DRAFT

TOXICOLOGICAL PROFILE FOR STODDARD SOLVENT

Prepared by:

Clement International Corporation
Under Contract No. 205-88-0608

Prepared for:

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

May 1993

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) amended the Comprehensive Environmental Response, Compensation, and Liability Act (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). Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological 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 which present a significant risk to human health of acute, subacute, and chronic health effects.

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. 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 is intended to characterize succinctly the toxicological 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 toxicological 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, where 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 of significance to protection of public health will be identified by ATSDR and the Environmental Protection Agency (EPA). The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use. Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
Mail Stop E-29
Atlanta, Georgia 30333

This profile reflects our assessment of all relevant toxicological 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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

CONTENTS

FOREWORD iii

LIST OF FIGURES ix

LIST OF TABLES xi

1. PUBLIC HEALTH STATEMENT 1
   - 1.1 WHAT IS STODDARD SOLVENT? 1
   - 1.2 WHAT HAPPENS TO STODDARD SOLVENT WHEN IT ENTERS THE ENVIRONMENT? 1
   - 1.3 HOW MIGHT I BE EXPOSED TO STODDARD SOLVENT? 2
   - 1.4 HOW CAN STODDARD SOLVENT ENTER AND LEAVE MY BODY? 2
   - 1.5 HOW CAN STODDARD SOLVENT AFFECT MY HEALTH? 3
   - 1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO STODDARD SOLVENT? 3
   - 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 3
   - 1.8 WHERE CAN I GET MORE INFORMATION? 3

2. HEALTH EFFECTS 5
   - 2.1 INTRODUCTION 5
   - 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 5
     - 2.2.1 Inhalation Exposure 6
       - 2.2.1.1 Death 6
       - 2.2.1.2 Systemic Effects 14
       - 2.2.1.3 Immunological Effects 20
       - 2.2.1.4 Neurological Effects 20
       - 2.2.1.5 Developmental Effects 21
       - 2.2.1.6 Reproductive Effects 22
       - 2.2.1.7 Genotoxic Effects 22
       - 2.2.1.8 Cancer 22
     - 2.2.2 Oral Exposure 22
       - 2.2.2.1 Death 23
       - 2.2.2.2 Systemic Effects 23
       - 2.2.2.3 Immunological Effects 23
       - 2.2.2.4 Neurological Effects 23
       - 2.2.2.5 Developmental Effects 23
       - 2.2.2.6 Reproductive Effects 23
       - 2.2.2.7 Genotoxic Effects 23
       - 2.2.2.8 Cancer 23
     - 2.2.3 Dermal Exposure 23
       - 2.2.3.1 Death 23
       - 2.2.3.2 Systemic Effects 23
       - 2.2.3.3 Immunological Effects 23
       - 2.2.3.4 Neurological Effects 24
       - 2.2.3.5 Developmental Effects 24
       - 2.2.3.6 Reproductive Effects 24

2.2.3.7 Genotoxic Effects 24
2.2.3.8 Cancer 24
2.3 TOXICOKINETICS 25
2.3.1 Absorption 25
2.3.1.1 Inhalation Exposure 25
2.3.1.2 Oral Exposure 25
2.3.1.3 Dermal Exposure 26
2.3.2 Distribution 26
2.3.2.1 Inhalation Exposure 26
2.3.2.2 Oral Exposure 26
2.3.2.3 Dermal Exposure 26
2.3.3 Metabolism 26
2.3.4 Excretion 27
2.3.4.1 Inhalation Exposure 27
2.3.4.2 Oral Exposure 27
2.3.4.3 Dermal Exposure 27
2.4 RELEVANCE TO PUBLIC HEALTH 27
2.5 BIOMARKERS OF EXPOSURE AND EFFECT 35
2.5.1 Biomarkers Used to Identify or Quantify Exposure to Stoddard Solvent 36
2.5.2 Biomarkers Used to Characterize Effects Caused by Stoddard Solvent 36
2.6 INTERACTIONS WITH OTHER CHEMICALS 36
2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 37
2.8 MITIGATION OF EFFECTS 37
2.9 ADEQUACY OF THE DATABASE 38
2.9.1 Existing Information on Health Effects of Stoddard Solvent 38
2.9.2 Identification of Data Needs 38
2.9.3 On-going Studies 42

3. CHEMICAL AND PHYSICAL INFORMATION 43
3.1 CHEMICAL IDENTITY 43
3.2 PHYSICAL AND CHEMICAL PROPERTIES 43

4. PRODUCTION, IMPORT, USE, AND DISPOSAL 47
4.1 PRODUCTION 47
4.2 IMPORT/EXPORT 47
4.3 USE 47
4.4 DISPOSAL 47

5. POTENTIAL FOR HUMAN EXPOSURE 49
5.1 OVERVIEW 49
5.2 RELEASES TO THE ENVIRONMENT 49
5.2.1 Air 51
5.2.2 Water 51
5.2.3 Soil 51
5.3 ENVIRONMENTAL FATE 51
5.3.1 Transport and Partitioning 51
5.3.2 Transformation and Degradation 52
5.3.2.1 Air 52
5.3.2.2 Water 52
5.3.2.3 Soil 53

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 53
5.4.1 Air 53
5.4.2 Water 54
5.4.3 Soil 54
5.4.4 Other Environmental Media 54
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 54
5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 55
5.7 ADEQUACY OF THE DATABASE 55
5.7.1 Identification of Data Needs 55
5.7.2 On-going Studies 57

6. ANALYTICAL METHODS 59
6.1 BIOLOGICAL MATERIALS 59
6.2 ENVIRONMENTAL SAMPLES 59
6.3 ADEQUACY OF THE DATABASE 63
6.3.1 Identification of Data Needs 63
6.3.2 On-going Studies 64

7. REGULATIONS AND ADVISORIES 65

8. REFERENCES 69

9. GLOSSARY 85

APPENDICES

A. USER'S GUIDE A-1

B. ACRONYMS, ABBREVIATIONS, AND SYMBOLS B-1

C. PEER REVIEW C-1

LIST OF FIGURES

2-1. Levels of Significant Exposure to Stoddard Solvent and Related Compounds - Inhalation 11

2-2. Existing Information on Health Effects of Stoddard Solvent 39

5-1. Frequency of NPL Sites with Stoddard Solvent Contamination 50

LIST OF TABLES

2-1. Levels of Significant Exposure to Stoddard Solvent and Related Compounds - Inhalation 7

2-2. Genotoxicity of Stoddard Solvent and Related Compounds *In Vivo* 33

2-3. Genotoxicity of Stoddard Solvent and Related Compounds *In Vitro* 34

3-1. Chemical Identity of Stoddard Solvent 44

3-2. Physical and Chemical Properties of Stoddard Solvent 45

3-3. Possible Formulations of Stoddard Solvent 46

6-1. Analytical Methods for Determining Stoddard Solvent in Biological Materials 60

6-2. Analytical Methods for Determining Stoddard Solvent in Environmental Samples 61

7-1. Regulations and Guidelines Applicable to Stoddard Solvent 66

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about Stoddard solvent and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Stoddard solvent has been found in at least 7 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for Stoddard solvent. As EPA evaluates more sites, the number of sites at which Stoddard solvent is found may change. This information is important for you to know because Stoddard solvent may cause harmful health effects and because these sites are potential or actual sources of human exposure to Stoddard solvent.

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 Stoddard solvent, 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.

1.1 WHAT IS STODDARD SOLVENT?

Stoddard solvent is a petroleum distillate mixture of alkanes, naphthenes, and aromatic compounds. The chemicals that are in Stoddard solvent are similar to those in white spirits, which are also discussed in this profile. The mixture is sometimes called Varsol. Stoddard solvent is used as a paint thinner, as a solvent in some types of photocopier toners, in some types of printing inks, in some adhesives, in some weed killers, and as a general cleaner and degreaser. Stoddard solvent smells and tastes like kerosene. You can smell it when the level in the air is about 2 milligrams of Stoddard solvent per cubic meter of air (mg/m^3). It is a colorless, flammable liquid. See Chapters 3 and 4 for more information.

1.2 WHAT HAPPENS TO STODDARD SOLVENT WHEN IT ENTERS THE ENVIRONMENT?

Stoddard solvent is a mixture of many chemicals. Some of these evaporate into the air when Stoddard solvent spills onto soils or surface waters. These chemicals may be broken down

by sunlight or by other chemicals in the air. Stoddard solvent itself does not dissolve well in water, but some of the chemicals in Stoddard solvent do dissolve when it spills on surface water or leaks from underground storage tanks. Some of the chemicals in Stoddard solvent can attach to particles in soil or water and, in water, may sink down to the sediment. In the soil or sediment, microorganisms may break down the chemicals. See Chapter 5 for more information on what happens to Stoddard solvent when it enters the environment.

1.3 HOW MIGHT I BE EXPOSED TO STODDARD SOLVENT?

You are most likely to be exposed to Stoddard solvent if you use a product such as paint or a paint thinner that contains it. If your work involves the use of Stoddard solvent in dry cleaning fluid, paints, coatings, waxes, or equipment cleaning fluid, you may breathe in some of the components of Stoddard solvent that evaporate into the air. You may be exposed to Stoddard solvent if you breathe in air that contains Stoddard solvent after it has spilled or leaked onto soils or surface water. When it is spilled, Stoddard solvent separates into its components. So, if you become exposed, you are actually exposed to these components rather than to a single compound called Stoddard solvent. You would only breathe the components that evaporate into the air. If Stoddard solvent has contaminated groundwater, you may be exposed if you drink this water or use it for bathing or washing. If you use products that contain Stoddard solvent and do not wear protective clothing, you may be exposed if it gets on your skin. We do not know how many people may be exposed near hazardous waste sites.

1.4 HOW CAN STODDARD SOLVENT ENTER AND LEAVE MY BODY?

It is unclear what routes of exposure are most significant at hazardous waste sites. It is likely that you might be exposed to Stoddard solvent near a hazardous waste site by breathing it in the air. Although some compounds in Stoddard solvent evaporate quickly, you may be continually exposed near hazardous waste sites if the material is leaking from buried or aboveground drums or is slowly moving through the soil and seeping through the walls of the basement of a building. If Stoddard solvent is buried in leaky drums at hazardous waste sites, you may also be exposed if your skin comes in contact with contaminated soil or if you drink contaminated groundwater. Stoddard solvent can enter your body if you breathe the air containing it. When you inhale it, it can quickly enter your bloodstream. It is stored in body fat and can enter the brain. Stoddard solvent separates into its chemical components in your body. We do not know where Stoddard solvent or its components go once in the body after contact with your skin or after drinking contaminated groundwater. We do not know exactly how the mixture or its components leave the body, but it can be predicted that some components or breakdown products leave in the breath, while others leave in the urine. About half of it will leave your body within 2 days.

1.5 HOW CAN STODDARD SOLVENT AFFECT MY HEALTH?

If you were to breathe the air containing it, Stoddard solvent could cause nervous system effects such as dizziness or headaches. People who have breathed the fumes in the workplace for several years have also experienced memory loss. Rats, cats, and dogs have had seizures after breathing large amounts for several hours. It can cause bronchitis in guinea pigs when they breathe it. Stoddard solvent has not caused these effects in the few known cases of exposure. When Stoddard solvent is in the air, it can cause eye, skin, or throat irritation. The available studies have not associated any birth defects or reproductive effects in humans or animals with exposure to Stoddard solvent. We do not know if Stoddard solvent causes cancer in humans.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO STODDARD SOLVENT?

There is no specific test to determine whether you have been exposed to Stoddard solvent. Stoddard solvent is a mixture of many chemicals, and there are tests to determine whether you have been exposed to some of these individual chemicals. However, these tests cannot tell you if you have been exposed to the specific mixture of chemicals found in Stoddard solvent. See Chapters 2 and 6 for more information.

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

The government has developed regulations and guidelines for Stoddard solvent that are designed to protect the public from potential harmful health effects. The Department of Transportation regulates the transportation of Stoddard solvent because it is a hazardous material.

The Occupational Safety and Health Administration (OSHA) regulates levels of hazardous materials in the workplace. The maximum allowable amount of Stoddard solvent in workroom air during an 8-hour workday, 40-hour workweek, is 100 parts per million parts of air (ppm). The Air Force also has an Occupational Safety and Health Standard an 8-hour exposure limit of 100 ppm and a 15-minute short-term exposure limit of 150 ppm for Stoddard solvent.

