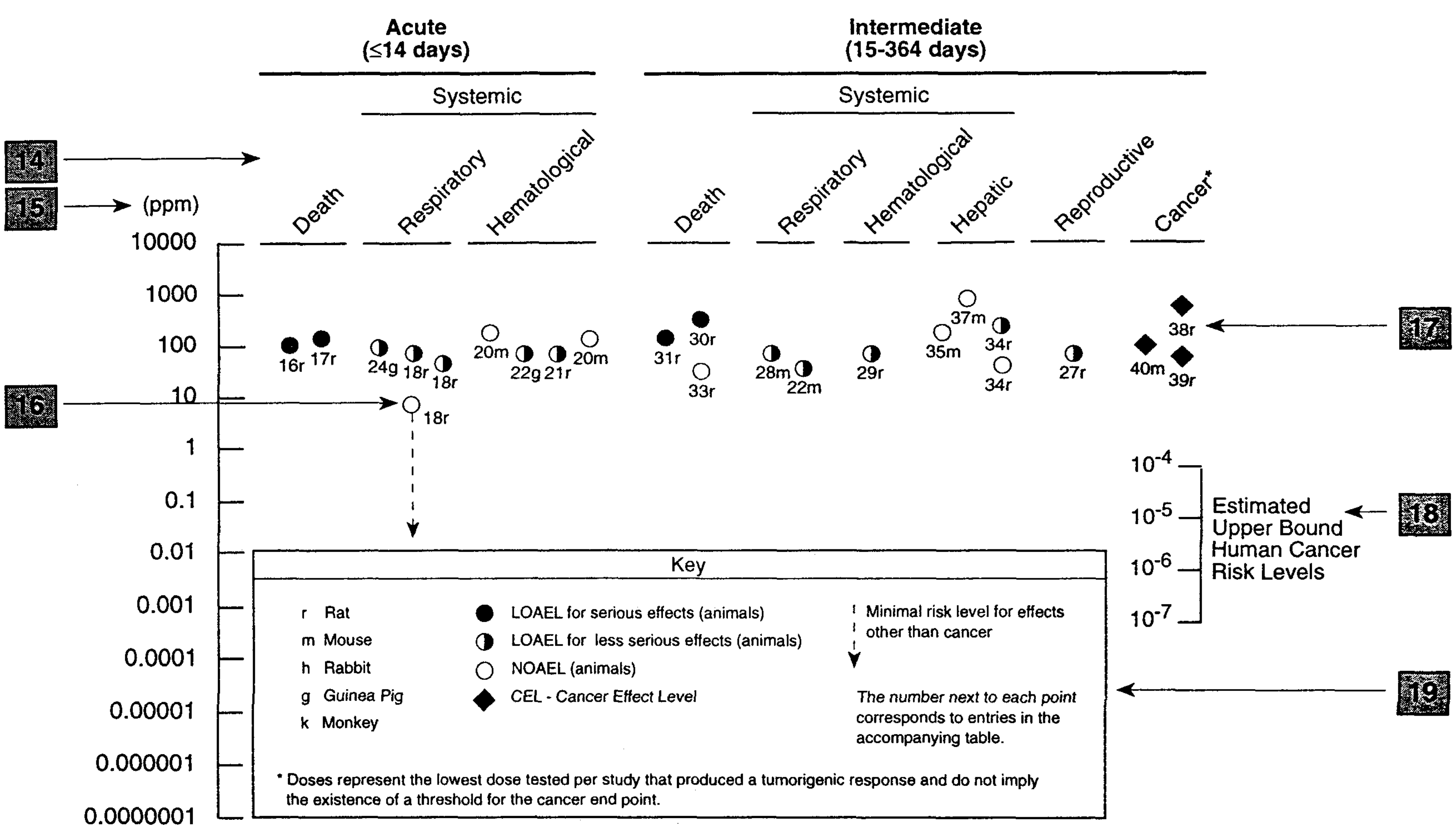
[a] *The number corresponds to entries in Figure 2-1.*

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minima1 risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.
Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure. MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.
MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	sphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
In	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K oc	organic carbon partition coefficient
K ow	octanol-water partition coefficient

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L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{L0}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mm01	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTI S	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmo1	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

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STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
GHO	World Health Organization
Wk	Week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
ϒ	gamma
μm	micron
μg	microgram

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