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

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 Stoddard solvent 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 Stoddard solvent based on toxicological studies and epidemiological investigations.

Stoddard solvent is a mixture of numerous hydrocarbons derived by refining crude oil. It is a petroleum distillate with a boiling range of 154–202°C and a flashpoint of 38–60°C. The hydrocarbon chain length ranges from C_7 to C_{12}, although a form of Stoddard solvent called 140 flash contains C_5 and C_6 hydrocarbons as well. The mixture consists of three major groups of components: linear and branched alkanes, also known as paraffins (30–50% of the total mixture); cycloalkanes, also called cycloparaffins or naphthenes (not to be confused with naphthalenes which are bicyclic aromatics) (30–40%), and aromatic hydrocarbons (10–20%). A complete list of the individual components of Stoddard solvent is not available (Air Force 1980); however, some possible components and hydrocarbon classes are presented in Chapter 3. Exposure to Stoddard solvent and white spirits, a somewhat synonymous substance, is discussed in this profile.

Stoddard Solvent is also considered to be a form of mineral spirits, white spirits, and naphtha; however, not all forms of mineral spirits, white spirits, or naphtha are considered to be Stoddard solvent. Other petroleum distillate mixtures are also the subject of ATSDR toxicological profiles, including gasoline (ATSDR 1993). Gasoline differs from Stoddard solvent by having more smaller-chained hydrocarbons (C_5–C_{12}). Kerosene, a fuel oil, has longer-chained hydrocarbons (C_{10}–C_{16}), and more aromatic components (30–40%) than Stoddard solvent (10–20%). Stoddard solvent contains few if any alcohols, glycols, or ketones. Stoddard solvent is not expected to contain hexane or polycyclic aromatic hydrocarbons, substances that are also known to be toxic.

Within the aromatic hydrocarbon group, there are several substances that are known to be toxic, including benzenes, naphthalenes, and toluenes. The contributions of benzenes, naphthalenes, and toluenes are slight since each contributes less than 1% of the total composition of the Stoddard solvent mixture. More information on these three substances can be found in other ATSDR toxicological profiles (ATSDR 1989, 1990, 1991). However, the toxicity of the mixture is probably not governed by any single component. The toxicity of the mixture would depend on the interactions of all the components. Some components, when found together, may act additively or synergistically to enhance toxic effects. Others components may be antagonistic in combination, thus diminishing toxic effects. It cannot always be predicted how a mixture will behave based on the toxicity of its individual components. However, the toxic characteristics of the individual components may be an indicator of the potential toxicological responses of the mixture.

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.

2.2.1 Inhalation Exposure

A few studies are available in which humans were acutely exposed in the laboratory to measured levels of Stoddard solvent or white spirits in the air. No studies are available regarding health effects in humans after intermediate-duration inhalation exposure to Stoddard solvent. Workers chronically exposed to combinations of solvents, including Stoddard solvent, have been studied.

There are only a few studies showing acute toxic effects in animals (API 1987a; Carpenter et al. 1975a, 1975b). The animals were exposed to vaporized Stoddard solvent, but in real life, human inhalation exposures might be primarily to the more volatile components. Two of these animal studies used multiple animal species, but only the representative data from rats are shown in Table 2-1 and Figure 2-1. The other species had effects at similar concentrations, but only a few animals were tested. One of the studies (Rector et al. 1966) used a mixture of chemicals called mineral spirits, but the authors stated that this particular mixture was similar to Stoddard solvent, so the information is included below. Other studies testing different formulations of mineral spirits are not included. No studies are available regarding health effects in animals after chronic-duration inhalation exposure to Stoddard solvent.

2.2.1.1 Death

The only available study in humans regarding death following inhalation exposure is a retrospective cohort study on workers at an aircraft maintenance facility exposed to very low levels of Stoddard solvent as well as numerous other chemicals for at least 1 year (Spirtas et al. 1991). An exposure index was developed by

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent and Related Compounds - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference
ACUTE EXPOSURE							
Death							
1	Cat	2.5-7.5 hr				10000 (4/4 died)	Carpenter et al. 1975a,1975b
Systemic							
2	Human	30 min	Cardio	2500			Astrand et al. 1975
3	Human	30 min	Resp Derm/oc	2400 1800	2400 (eye irritation)		Hastings et al. 1984
4	Human	30 min	Derm/oc	600			Hastings et al. 1984
5	Human	6 hr	Musc/skel Hepatic Renal Gastro	610 610 610 610			Pedersen and Cohr 1984a
6	Human	15min	Derm/oc	140	2700 (slight eye irritation)		Carpenter et al. 1975a,1975b
7	Rat	4 d 4hr/d	Resp	214			Riley et al. 1984
8	Rat	8 hr	Derm/oc	2400	4600 (eye irritation, bloody nose)		Carpenter et al. 1975a,1975b
9	Mouse	1 min	Resp	4400	10000 (50% respiratory rate depression)		Carpenter et al. 1975a,1975b
10	Dog	8 hr	Derm/oc	4000	8000 (eye irritation)		Carpenter et al. 1975a,1975b

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference
Immunological							
11	Human	5 d 6hr/d		616			Pedersen and Cohr 1984b
Neurological							
12	Human	30 min		2400			Hastings et al. 1984
13	Human	30 min		2500			Gamberale et al. 1975
14	Human	6 hr		610			Pedersen and Cohr 1984a
15	Human	50 min			4000[b] (prolonged reaction time)		Gamberale et al. 1975
16	Rat	8 hr		2400	8200 (incoordination)		Carpenter et al. 1975a, 1975b
17	Dog	8 hr		4000		8000 (tremors and clonic spasms)	Carpenter et al. 1975a, 1975b
18	Cat	2.5-7.5 hr			10000 (slowed light reaction)	10000 (convulsions and tremors)	Carpenter et al. 1975a, 1975b
Developmental							
19	Rat	Gd6-15 6hr/d		2356			API 1977
INTERMEDIATE EXPOSURE							
Death							
20	Gn pig	90 d 24hr/d				363 (4/15 died)	Rector et al. 1966
21	Gn pig	90 d 24hr/d				892 (33/60 died)	Jenkins et al. 1971

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference
Systemic							
22	Rat	4 wk 5d/wk 6hr/d	Renal		1840 (tubule damage in males)		Phillips and Cockrell 1984
23	Rat	13 wk 5d/wk 6hr/d	Hemato	1900			Carpenter et al. 1975a, 1975b
			Hepatic	1900			
			Renal	1100	1900 (tubule damage in males)		
			Other	1900			
24	Rat	8 wk 5d/wk 6hr/d	Renal		570 (tubule damage in males)		Phillips 1983
25	Rat	6 wk 5d/wk 8hr/d	Resp	1353			Rector et al. 1966
			Cardio	1353			
			Hemato	1353			
			Hepatic	1353			
			Renal	1353			
			Other	1353			
26	Rat	4 wk 5d/wk 6hr/d	Renal		1840 (tubule damage in males)		Phillips and Egan 1984a
27	Rat	5 wk 5d/wk 8hr/d	Renal		6500 (tubule damage in males)		Viau et al. 1986
28	Rat	90 d 24hr/d	Resp	619	1271 (bronchitis)		Rector et al. 1966
			Cardio	1271			
			Hemato	1271			
			Renal	1271			
			Other	1271			
29	Gn pig	90 d 24hr/d	Resp	619	1271 (bronchitis)		Rector et al. 1966
			Cardio	1271			
			Hemato	1271			
			Hepatic	1271			
			Renal	1271			
			Other	1271			

DRAFT FOR PUBLIC COMMENT

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference
30	Gn pig	6 wk 5d/wk 8hr/d	Resp	596	1353 (congestion/emphysema 7/8)		Rector et al. 1966
			Cardio	1353			
			Hemato	1353			
			Hepatic	1353			
			Renal	1353			
			Other	1353			
31	Gn pig	90 d 24hr/d	Resp	892			Jenkins et al. 1971
			Hepatic	892			
			Renal	892			
32	Dog	13 wk 5d/wk 6hr/d	Hemato	1900			Carpenter et al. 1975a,1975b
			Hepatic	1900			
			Renal	1900			
			Other	1900			
CHRONIC EXPOSURE							
Reproductive							
33	Human	1-17 yr		294			Tuohimaa and Wichmann 1981

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 1.4 mg/m^3/day; concentration was adjusted to account for a 24-hour exposure and divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestational day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); yr = year(s)

DRAFT FOR PUBLIC COMMENT

FIGURE 2-1. Levels of Significant Exposure to Stoddard Solvent and Related Compounds - Inhalation

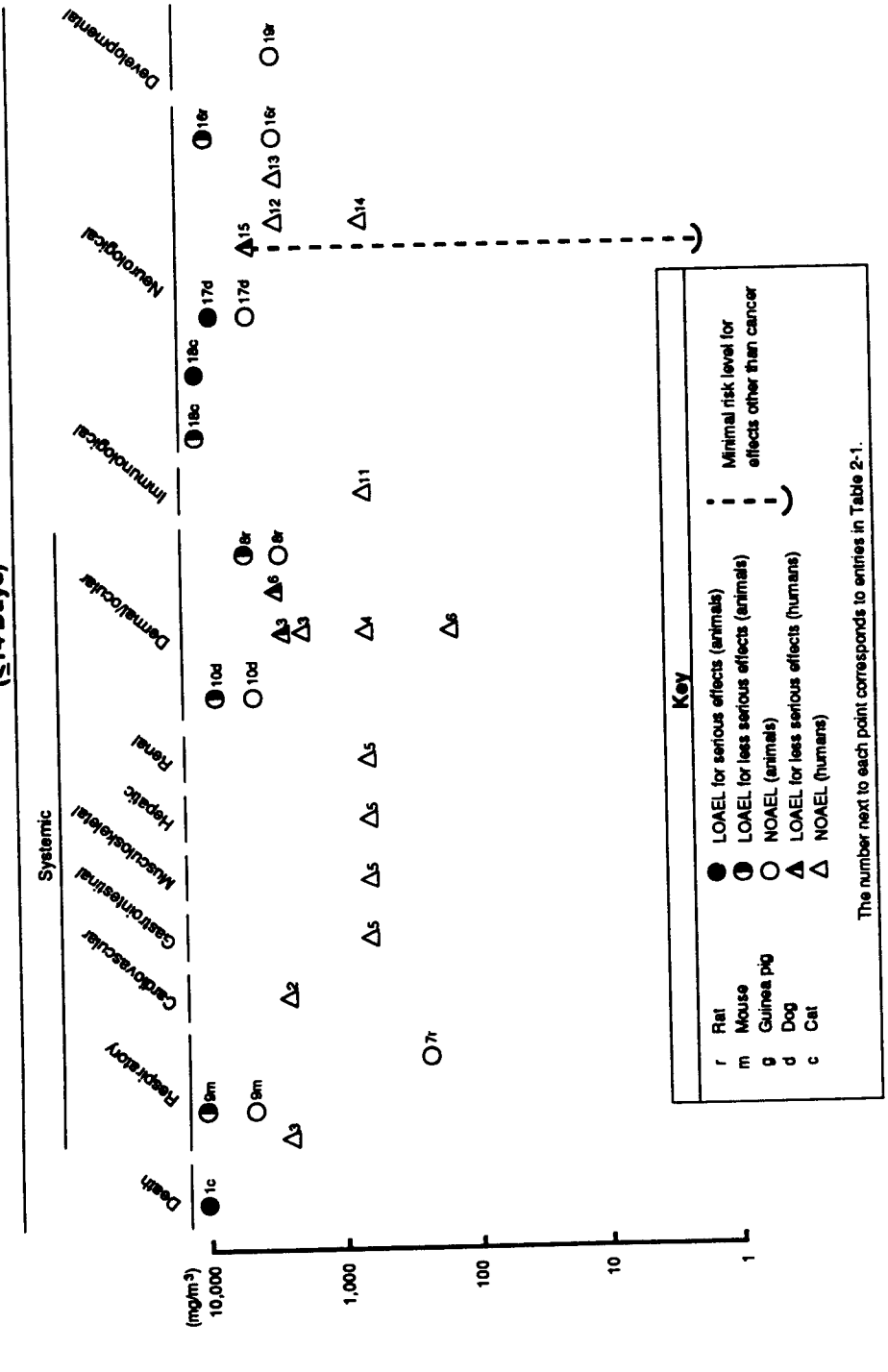


FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

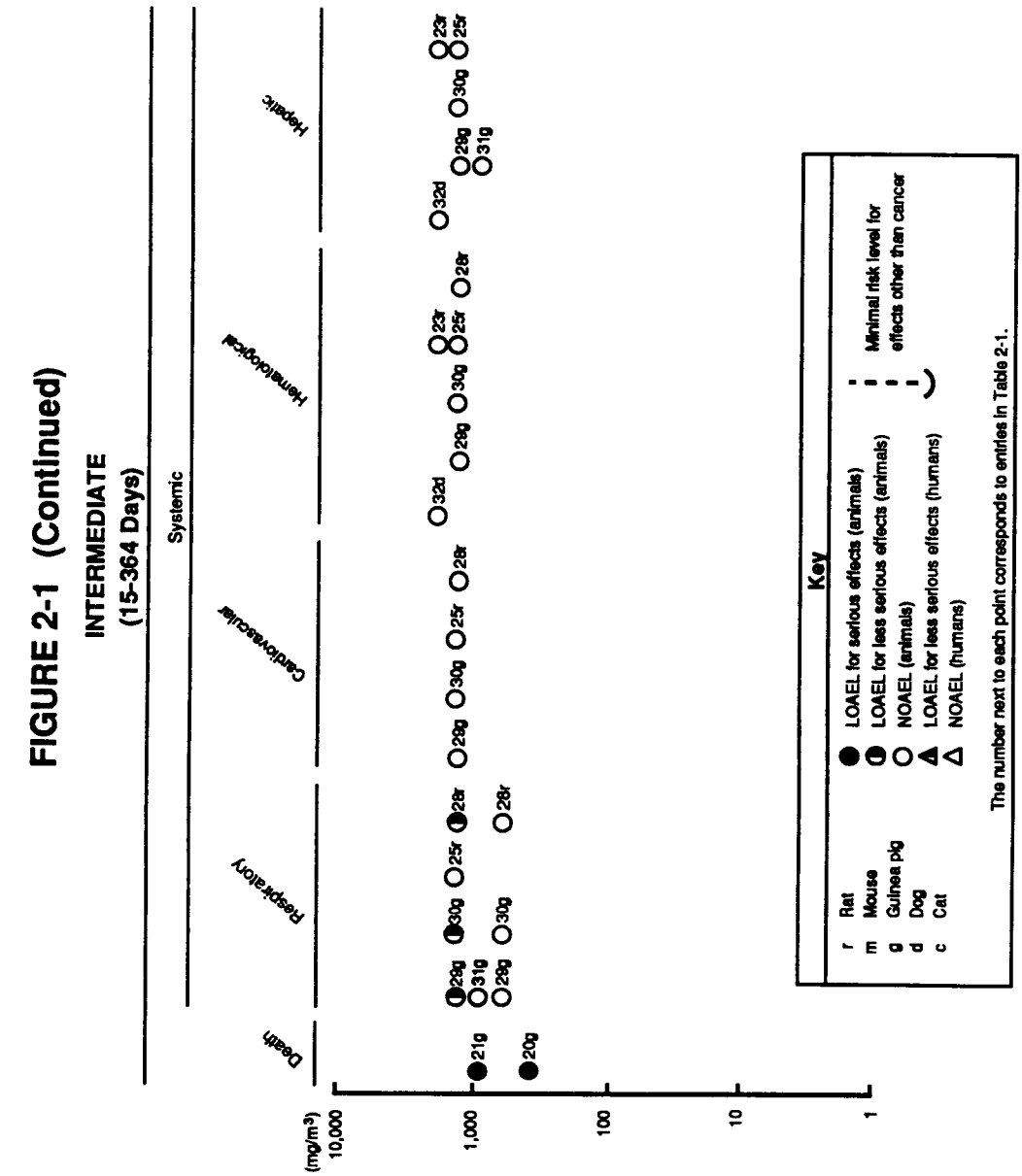
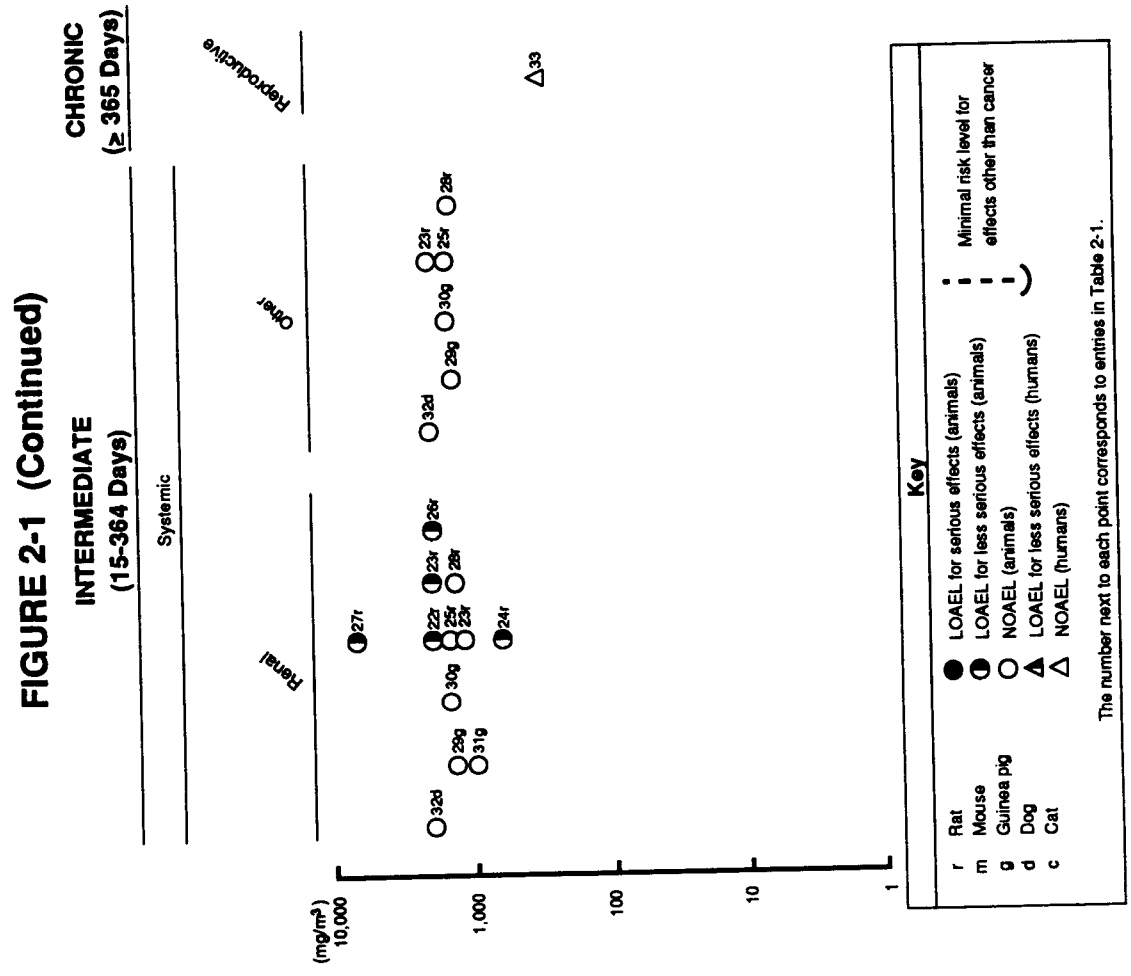


FIGURE 2-1 (Continued)



evaluating patterns of use that indicated comparative differences in exposure to various chemicals based on occupation. However, exposures could not be quantitated from these methods. The study did not show a statistically significant increase in mortality.

Rats that were exposed for 8 hours to 8,200 mg/m^3 of completely vaporized Stoddard solvent (48% alkanes, 26% monocycloalkanes, 12% dicycloalkanes, 14% aromatics) had no compound-related mortality when observed for up to 10 days (Carpenter et al. 1975a, 1975b). However, in a study with mixed breed cats, limited by the fact that there were only four, all animals died within 2.5–7.5 hours of an initiation exposure of 10,000 mg/m^3 (Carpenter et al. 1975a, 1975b). Rats, rabbits, dogs, and monkeys had no mortality immediately following continuous exposure to 1,271 mg/m^3 of vaporized mineral spirits (80–86% alkanes, 13–19% aromatics) for 90 days (Rector et al. 1966). However, the data for rabbits, dogs, and monkeys are limited by the use of three animals or less. Guinea pigs, however, were more sensitive, and 4 of 15 died after continuous exposure to 363 mg/m^3; no information on time of death was provided. The remaining test animals were sacrificed at the end of the exposure period. There were no adverse hematological, biochemical, or pathological findings that could account for the deaths of the guinea pigs. Many of the animals had liver parasites and occasionally pulmonary congestion, which indicates that poor health, rather than chemical exposure, could have contributed to the deaths. However, the worms and congestion were also present in the other tested species, which did not exhibit mortality. The study authors could not otherwise account for the species differences in mortality. When this study was repeated (continuous exposure to 892 mg/m^3 of vaporized mineral spirits [20% aromatics] for 90 days), there were deaths of 13/30 guinea pigs of the Hartley strain and 20/30 of the NMRI strain (Jenkins et al. 1971). More males than females died. In another test, male Hartley guinea pigs with a high ascorbic acid diet survived better (2/15 deaths) than those on a low ascorbic acid diet (10/15 deaths). No deaths occurred in guinea pigs or any of the other species after repeated exposures (6 weeks, 5 days/week, 8 hours/day) to 1,353 mg/m^3 (Rector et al. 1966). It is possible that the difference in guinea pig mortality between the two protocols was due to recovery time during the intermittent exposures. The reason for the apparent species difference in susceptibility to the toxic effects of Stoddard solvent is unknown. The LOAELs for death for intermediate exposure are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

For systemic effects, the highest NOAEL and all reliable LOAEL values for each species, end point, and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Two human studies regarding respiratory effects are available. In an experimental study, there was no change in respiratory rate in 10 males who were exposed to 2,400 mg/m^3 of completely vaporized Stoddard solvent for 30 minutes (Hastings et al. 1984). In a retrospective cohort study, house painters breathed paint solvents containing Stoddard solvent for 4–42 years. Precise exposure levels were not available. Each painter was given a health interview and a traditional medical examination 15 hours after exposure. They had no decrease in lung vital capacity or forced expiratory volume, as compared to workers in other industries (Hane et al. 1977).

In an acute exposure study, mice exposed to 10,000 mg/m^3 of completely vaporized Stoddard solvent for 1 minute had a reduction in respiratory rate, which was not seen at 4,400 mg/m^3 (Carpenter et al. 1975a, 1975b). Recovery tests were not performed. Rats exposed to 214 mg/m^3 of vaporized white spirits (61% alkanes, 20% cycloalkanes, 19% aromatics) for 4 hours/day for 4 days had irritation of the upper respiratory tract lining as evidenced by inflammatory cell infiltrate of the nasal cavity, trachea, and larynx and

loss of cilia, hyperplasia of basal cells, and squamous metaplasia (Riley et al. 1984). According to the authors these histopathological changes represent minimal signs of lung injury.

In an intermediate exposure study rats, rabbits, guinea pigs, dogs, and monkeys that were exposed to 1,271 mg/m^3 of vaporized mineral spirits with a composition similar to Stoddard solvent continuously for 90 days had congestion of the lungs, bronchitis, and mixed inflammatory cell infiltration (Rector et al. 1966). However, some control animals had mild congestion on gross examination, but histopathology confirmed effects in the exposed animals only. Occasional signs of lung irritation were observed at lower concentrations. The data for rabbits, dogs, and monkeys are limited by the use of three animals or less. In a protocol using repeated exposures (6 weeks, 5 days/week, 8 hours/day), only guinea pigs showed histopathological changes, which included some congestion and emphysema at 1,353 mg/m^3; this was interpreted as a possible mild irritant effect. In another study, some guinea pigs exposed continuously for 90 days to 892 mg/m^3 of vaporized mineral spirits (20% aromatics) also had pneumonitis, but the authors did not associate the disorder with the exposure (Jenkins et al. 1971). No other lung injury was evident in this latter study either.

Cardiovascular Effects. Men exposed in an experimental setting to up to 2,500 mg/m^3 of vaporized white spirits (83% aliphatic and 17% aromatic components) for 30 minutes had no compound-related changes in electrocardiograms, oxygen uptake, cardiac output, alveolar ventilation, or heart rate measured at rest or during exercise (Astrand et al. 1975). A retrospective cohort study showed no changes in blood pressure in house painters who were exposed to unspecified levels of various solvents for 4–42 years as compared to unexposed workers from other industries (Hane et al. 1977).

Studies in animals showed no histopathology in the hearts of rats, rabbits, guinea pigs, dogs, or monkeys exposed to 1,271 mg/m^3 of vaporized mineral spirits with a composition similar to Stoddard solvent continuously for 90 days or up to 1,353 mg/m^3 intermittently for 6 weeks (Rector et al. 1966). The data for rabbits, dogs, and monkeys are limited by the use of three animals or less.

Gastrointestinal Effects. Twelve volunteers exposed to 610 mg/m^3 of vaporized white spirits (57% alkanes, 25% cycloalkanes, 18% aromatics) for 6 hours reported no nausea, diarrhea, or vomiting (Pedersen and Cohr 1984a). When Stoddard solvent was used as a machine cleaner, only one of nine workers interviewed complained of nausea (Larsen and Schmunes 1974); exposure duration and levels were not reported.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to Stoddard solvent.

Hematological Effects. Case reports and epidemiological studies of humans exposed to unspecified levels of Stoddard solvent or white spirits in the workplace revealed mixed results. From the limited data available, it is not possible to conclude whether Stoddard solvent adversely affects the hematological system or not. A study of 45 car repair workers who were exposed to a variety of solvents showed statistically significant decreased red blood cell counts, increased mean erythrocyte volumes, and increased platelet volumes when compared to office workers who had no contact with organic solvents (Beving et al. 1991). One study of 52 house painters who were chronically exposed to solvents found statistically significant increases in hemoglobin concentration as compared to unexposed workers from other industries (Hane et al. 1977). In one series of case reports, normal hematological values were noted in 128 painters (Flodin et al. 1984). Case reports exist for persons who had aplastic anemia and who also were exposed to Stoddard solvent, but a causal relationship was not established (Prager and Peters 1970; Scott et al. 1959).

Normal leukocyte, hemoglobin, and hematocrit levels were found in rats, rabbits, guinea pigs, dogs, and monkeys exposed to 1,271 mg/m^3 of vaporized mineral spirits continuously for 90 days or up to 1,353 mg/m^3 intermittently for 6 weeks (Rector et al. 1966). The data for rabbits, dogs, and monkeys is limited by the use of three animals or less. These results were repeated in another 13-week exposure study that intermittently exposed rats and dogs to higher levels of completely vaporized Stoddard solvent (1,900 mg/m^3) (Carpenter et al. 1975a, 1975b).

Musculoskeletal Effects. The only available human information is from two laboratory studies. One found no changes in serum creatine kinase (an indicator of muscle cell membrane integrity) in 12 men exposed to 610 mg/m^3 of three different formulations of white spirits for 6 hours (Pedersen and Cohr 1984a). The subjects did not complain of muscle weakness. Another study of the alkane components did show increased creatine kinase (59% and 76% above baseline for 96 and 168 hours post-exposure, respectively) from exposure to 616 mg/m^3 of vaporized white spirits (99% alkanes; i.e., lacking aromatic components) for a slightly longer period (6 hours/day for 5 days) (Pedersen and Cohr 1984b). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to Stoddard solvent.

Hepatic Effects. The few available studies regarding hepatic effects indicate that acute, low-level exposures to Stoddard solvent have very minor, if any, effects on liver function. A laboratory study of 12 men exposed to 610 mg/m^3 of vaporized white spirits (with a composition similar to Stoddard solvent) for 6 hours revealed no changes in serum liver products (glucose, triglycerides, cholesterol, or urate) (Pedersen and Cohr 1984a) as compared to pre-exposure control levels. A case report describes painters who were exposed to unspecified levels of white spirits and other chemicals for chronic periods; elevated levels of serum alanine aminotransferase, but normal liver biopsies (no necrosis, steatosis, or portal tract changes), were reported (Dossing et al. 1983). A second case report describes another group of painters who had mostly normal liver parameters, except for elevated glutamyl transferase levels (Flodin et al. 1984). In an epidemiological study, a third group of painters showed normal serum transaminase levels when compared to unexposed industrial workers (Hane et al. 1977).

Guinea pigs exposed to 1,271 mg/m^3 of vaporized white spirits continuously for 90 days had no consistent pathological liver effects (Rector et al. 1966). Guinea pigs exposed to 892 mg/m^3 of vaporized white spirits continuously for 90 days had minimal fatty changes in the liver (Jenkins et al. 1971). No consistent liver histopathology was seen in rats or guinea pigs exposed to 1,353 mg/m^3 (8 hours/day, 5 days/week) intermittently for 6 weeks (Rector et al. 1966). Serum indicators of liver function were normal in rats and dogs exposed to 1,900 mg/m^3 of completely vaporized Stoddard solvent for 90 days (Carpenter et al. 1975a, 1975b).

Renal Effects. While the available human studies do not indicate that Stoddard solvent is harmful to human kidneys, the studies lack sufficient exposure data to draw any firm conclusions. In laboratory studies, humans exposed to 610 mg/m^3 for 6 hours showed normal serum sodium and potassium, normal urine albumin, and normal ß-2-microglobulin levels as compared to pre-exposure levels (Pedersen and Cohr 1984a). ß-2-Microglobulin is a protein found in humans, and it should not be confused with α_{2u}-globulin which is primarily found in male rats. One case-control study of persons with glomerulonephritis revealed no differences in occupational and/or household use exposures to organic solvents between cases and controls (van der Laan 1980). In a case report, painters who were exposed to white spirits and other solvents for 3–22 years exhibited serum and urinary parameters for kidney function within the normal range for the general population (Flodin et al. 1984). A 29-year-old male exposed by direct dermal contact and inhalation of Stoddard solvent vapors exhibited glomerulonephritis (Daniell et al. 1988). See Section 2.2.3.2 for additional details of this case.

A cause-effect relationship could not be established in one case where renal failure occurred in an individual exposed to mineral spirits (Narvarte et al. 1989).

Rabbits, guinea pigs, dogs, and monkeys that were exposed to vaporized mineral spirits at 1,271 mg/m^3 for 90 days did not have kidney pathology (Rector et al. 1966). The data for rabbits, dogs, and monkeys are limited by the use of three animals or less. No kidney histopathology was observed in guinea pigs exposed to 1,353 mg/m^3 (8 hours/day, 5 days/week) intermittently for 6 weeks (Rector et al. 1966). Dogs that were exposed to 1,900 mg/m^3 of completely vaporized Stoddard solvent for 90 days had no adverse kidney effects (Carpenter et al. 1975a, 1975b). Guinea pigs exposed to 892 mg/m^3 of vaporized white spirits for 90 days also had no kidney pathology (Jenkins et al. 1971).

In contrast, studies with Stoddard solvent and closely related mixtures demonstrated renal damage in male rats. When compared to controls, significantly more proximal renal tubule regeneration and dilated, debris-filled loops of Henle were observed in male rats exposed for 13 weeks to 1,900 mg/m^3 of completely vaporized Stoddard solvent (boiling range, 152.7-194.4°C; 47.7% paraffins, 26% monocycloparaffins, 11.6% dicycloparaffins, and 14.1% alkylbenzenes) (Carpenter et al. 1975a, 1975b). More detailed studies were conducted with hydrocarbons corresponding to the C_{10}–C_{11} or C_{12} alkane fractions of Stoddard solvent.

Fischer-344 rats of both sexes were exposed to 1,840 mg/m^3 or 5,450 mg/m^3 C_{10}–C_{11} isoparaffinic solvent (boiling point range, 156–176°C) for up to 8 weeks (Phillips and Egan 1984a). No differences from unexposed controls were observed in the female rats, except that after 4 weeks of exposure to 5,450 mg/m^3, they excreted significantly more urinary protein, but this effect was not seen at other times or doses. In contrast, exposed males consistently showed a variety of effects suggestive of mild proximal tubule damage. At both doses, urine concentrating ability after overnight water deprivation decreased significantly compared to controls after 4 or 8 weeks of exposure. After 4 weeks of recovery from the 8-week exposure to 5,480 mg/m^3, the urine concentrating ability remained significantly different from controls. Four or 8 weeks of exposure also caused a significant increase in total urine protein and glucose excreted in the urine at either dose, but this effect disappeared after 4 weeks of recovery. In the serum, coordinate changes were seen with increased BUN and creatinine and reduced glucose levels. Creatinine clearance was significantly decreased after 8 weeks of exposure to 5,450 mg/m^3, but recovered to control levels after 4 weeks with no exposure. At both doses after 4 or 8 weeks of exposure, there was a remarkable increase in epithelial cells sloughed into the tubule and recovered in the urine; this ceased after 4 weeks of recovery time. In histological sections, epithelial regeneration and tubular dilation were scored, and their incidence and degree increased with time at both exposure levels; the 4-week absence from exposure did not result in complete recovery. However, the authors emphasized that this structural damage was only observed in 5–10% of tubules. Increased numbers of protein droplets were observed in the cytoplasm of renal tubular epithelial cells from 1 week after exposure began onward, but these droplets were not assayed to determine their α_{2u}-globulin content (Phillips and Egan 1984a). A parallel experiment using both electron and light microscopy showed an increase in the number of hyaline droplets, which are characteristic of resorbed protein; this increase was proportional to exposure duration and concentration and could be observed after 5 days of exposure (Phillips and Cockrell 1984). The S_2 portion of the proximal convoluted tubule was most affected. The severity of the droplet accumulation and other pathological changes decreased after the 4-week recovery period. Positive acid phosphatase staining was consistent with the droplets being lysosomes, and electron microscopy demonstrated that the droplets were membrane enclosed, as expected of lysosomes (Phillips and Cockrell 1984). Parallel experiments in Sprague-Dawley rats with dearomatized white spirit (aromatics <0.5%, 58% paraffins, 42% naphthenes, mainly C_{11}–C_{12}; boiling range, 155–193°C) and C_{10}–C_{11} isoparaffins (boiling range, 156–176°C) resulted in similar, but less pronounced, renal histopathology (Phillips and Egan 1984b). In male but not female Fischer-344 rats, similar experiments with Stoddard solvent of unspecified composition showed comparable pathological changes

and significant differences from control in urinary glucose and protein excretion and urine concentration at 570 mg/m^3 and 4,580 mg/m^3, respectively, after as few as 4 weeks of exposure (Phillips 1983). All the pathological and functional changes observed in this experimental series are consistent with an α_{2u}-globulin mechanism for renal toxicity to the proximal tubule (Phillips 1983; Phillips and Cockrell 1984; Phillips and Egan 1984a, 1984b).

Similarly, male Sprague-Dawley rats exposed to completely vaporized white spirits (99% C_{10}-C_{12} alkanes) at 6,500 mg/m^3 for 5 weeks (8 hours/day, 5 days/week) or more showed increased excretion of albumin; female rats and castrated males were unaffected (Viau et al. 1986). The authors attributed this albuminuria to glomerular leakage since tubular resorption of a smaller filtered blood protein, β_2-microglobulin, was unaffected. After 5 weeks of exposure to 6,500 mg/m^3, there was a significant decrease in the ability to concentrate urine after 24 hours of water deprivation in exposed male rats, but not in female rats or castrated males. Histopathology in male rats exposed to 6,500 mg/m^3 revealed many hyaline droplets in S_2 proximal tubule cells (seen after 5.5, 46, or 68 weeks of exposure), tubular dilation with granular casts (seen only in rats after 5.5 weeks of exposure), and regenerative epithelia in both the proximal and distal tubules. Both intact and castrated males exposed to 6,500 mg/m^3 for 5.5 weeks had significant increases (10-fold) in kidney levels of α_{2u}-globulin compared to their respective controls; the baseline level in castrates was an order of magnitude lower initially. No differences were observed in levels of this protein in the liver, the site of synthesis. The exposed intact males also had significantly increased plasma concentrations of α_{2u}-globulin (Viau et al. 1986).

Monitoring of urinary enzyme activities suggested renal damage at sites other than the proximal tubule. After 2 weeks of exposure to either 6500 or 580 mg/m^3, there was a significant increase in urinary lactate dehydrogenase, but not in β-N-acetyl-D-glucosaminidase activity, in male rats exposed to 6,500 or 580 mg/m^3; lactate dehydrogenase activity was unchanged in castrated males and females exposed similarly (Viau et al. 1986). Since β-N-acetyl-D-glucosaminidase is a proximal tubule lysosomal enzyme while lactate dehydrogenase is a cytosolic enzyme characteristic of lower nephron regions including the loop of Henle, distal tubule, and collecting duct, the authors' interpretation of their results was that the damage is in the distal tubule rather than the proximal tubule (Viau et al. 1986; WHO 1991). However, this conclusion should be regarded with caution since activities rather than enzyme molecules were measured and other substances in urine can sometimes effect these enzyme activities (WHO 1991).

A number of the observed renal effects of Stoddard solvent are consistent with a mechanism which appears to be unique to male rats. Male rodents scent mark their territories with pheromones secreted in the urine. These pheromones are transported to the urine by low molecular weight serum binding proteins which are members of the lipocalin family (Bocskei et al. 1992). In male rats, the carrier protein is α_{2u}-globulin, which is synthesized in large quantities in the liver (Bocskei et al. 1992). X-ray crystallography has demonstrated that α_{2u}-globulin is a tetramer which has a doughnut hole in the center for transport of the ligand (Bocskei et al. 1992). Although the preferred pheromone ligand for the analogous dimeric mouse protein, mouse urinary protein, has been identified through x-ray crystallography of the bound complex, the particular pheromone with the best fit to the α_{2u}-globulin tetramer has not yet been identified (Bocskei et al. 1992). After glomerular filtration with their ligand, these carrier proteins are resorbed in massive amounts in the P_2 section of the proximal renal tubule and then catabolized in lysosomes (EPA 1991a; Kimura et al. 1991a).

Unfortunately, the α_{2u}-globulin tetramer seems to be proficient at transporting other hydrophobic molecules besides pheromones through the blood and into the urine. Other substances which apparently also bind to this carrier protein include a number of hydrophobic xenobiotics such as petroleum-derived hydrocarbons or their constituents or metabolites, including decalin and the gasoline constituent trimethylpentane (EPA 1991a). The xenobiotic-α_{2u}-globulin complex is then reabsorbed in the proximal tubule and accumulates in lysosomes

where it resists degradation. Accumulation of this complex is thought to trigger pathological responses within the kidney. This α_{2u}-globulin nephropathy syndrome is characterized by the following lesions (Alden 1986; EPA 1991a; Short et al. 1987): excessive accumulation of hyaline droplets in the P_2 segment of the proximal tubule region of the kidney; association of the hyaline droplets with the protein α_{2u}-globulin; single-cell necrosis in the P_2 segment epithelium and exfoliation of these degenerated cells; sustained regenerative tubule cell proliferation, often with tubular dilation and tubular epithelial necrosis; accumulation of granular casts formed from the cellular debris and subsequent tubule dilation at the junction of the P_3 segment and the thin loop of Henle; linear mineralization of the renal papillar tubules with hyperplasia of the renal pelvic urothelium.

The hepatic synthesis of α_{2u}-globulin is under androgenic control, and the protein is found at concentrations 100–300 times higher in male rat urine than in female rat urine (Shapiro and Sachchidananda 1982; Van Doren et al. 1983). Neither female rats nor castrated male rats show the characteristic renal pathology associated with α_{2u}-globulin nephropathy. Aging male rats show chronic progressive nephropathy symptoms that are similar to α_{2u}-globulin nephropathy, so it is important to run concurrent controls when assessing renal toxicity. α_{2u}-Globulin is not present in other rodents, but mice have a similar pheromone carrier, mouse urinary protein, which does not cause the same effects. Although other members of the lipocalin protein family do occur in non-rodent species, including humans, they are not produced in such massive quantities, and these species do not exhibit renal toxicity in response to the same set of substances that produce this characteristic toxicity in male rats (Swenberg et al. 1989).

The data discussed above suggest an α_{2u}-globulin interaction as the mechanism for Stoddard solvent–induced nephrotoxicity in the rat. The renal toxicity seems to be androgen dependent since it does not occur in female rats and is absent or greatly attenuated in castrated male rats, which only have residual levels of α_{2u}-globulin left (Borghoff et al. 1990). The pathological sequence is consistent with α_{2u}-globulin nephropathy. Hyaline droplets enclosed in lysosomes are increased in number and size in the P_2 section of the proximal renal tubule; however, no immunohistochemistry has been done to confirm that the protein in these droplets is actually α_{2u}-globulin, although the levels of this protein are elevated in the kidney as a whole in symptomatic exposed male rats (Viau et al. 1986). The fact that similar petroleum distillate mixtures and alkanes seem to cause renal toxicity via α_{2u}-globulin interactions increases the plausibility that Stoddard solvent also acts via the same mechanism.

There are two respects in which the data on the renal toxicity of Stoddard solvent are less than ideal. First, not all the studies mentioned above used complete Stoddard solvent; several focused on the predominant alkane components, so the potential contributions of the aromatic constituents have not been as well tested. A second question is whether all the renal toxicity observed is due to interactions with α_{2u}-globulin or whether simultaneous kidney damage by another subset of components via other mechanisms could have been overlooked. The urinary enzyme activity ratios suggesting distal tubule damage (Viau et al. 1986) raise some doubts in this category since α_{2u}-globulin–induced damage is typically confined to the proximal tubule.

If all the renal damage caused by Stoddard solvent in rats is due to α_{2u}-globulin interactions, then it probably does not pose a large risk of nephrotoxicity to humans. Since humans do not have α_{2u}-globulin, the issue becomes whether analogous human proteins could possibly undergo the same interactions as α_{2u}-globulin if they were produced in similar quantities. Because humans are not known to synthesize and resorb other lipocalin proteins in such massive quantities as rats do with α_{2u}-globulin, it is unlikely that Stoddard solvent would cause such remarkable toxicity even if an interaction did occur. To completely dismiss the possibility of human risk, members of the human lipocalin family which are filtered and resorbed in the kidney could be

assayed to determine their ability to bind similar xenobiotics or metabolites and whether this binding inhibited catabolism.

Dermal/Ocular Effects. Humans exposed to 600 mg/m^3 of completely vaporized Stoddard solvent for 30 minutes in a controlled laboratory setting showed no eye, throat, or nasal irritation as indicated by eye blink, swallowing, or respiratory rates, respectively (Hastings et al. 1984). Similarly, subjective reports of eye, throat, and nasal irritation were not statistically different between individuals exposed to 2,400 mg/m^3 Stoddard solvent and those exposed to air, but the increase in the number of reports of eye irritation was dose related in exposed individuals (Hastings et al. 1984). However, subjectively reported slight eye irritation occurred in individuals exposed to 2,700 mg/m^3 of completely vaporized Stoddard solvent for 15 minutes (Carpenter et al. 1975a, 1975b). Also, individuals exposed to 2,400 mg/m^3 for 30 minutes exhibited eye irritation as measured by the eye blink rate (Hastings et al. 1984).

Eye irritation was also seen in rats during acute exposure to 4,600 mg/m^3 of completely vaporized Stoddard solvent and in dogs exposed to 8,000 mg/m^3 (Carpenter et al. 1975a, 1975b).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to Stoddard solvent.

Rats, rabbits, guinea pigs, dogs, and monkeys exposed to 1,271 mg/m^3 of vaporized mineral spirits for 90 days had normal body weight gain (Rector et al. 1966). However, the data for rabbits, dogs, and monkeys are limited by the use of three animals or less. These results were also noted following intermittent exposure to up to 1,353 mg/m^3 mineral spirits for 6 weeks (Rector et al. 1966). No adverse effects on body weight were seen in rats or dogs exposed to 1,900 mg/m^3 completely vaporized Stoddard solvent for 90 days (Carpenter et al. 1975a, 1975b).

2.2.1.3 Immunological Effects

In a laboratory study, humans exposed to 616 mg/m^3 of vaporized white spirits (Shellsol, approximately 99% alkanes) for 5 days, 6 hours/day, showed no changes in serum immunoglobulins (IgG, IgA, IgM) (Pedersen and Cohr 1984b). However, this is not a complete test of immune function.

No studies were located regarding immunological effects in animals after inhalation exposure to Stoddard solvent.

2.2.1.4 Neurological Effects

The most sensitive indicator of toxic effects of Stoddard solvent is effects on the nervous system. Sensitive neurological tests have revealed neurological dysfunction in humans. In a laboratory experiment, eight sedentary men were exposed to 4,000 mg/m^3 of completely vaporized white spirits for 50 minutes (Gamberale et al. 1975). Changes were found in simple reaction time but not in perceptual speed, short-term memory, or manual dexterity when compared with pre- and post-exposure self controls. An acute inhalation MRL was derived from a LOAEL of 4,000 mg/m^3. The concentration for the MRL was adjusted to account for a 24-hour exposure, and appropriate uncertainty factors were applied. Another human study also showed minor neurological effects (dizziness in two of six men tested) from a 15-minute exposure to 2,700 mg/m^3 Stoddard solvent (Carpenter et al. 1975a, 1975b). However, controls were not used for comparison in this study.

Additional data from human studies indicate levels at which neurological effects did not occur. Men exposed for 30 minutes to up to 2,400 mg/m^3 of completely vaporized Stoddard solvent had no dose-related changes in hand-eye coordination, reaction time, or motor skills (Hastings et al. 1984). Similarly, perceptual speed, numerical ability, manual dexterity, reaction time, and short-term memory were not altered by exposure to 2,500 mg/m^3 of white spirits for 30 minutes; however, testing began after only 10 minutes of this exposure (Gamberale et al. 1975). Humans exposed to 610 mg/m^3 of Varnoline for 6 hours had no complaints of headache, dizziness, visual disturbances, tremor, muscle weakness, incoordination, sleep disturbances, or skin paraesthesia within 48 hours of the initiation of the exposure (Pederson and Cohr 1984a).

Neurological effects have been described in several case reports (Bruhn et al. 1981; Daniell et al. 1988; Flodin et al. 1984), epidemiological studies (Hane et al. 1977), and cohort studies (Arlien-Soborg et al. 1979; Gregersen et al. 1984; Mergler et al. 1988; Olson 1982) in which workers were chronically exposed to Stoddard solvent via the inhalation or dermal routes. In these retrospective studies, the exposure concentrations were not measured. In most cases, the exposure levels were not known and the estimated exposure did not correlate well with the degree of impairment. Additionally, the workers were exposed to a variety of solvents in addition to Stoddard solvent. Therefore, cause-effect relationships cannot be established. Exposed persons have had a variety of neurological findings including headaches (in 29/50; Arlien-Soborg et al. 1979), color blindness (66.6% of printshop workers; Mergler et al. 1988), cerebral atrophy (Mikkelsen et al. 1988), memory deficits (in 45/50; Arlien-Soborg et al. 1979; in 38/65; Gregersen et al. 1984), and fatigue (in 38/50; Arlien-Soborg et al. 1979; in 28/65; Gregersen et al. 1984). The reversibility of headaches and fatigue was not addressed in Arlien-Soborg (Arlien-Soborg et al. 1979) and Gregersen (Gregersen et al. 1984) studies. In another study however, the headaches and fatigue did not occur once the workers were off the job for a few days (Daniell et al. 1988). In contrast, the cerebral atrophy and memory deficits persisted several years after the workers were no longer exposed (Bruhn et al. 1981; Gregersen 1988). The cerebral atrophy was measured by a computerized tomography scan, and the memory deficits were revealed by a psychological examination. Neurological examinations were also performed on these subjects. Information regarding dermal-exposure toxicity is also discussed for some studies (Daniell et al. 1988; Mergler et al. 1988) because both inhalation and dermal exposures may have occurred in these cases (see Section 2.2.3.4.).

When exposed for 8 hours, rats showed incoordination at 8,200 mg/m^3 and dogs had tremors and convulsions at 8,000 mg/m^3; cats, exposed for 2.5–7.5 hours, exhibited slowed light reaction, convulsions, and tremors at 10,000 mg/m^3 (Carpenter et al. 1975a, 1975b). The reversibility of the effects short of death were not studied. The data are limited for dogs and cats because only one female dog and four male cats were tested. There are no available intermediate- or chronic-duration studies of neurophysiological or behavioral effects in animals. All reliable NOAELs and LOAELs for neurological effects in humans and animals are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to Stoddard solvent.

Rats exposed to up to 2,356 mg/m^3 of Stoddard solvent vapor, for 6 hours/day during gestation days 6–15, had no compound-related skeletal or visceral abnormalities from exposure during organogenesis. Average fetal weights were not changed, nor was the mean litter size (API 1977). There was no compound-related maternal toxicity. Some of the litters included animals with skeletal variations, but the incidences of these variations were not dose related and were not considered to be malformations by the study authors. The NOAEL value is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

Seven men who were exposed for 6 hours/day for 5 days to 616 mg/m^3 of vaporized white spirits (with a composition of 99% alkanes, as compared to 30–50% alkanes in Stoddard solvent) had a decrease ($p<0.05$) in serum follicle-stimulating hormone levels 3 days post-exposure as compared to pre-exposure levels (Pedersen and Cohr 1984b). This change did not correspond to blood or adipose levels of white spirits. No tests of reproductive function were performed. In another study, 11 men in a printing factory were occupationally exposed to a wide variety of solvents, including 294 mg/m^3 of white spirits for 1–17 years. Sperm counts, motility, and morphology were monitored for 2 months, and all values were normal (Tuohimaa and Wichmann 1981).

No studies were located regarding reproductive effects in animals after inhalation exposure to Stoddard solvent.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to Stoddard solvent.

Exposure to vaporized white spirits at 50,000 mg/m^3 for five periods lasting 5 minutes each failed to significantly increase bone marrow micronuclei in four male mice (Gochet et al. 1984). Each 5-minute period of exposure was separated from the next by an additional 5 minutes.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

The only available human data are from a case-control study of 32–100 individuals who had cancer and who were questioned on their exposure to petroleum products (Siemiatycki et al. 1987). Statistically significant positive odds ratios were found for mineral spirits and prostate cancer. Nonsignificant but positive odds ratios were also reported for non-Hodgkin's lymphoma and squamous cell carcinoma of the lung. The study only tested one hypothesis, based on the association between exposure and cancer. The study authors could not provide a mechanistic explanation for the association between solvent exposure and prostate cancer or lymphomas. The study did not have the statistical power to establish a link between exposure to mineral spirits and lung cancer because the confidence intervals around the odds ratio estimates were too wide to suggest a correlation.

No studies were located regarding cancer in animals after inhalation exposure to Stoddard solvent.

2.2.2 Oral Exposure

No studies were located regarding human or animal health effects following oral exposure to Stoddard solvent for any end point or duration category. In general, ingestion of most petroleum distillates at doses less than 1,000 mg/kg causes little toxicity (Ellenhorn and Barceloux 1988). For further information, see the ATSDR toxicological profiles on gasoline, jet fuels, or fuel oils (ATSDR 1993). It is possible that if Stoddard solvent were swallowed, some would be taken into the lungs by aspiration, and this would be expected to cause pneumonitis (Ellenhorn and Barceloux 1988).

No studies were located regarding the following end points after oral exposure to Stoddard solvent:

2.2.2.1 Death
2.2.2.2 Systemic Effects
2.2.2.3 Immunological Effects
2.2.2.4 Neurological Effects
2.2.2.5 Developmental Effects
2.2.2.6 Reproductive Effects
2.2.2.7 Genotoxic Effects
2.2.2.8 Cancer

2.2.3 Dermal Exposure

Because of the lack of quantifiable exposure data, no studies regarding dermal exposure are suitable for presentation in tables on levels of significant exposure.

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to Stoddard solvent.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or hepatic effects in humans or animals after dermal exposure to Stoddard solvent.

Renal Effects. The only information on the possible effects of Stoddard solvent on the kidneys of humans after dermal exposure comes from an occupational case study. A 29-year-old man handled brushes soaked in Stoddard solvent while not wearing gloves for 1 year and developed glomerulonephritis (Daniell et al. 1988). On a typical day, he spent about 6 hours using the solvent. The patient's glomerulonephritis was associated with antibodies to the glomerular basement membrane. Exposure concentrations were not reported. Both dermal and inhalation exposure are likely in this case.

No studies were located regarding renal effects in animals after dermal exposure to Stoddard solvent.

Dermal/Ocular Effects. Five men who wore coveralls that were damp from dry cleaning with Stoddard solvent developed sores on the penis and buttocks (Nethercott et al. 1980). None had an allergic reaction in a patch test. Standard texts on industrial hygiene list Stoddard solvent as a possible eye, skin, nose, and throat irritant (McDermott 1975; NIOSH 1990; Sax and Lewis 1989).

Dermal exposure to white spirits (three times daily for 3 days) resulted in skin irritation in guinea pigs as evidenced by an increase in mean epidermal thickness, visible redness, palpable induration, and evident swelling (Anderson et al. 1986).

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to Stoddard solvent.

2.2.3.4 Neurological Effects

A 29-year-old man who used Stoddard solvent as a cleaning agent while not wearing gloves, for approximately 6 hours per day for 1 year, occasionally reported feeling "high" and experienced bifrontal headaches that began during work and subsided in the evenings and over weekends (Daniell et al. 1988). Exposure concentrations were not reported. Both dermal and inhalation exposure are likely in this case.

In another occupational study, the incidence of acquired color vision loss (dyschromatopsia) was investigated in 30 printshop employees exposed by the inhalation and dermal routes (Mergler et al. 1988). The employees were divided into three groups based on product exposure: (1) graphics department workers with occasional exposure to heated wax, (2) photo- and polycopy operators with exposure to solvents containing alcohols, perchloroethylene, and Stoddard solvent, and (3) bookbinders and printers with exposure to solvents containing methylene chloride, xylene, toluene, and Stoddard solvent. When compared to the controls, the printshop employees as a whole had a significantly higher mean color confusion index. Furthermore, groups 2 and 3 of the solvent-exposed employees had higher incidences of color confusion than group 1. The employees in groups 2 and 3 also exhibited complex color vision loss (i.e., both blue-yellow and red-green loss), whereas the controls and exposure group 1 only had blue-yellow loss. The color confusion index was related to both age and job type, but complex color loss was only related to job type. This study suggests that solvents, possibly including Stoddard solvent, may cause neurological damage in the form of acquired color vision loss. However, since the workers were exposed to multiple solvents simultaneously, it is impossible to determine which solvent or combination of solvents may have produced the dyschromatopsia. In addition, neither exposure doses nor durations were discussed.

Only one study was located regarding neurological effects in animals after dermal exposure to Stoddard solvent. Rats had a daily 3-hour exposure to white spirits for 6 weeks on a 12-cm^2 area of the tail (Verkkala et al. 1984). The absorbed dose was calculated by the authors to be 210 mg, but they did not describe how the calculation was performed. Exposure had little effect on motor conduction velocity or motor amplitudes in response to stimulation. Histological analysis revealed axonal prenodal swellings. No other functional or behavioral tests were performed.

No studies were located regarding the following health effects in humans or animals after dermal exposure to Stoddard solvent:

2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to Stoddard solvent.

Squamous cell carcinomas were found in 6 out of 50 exposed mice from a lifetime skin-painting study using a rust-preventive compound consisting of 90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether (EPA 1984c). No tumors were found in mineral oil controls. Since the test involved three constituents, it is not possible to determine which one or combination was responsible for the tumors. In fact, none of the three substances has previously been identified as a carcinogen. The design of this study makes the results too ambiguous to determine whether Stoddard solvent is carcinogenic, but it does suggest a potential area of concern. The possibility that Stoddard solvent could initiate or promote squamous

cell carcinomas should not be completely discounted until a similar experiment using Stoddard solvent alone is conducted.

2.3 TOXICOKINETICS

The toxicokinetic properties of Stoddard solvent are not well defined by the available data. Toxicokinetic data that are specific to the three classes of Stoddard solvent components (i.e., alkanes, cycloalkanes, and aromatics) are also lacking.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Following acute inhalation exposure to white spirits (600 mg/m^3 in a laboratory setting), white spirits was found in the blood and subcutaneous fat (Pedersen et al. 1984, 1987). The white spirits consisted of 99% alkanes (C_8-C_{12}), which is greater than the 30–50% alkanes found in Stoddard solvent. The spectrometrical pattern produced by the evaporation of the biopsy samples indicated that the approximately 200 constituents of the white spirits were absorbed differently. The calculated pulmonary uptake from an exposure to 600 mg/m^3 for 3 hours was about 400 mg (133 mg/hour) in men who weighed an average of 73±8 kg (Pedersen et al. 1987). Mean residence time was 47.5 hours (Pedersen et al. 1987). The volume of distribution at steady state was 749 L, indicating that concentration was occurring in a compartment such as adipose tissue. Total body clearance was 263 mL/minute (Pedersen et al. 1987). The calculated uptake for exposure to the same level for a longer period (5 days, 6 hours/day) was 3,464±329 mg (115±11 mg/hour). Thus, the rate of inhalation absorption was fairly constant over the different exposure intervals measured here. Mean blood concentration was 2 mg/L on day 1 and 2.54 mg/L on day 5, showing accumulation of white spirits in the blood (Pedersen et al. 1984). There are no other studies from animals or humans that can be used to verify these results.

In general, it can be expected that the more highly volatile components of Stoddard solvent would cross from the lungs into the bloodstream more readily than other components (Klaassen 1991). The components with higher blood/gas phase solubility ratios (such as the aromatics: substituted benzenes and toluenes) would be expected to be absorbed more completely than those with lower ratios (such as the cyclohexanes) (Klaassen 1991).

Men exposed to up to 2,500 mg/m^3 of white spirits (83% aliphatic and 17% aromatics) during rest and exercise in the laboratory had average uptakes of 50% for the aliphatic components and 62% for the aromatics, as determined by measuring the representative components (n-decane and 1,2,4-trimethylbenzene) in inspiratory and expiratory air (Astrand et al. 1975). The exposure consisted of 30-minute exposure periods interrupted by three 30-minute exercise periods. Pre-exercise concentrations of alveolar air were 255 mg/m^3 of aliphatic components and 30 mg/m^3 of aromatic components. Exposure to 1,250 mg/m^3 of white spirits for 30 minutes resulted in arterial blood concentrations of 1.7 mg/kg for the aliphatics and 0.2 mg/kg for the aromatics. Thus, the aromatics appear to be more soluble in blood and more efficiently absorbed through the lungs.

2.3.1.2 Oral Exposure

No studies were located regarding absorption of Stoddard solvent following oral exposure in humans or animals. Other petroleum distillates with longer carbon chains, such as kerosene (C_{10}-C_{16}), are very poorly absorbed from the gastrointestinal tract (Dice et al. 1982; Mann et al. 1977; Wolfsdorf and Kundig 1972). The

smaller (C_9-C_{11}), alkane or aromatic hydrocarbons (10–20% in Stoddard solvent) may be more readily absorbed (Litovitz and Greene 1988). The absorption of gasoline, which contains a higher proportion of aromatics (20–50%) but also smaller components (C_4-C_{12}), appears to be relatively complete (NESCAUM 1989). The rate and extent of gastrointestinal absorption would be expected to be dependent on the lipophilicity and size of the various components and the amount of food in the stomach.

2.3.1.3 Dermal Exposure

No studies were located that evaluated absorption following dermal exposure to Stoddard solvent in humans or animals. However, daily applications of white spirits (absorbed dose of 210 mg) for 6 weeks on the tail of rats were associated with axonal prenodal swellings (Verkkala et al. 1984), indicating that dermal absorption had occurred. The aromatic hydrocarbons are expected to have higher skin penetration than the aliphatic hydrocarbons.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Following acute inhalation exposure of eight male individuals to white spirits (Shellsol, 99% alkanes, at 600 mg/m^3 for 3 hours or 6 hours/day for 5 days), white spirits was found to accumulate in the blood and subcutaneous fat (Pedersen et al. 1984, 1987). For the single exposure, the estimated mean half-life in fat was 46 hours. Following repeated exposures to white spirits, the mean concentration in the fat was 41.1 mg/kg (Friday afternoon) (Pedersen et al. 1984). On Monday morning, the concentration in fat was 31.7 mg/kg, indicating that only 23% was removed over the period of non-exposure. The concentration of white spirit in fat found each afternoon correlated significantly with the total dose (Pedersen et al. 1984). A mathematical model was developed using measured blood values to calculate concentrations in various tissues (Pedersen et al. 1987). The model was considered to be a good predictor of tissue concentration since measured blood and fat values closely followed the fitted values. The partition coefficient for adipose tissue:blood was calculated to be 47. Estimated maximum steady-state concentrations were about 55 mg/kg for fat and 5 mg/kg for brain; estimated minimum steady-state concentrations were 35 mg/kg for fat and 0.6 mg/kg for brain (Pedersen et al. 1987). No other human or animal data are available to verify this calculation. Since central nervous system effects are common following exposure to white spirits, it can probably enter the brain. The study described above uses mathematical calculations to estimate how much could enter the brain, based on distribution to fat and to blood, but the study did not actually measure distribution to this organ. No studies were available in which distribution to any other organs nor the distribution of the aromatic components was measured.

2.3.2.2 Oral Exposure

No studies were located regarding distribution following oral exposure in humans or animals.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution following dermal exposure in humans or animals.

2.3.3 Metabolism

Men who were exposed to a mist of a specific type of Finnish white spirits used for washing cars (Pfaffli et al. 1985) had elevated levels of dimethylbenzoic acid, a metabolite of trimethylbenzene, in their urine following

the workshift. This study attempted to quantify exposure to white spirits through the analysis of dimethylbenzoic acid isomers, which are easily detected markers. The amount excreted was linearly related to the estimated exposure level. The composition of the white spirits in this study included 11% aromatics with 1% trimethylbenzene isomers, which is similar to the compositions of Stoddard solvent used in the United States.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion of Stoddard solvent following inhalation exposure in humans or animals. It is expected that components or metabolites of Stoddard solvent that are volatile but have low solubility in the blood, would be rapidly exhaled from the lungs. Like absorption, this process is governed by blood/gas solubility ratios (Klaassen 1991). Components with low blood/gas ratios would be most rapidly excreted from the lungs because of their low blood solubility, while those with high blood/gas solubility ratios would be eliminated less efficiently by the lungs due to their high blood solubility; this situation is exactly the reverse of that for inhalation absorption (Klaassen 1991). The aromatic hydrocarbons are expected to be excreted primarily in the urine (Klaassen 1991).

2.3.4.2 Oral Exposure

No studies were located regarding excretion following oral exposure in humans or animals. It is expected that the poorly absorbed components of Stoddard solvent would continue through the gastrointestinal tract to the feces.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion following dermal exposure in humans. Rats exposed to daily applications of white spirits (absorbed dose of 210 mg) on the tail for 6 weeks excreted dimethylbenzoic acid isomers (2,3-, 2,4-, 2,5-, 3,4-, 3,5-dimethylbenzoic acid) in the urine (Verkkala et al. 1984). For more information on the significance of dimethylbenzoic acid, see Section 2.2.3. No other metabolic parameters have been measured.

2.4 RELEVANCE TO PUBLIC HEALTH

Very little information is available on the effects other than neurotoxicity of Stoddard solvent on humans and animals. No studies have been performed regarding oral exposure in humans or animals. Most of the toxicological investigations of Stoddard solvent have focused on inhalation exposures. In almost all cases, it was completely vaporized. Although Stoddard solvent as a whole is relatively volatile, most human exposure scenarios are likely to result in greater exposure to the more volatile fractions, including the aromatics, than to the less volatile components. If a significant amount of toxicity is due to the less volatile fractions, the studies using completely vaporized Stoddard solvent may exaggerate the effects expected when extrapolated to more realistic human exposure situations. On the other hand, if most of the toxicity is due to the more volatile components, and substituted aromatics and naphthalenes do tend to be more toxic than alkanes in general, then the complete vaporization experiments may fairly accurately represent the effects from exposure to Stoddard solvent fumes. In the absence of other data, it is reasonable to extrapolate human risk from these inhalation exposure studies to completely vaporized Stoddard solvent.

The effects that are the most likely to occur following inhalation or dermal exposure are neurological effects, which are discussed below. Adverse respiratory effects have been seen in a few animal studies, although the reliability of the findings in some of the studies is questionable because of similar adverse findings in the controls. Adverse respiratory effects have not been seen in humans. It is possible that aspiration of Stoddard solvent may result in pneumonitis, assuming that the Stoddard solvent acts in a manner similar to the related mixture, kerosene. The reports on developmental and reproductive effects are minimal and negative. Evidence of genotoxicity is generally negative. The evidence of carcinogenicity is negative in humans. However, positive findings of squamous cell carcinomas were reported in one mouse study. Conclusions specific to Stoddard solvent are limited because the study tested a rust-preventive compound that consists of 90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether. However, the data identify a potential area of concern.

The available evidence indicates that the nervous system is the most sensitive target for acute exposure to Stoddard solvent. The studies on which this Minimal Risk Level (MRL) is based have not been replicated in their entirety, so data from further research may provide a basis for reconsideration of this MRL.

An acute inhalation MRL of 1.4 mg/m^3/day has been derived from the less serious Lowest Observed Adverse Effect Level (LOAEL) of 4,000 mg/m^3 based on prolonged reaction time in sedentary male human volunteers exposed to completely vaporized Stoddard solvent for 50 minutes (Gamberale et al. 1975). Central nervous system function was evaluated in multiple tests including perceptual speed, simple reaction time, short-term memory, numerical ability, and manual dexterity. When control results in the same volunteers were compared to results during the exposures, the only significant difference was in the simple reaction time test. Since there was only one exposure concentration of 4,000 mg/m^3, the MRL was derived by normalizing to a 24-hour exposure, and then uncertainty factors of 10 each were applied for human variability and the use of a LOAEL. It should be noted that because of practical constraints, these tests were conducted on volunteers at rest and that parallel pharmacokinetic studies have demonstrated greater uptake during exercise (Astrand et al. 1975). However, the uncertainty factors used in deriving the MRL should be adequate to account for the differences between rest and exercise.

There are other studies that support the hypothesis that the central nervous system is the most sensitive target for acute exposure to Stoddard solvent and suggest that exposures below 1.4 mg/m^3/day will not result in central nervous system toxicity. Several of these studies involve effects on central nervous system–mediated motor coordination. For example, in one human study (Hastings et al. 1984), male volunteers were exposed for 30 minutes to completely vaporized Stoddard solvent at 0, 600, 1,200, 1,800, and 2,400 mg/m^3. CNS/motor function was tested in three ways, through eye-hand coordination, reaction time/decision making, and video game visual-motor skill/eye-hand coordination challenges. When results during all exposures were compared to pre- and post-exposure control performances, there was a statistically significant difference for only the video game eye-hand coordination test. However, this difference was due to impairment only at 600 mg/m^3; the results at other exposure levels did not differ from the controls. Since the putative effect seen at 600 mg/m^3 was not observed at the higher doses, 2,400 mg/m^3 was considered a NOAEL. Another human volunteer study of 12 males showed no changes in subjective symptoms such as headache, dizziness, visual disturbances, tremor, muscle weakness, incoordination, or skin paraesthesia, as determined by a questionnaire on subjective symptoms after a 6-hour exposure to 610 mg/m^3 of Varnoline (Pedersen and Cohr 1984a). This questionnaire on subjective experiences is only a crude indicator of central nervous system effects compared to the more sensitive functional tests used in the MRL study. In a test of human volunteers, two out of six reported slight dizziness after a 15-minute exposure to 2,700 mg/m^3 (Carpenter et al. 1975a, 1975b). In rats, a slight coordination loss after an 8-hour exposure to 8,000 mg/m^3, but not to 2,400 mg/m^3, was observed (Carpenter et al. 1975a, 1975b). Since the incoordination was seen during case-side observation, rather than

in more sensitive functional tests, it is not surprising that the effect is not seen until a somewhat higher integrated concentration is administered than that in the study from which the MRL is derived. If calculations similar to those used for MRL derivation were applied to the three NOAEL exposures discussed above, the results would be within an order of magnitude (ten fold) of the MRL actually derived. Thus, these three studies are supportive of the MRL. Furthermore, much higher acute inhalation doses have caused much more blatant nervous system effects. Incoordination or seizures have been observed in rats, cats, and dogs after an inhalation exposure to 1400 ppm for 8 hours, 2 hours and 5 hours, respectively; cats also exhibited slowed light reaction (Carpenter et al. 1975a, 1975b). Other chronic epidemiological studies on the neurological effects of Stoddard solvent are discussed below.

There were no human or animal studies suitable for developing MRLs for intermediate- or chronic-duration exposures to Stoddard solvent in the air. There are no oral studies in either humans or animals. The dermal effects in humans and animals are skin irritation and possible neurological effects, but the methodology for developing MRLs based on dermal exposure is not available.

Death. There is no reliable information regarding doses of Stoddard solvent that could cause death in humans or animals. It is possible that exposure to very high concentrations of this petroleum distillate could pose a serious health hazard and possibly even cause death from central nervous system depression culminating in an anesthetic state. However, since Stoddard solvent contains very little of the smaller carbon chains (C_8 and below), which are highly volatile and highly toxic, death from acute or chronic exposures is exceedingly unlikely. There is also a remote risk of death due to pulmonary pathology from aspiration (Ellenhorn and Barceloux 1988). Levels that may pose a mortality risk to humans are not known and cannot be determined from animal studies. Nonlethal levels were reported for rats, rabbits, dogs, and monkeys following a continuous exposure for 90 days to 1,271 mg/m^3 vaporized mineral spirits; for guinea pigs, rats, rabbits, dogs, or monkeys following repeated, 6-week intermediate exposure to 1,353 mg/m^3 mineral spirits; and for rats following acute exposures of up to 8,200 mg/m^3 of completely vaporized Stoddard solvent (Carpenter et al. 1975a, 1975b; Rector et al. 1966). Higher concentrations of 10,000 mg/m^3 Stoddard solvent were lethal to cats (Carpenter et al. 1975a, 1975b), and death from unexplained causes was noted in guinea pigs exposed for 90 days to 363 and 892 mg/m^3 vaporized mineral spirits (Jenkins et al. 1971; Rector et al. 1966). These data do not demonstrate a dose-response relationship for guinea pigs but indicate that the duration of exposure may contribute more to lethality than exposure concentration.

Systemic Effects. There is very little information on the health effects of Stoddard solvent in either humans or animals. There was a lack of gastrointestinal, musculoskeletal, hepatic, and renal effects in a laboratory experiment in humans exposed to 610 mg/m^3 of Stoddard solvent in the air for 6 hours (Pedersen and Cohr 1984a).

Respiratory Effects. It is possible that Stoddard solvent would adversely affect the lungs. There are two human studies on respiratory effects. One found no change in respiratory rate from a 30-minute exposure (Hastings et al. 1984), and the other found no adverse effects on respiratory function in men exposed to paint solvents in the air for 4–42 years (Hane et al. 1977). The data on respiratory effects in animals are limited but show irritant effect in rats from acute exposure (Riley et al. 1984) and decreased respiratory rate in mice (Carpenter et al. 1975a, 1975b). No evidence of lung effects was found following acute exposures. However, congestion, bronchitis, and mixed inflammatory cell infiltration were noted in rats, rabbits, guinea pigs, dogs, and monkeys exposed to vaporized mineral spirits at 1,271 mg/m^3 for 90 days (Rector et al. 1966). Also, guinea pigs exposed to concentrations of 1,353 mg/m^3 exhibited pulmonary congestion and emphysema from intermediate exposures for 6 weeks (Rector et al. 1966). However, the data for rabbits, dogs, and monkeys are limited by the use of three animals or less. Based on information from other petroleum distillates, for

instance, kerosene, it is possible that if Stoddard solvent is taken into the mouth, it would be aspirated into the lungs and might then cause pneumonitis (Coruh and Inal 1966; Majeed et al. 1981; Nouri and Al-Rahim 1970). No other significant adverse respiratory effects were seen in other animal studies (Carpenter et al. 1975a, 1975b; Rector et al. 1966).

Renal Effects. Although no human studies have reported renal toxicity that could be attributed to Stoddard solvent, several investigations have reported proximal tubule damage in male rats. A number of the observed renal effects of Stoddard solvent are consistent with a mechanism which appears to be unique to male rats. Male rodents scent mark their territories with pheromones secreted in the urine. These pheromones are transported to the urine by low molecular weight serum binding proteins which are members of the lipocalin family (Bocskei et al. 1992). In male rats, the carrier protein is α_{2u}-globulin, which is synthesized in large quantities in the liver (Bocskei et al. 1992). X-ray crystallography has demonstrated that α_{2u}-globulin is a tetramer which has a doughnut hole in the center for transport of the ligand (Bocskei et al. 1992). Although the preferred pheromone ligand for the analogous dimeric mouse protein, mouse urinary protein, has been identified through x-ray crystallography of the bound complex, the particular pheromone with the best fit to the α_{2u}-globulin tetramer has not yet been identified (Bocskei et al. 1992). After glomerular filtration with their ligand, these carrier proteins are resorbed in massive amounts in the P_2 section of the proximal renal tubule and then catabolized in lysosomes (EPA 1991a; Kimura et al. 1991a).

Unfortunately, the α_{2u}-globulin tetramer seems to be proficient at transporting other hydrophobic molecules besides pheromones through the blood and into the urine. Other substances which apparently also bind to this carrier protein include a number of hydrophobic xenobiotics such as petroleum-derived hydrocarbons or their constituents or metabolites, including decalin and the gasoline constituent trimethylpentane (EPA 1991a). The xenobiotic-α_{2u}-globulin complex is then reabsorbed in the proximal tubule and accumulates in lysosomes where it resists degradation. Accumulation of this complex is thought to trigger pathological responses within the kidney. This α_{2u}-globulin nephropathy syndrome is characterized by the following lesions (Alden 1986; EPA 1991a; Short et al. 1987): excessive accumulation of hyaline droplets in the P_2 segment of the proximal tubule region of the kidney; association of the hyaline droplets with the protein α_{2u}-globulin; single cell necrosis in the P_2 segment epithelium and exfoliation of these degenerated cells; sustained regenerative tubule cell proliferation, often with tubular dilation and tubular epithelial necrosis; accumulation of granular casts formed from the cellular debris and subsequent tubule dilation at the junction of the P_3 segment and the thin loop of Henle; linear mineralization of the renal papillar tubules with hyperplasia of the renal pelvic urothelium.

The hepatic synthesis of α_{2u}-globulin is under androgenic control, and the protein is found at concentrations 100–300 times higher in male rat urine than in female rat urine (Shapiro and Sachchidananda 1982; Van Doren et al. 1983). Neither female rats nor castrated male rats show the characteristic renal pathology associated with α_{2u}-globulin nephropathy. Aging male rats show chronic progressive nephropathy symptoms that are similar to α_{2u}-globulin nephropathy, so it is important to run concurrent controls when assessing renal toxicity. α_{2u}-Globulin is not present in other rodents, but mice have a similar pheromone carrier, mouse urinary protein, which does not cause the same effects. Although other members of the lipocalin protein family do occur in non-rodent species, including humans, they are not produced in such massive quantities, and these species do not exhibit renal toxicity in response to the same set of substances that produce this characteristic toxicity in male rats (Swenberg et al. 1989).

The data discussed above suggest an α_{2u}-globulin interaction as the mechanism for Stoddard solvent–induced nephrotoxicity in the rat. The renal toxicity seems to be androgen dependent since it does not occur in female rats and is absent or greatly attenuated in castrated male rats, which only have residual levels of α_{2u}-globulin

left (Borghoff et al. 1990). The pathological sequence is consistent with α_{2u}-globulin nephropathy. Hyaline droplets enclosed in lysosomes are increased in number and size in the P_2 section of the proximal renal tubule; however, no immunohistochemistry has been done to confirm that the protein in these droplets is actually α_{2u}-globulin, although the levels of this protein are elevated in the kidney as a whole in symptomatic exposed male rats (Viau et al. 1986). The fact that similar petroleum distillate mixtures and alkanes seem to cause renal toxicity via α_{2u}-globulin interactions increases the plausibility that Stoddard solvent also acts via the same mechanism.

There are two respects in which the data on the renal toxicity of Stoddard solvent are less than ideal. First, not all the studies mentioned above used complete Stoddard solvent; several focused on the predominant alkane components, so the potential contributions of the aromatic constituents have not been as well tested. A second question is whether all the renal toxicity observed is due to interactions with α_{2u}-globulin or whether simultaneous kidney damage by another subset of components via other mechanisms could have been overlooked. The urinary enzyme activity ratios suggesting distal tubule damage (Viau et al. 1986) raise some doubts in this category since α_{2u}-globulin–induced damage is typically confined to the proximal tubule.

If all the renal damage caused by Stoddard solvent in rats is due to α_{2u}-globulin interactions, then it probably does not pose a large risk of nephrotoxicity to humans. Since humans do not have α_{2u}-globulin, the issue becomes whether analogous human proteins could possibly undergo the same interactions as α_{2u}-globulin if they were produced in similar quantities. Because humans are not known to synthesize and resorb other lipocalin proteins in such massive quantities as rats do with α_{2u}-globulin, it is unlikely that Stoddard solvent would cause such remarkable toxicity even if an interaction did occur. To completely dismiss the possibility of human risk, members of the human lipocalin family which are filtered and resorbed in the kidney could be assayed to determine their ability to bind similar xenobiotics or metabolites and whether this binding inhibited catabolism. Since the renal damage may be exclusive to male rats, no human MRLs have been derived from data regarding this end point.

Dermal/Ocular Effects. Dermal or eye irritation is another possible effect of exposure to Stoddard solvent. Experimental studies in humans have indicated that eye irritation may be induced by Stoddard solvent vapors (Carpenter et al. 1975a, 1975b; Hastings et al. 1984). Case studies in humans (Nethercott et al. 1980) and experimental studies in guinea pigs (Anderson et al. 1986) indicate that skin irritation can occur following acute dermal exposure. Other petroleum distillates, such as kerosene (Annobil 1988; Mosconi et al. 1988; Tagami and Ogino 1973) or gasoline (Beck et al. 1983; Vernot et al. 1990), are also known to cause skin irritation.

Immunological Effects. There is only one human study on immunological effects available, and it reported no adverse effects on immunoglobulin levels when men were exposed to 616 mg/m^3 of white spirits (99% alkanes) in the air (Pedersen and Cohr 1984b). However, it is possible that Stoddard solvent may affect the immune system in ways that cannot be measured by this type of test. No animal studies are available. No immunological data regarding the aromatic components of Stoddard solvent were located. Therefore, the effects induced by these components could not be determined.

Neurological Effects. Inhalation exposure to Stoddard solvent or white spirits has caused prolonged reaction time (Gamberale et al. 1975) and dizziness (Carpenter et al. 1975a, 1975b) from acute exposures. An MRL was derived from the finding of impaired reaction time in humans exposed to 4,000 mg/m^3 (Gamberale et al. 1975). Headaches, memory deficits, and fatigue were reported in humans from chronic exposure to several solvents, including Stoddard solvent (Daniell et al. 1988; Flodin et al. 1984; Gregersen et al. 1984; Hane et al. 1977; Olson 1982). These effects may or may not be due to Stoddard solvent since other chemicals were

also present during exposure. No data are available for neurological effects from oral exposure. Similar neurological effects have also been found in humans following combined dermal and inhalation exposure to solvents which may include Stoddard solvent. Stoddard solvent does not contain the (C_2–C_3) hydrocarbons that are known to cause anesthesia. Other solvents and petroleum distillates with longer carbon chains, such as fuel oils, have been known to cause more severe central nervous system depression than that observed with Stoddard solvent (Kainz and White 1984; Knave et al. 1978; Porter 1990).

Developmental Effects. No human studies are available for any route of exposure. Stoddard solvent vapor did not cause maternal toxicity, structural teratogenesis, or decreased fetal weight when administered during organogenesis in the rat, although some skeletal variations did occur (API 1977). Other petroleum distillates (gasoline or fuel oils) have also shown very few adverse developmental effects (API 1979a, 1979b; Beliles and Mecler 1983; Litton Bionetics 1978).

Reproductive Effects. Men exposed to white spirits (composition, 99% alkanes) in the air (616 mg/m^3 for 30 minutes) had slightly (9–11%) decreased ($p<0.005$) serum levels of follicle-stimulating hormone (Pedersen and Cohr 1984b). The possible reproductive outcome of this change is not known. Another study shows that men who were occupationally exposed for 1–17 years to Stoddard solvent in the air had normal sperm counts, motility, and morphology (Tuohimaa and Wichmann 1981). This study was limited because a small population was tested and by the accuracy of the exposure assessment, mixed solvent exposure, and variability of sperm parameters. There were no data regarding reproductive effects in animals. It is not possible to draw conclusions from the available data regarding the possible reproductive effects of Stoddard solvent on persons exposed at hazardous waste sites.

Genotoxic Effects. No genotoxicity studies were located regarding in vivo human exposure to Stoddard solvent. However, one in vitro study was located in which human peripheral lymphocytes were incubated in the presence of white spirits (a petroleum distillate composed of 85% aliphatic and 15% aromatic hydrocarbons and also referred to as Stoddard solvent), in four different white spirits/ethanol dilutions, and investigated for increased sister chromatid exchange. Two incubation periods were employed for each concentration: 1 hour and 24 hours. No significant increase in sister chromatid exchange frequency was observed for either concentration at either incubation period (Gochet et al. 1984). Refer to Table 2-2.

In vivo animal studies involving either Stoddard solvent or white spirits provide no evidence of genotoxicity. Neither inhaled (8,489 ppm for 25 minutes) nor intraperitoneal (0.1, 0.05, or 0.01 mL) doses of white spirits produced a significant increase in micronuclei in mouse bone marrow (Gochet et al. 1984). Accordingly, rats given 0.087, 0.289, or 0.868 mL/kg Stoddard solvent intraperitoneally were negative for chromosomal aberrations in bone marrow cells. The Stoddard solvent used for the study contained 18.9% aromatic hydrocarbons (see Table 3.3, Stoddard solvent[d] for a further analysis of the composition) (Conaway et al. 1984). In a dominant lethal study, mice were dosed subcutaneously and rats intraperitoneally with 1.0 mL/kg Stoddard solvent (API 1982). Fifteen males of each species were allowed to mate with two or three females per week for one complete sperm cycle (8 weeks for mice and 10 weeks for rats). The rat pregnancy index was significantly lower than the corresponding control for the 1st week only; otherwise, the results for both species were negative (API 1982). Refer to Table 2-3 for a further summary of these results.

In vitro tests using Salmonella typhimurium (Conaway et al. 1984; Gochet et al. 1984) and mouse L5178Y lymphoma cells (API 1987b; Conaway et al. 1984) to screen for gene mutations support the negative results observed in the mammalian in vivo and human in vitro studies mentioned above. One mouse L5178Y gene study does report significant mutation frequencies at high doses (50–60 nL/mL for nonactivation and 60–80 nL/mL for activation); however, these results are equivocal because the same doses were highly

TABLE 2-2. Genotoxicity of Stoddard Solvent and Related Compounds In Vivo

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	-	Conaway et al. 1984
Mouse (bone marrow)[a]	Micronucleus	-[b]	Gochet et al. 1984
Rat (germinal cells)	Dominant lethal mutation	-	API 1982
Mouse (germinal cells)	Dominant lethal mutation	-	API 1982

[a]White spirits used

[b]Result obtained for both intraperitoneal and inhalation exposure.

- = negative result

DRAFT FOR PUBLIC COMMENT

DRAFT FOR PUBLIC COMMENT

TABLE 2-3. Genotoxicity of Stoddard Solvent and Related Compounds In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (TA1530, TA100, TA98, TA1538, TA1537)[a]	Gene mutation	-	-	Gochet et al. 1984
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	-	-	Conaway et al. 1984
Eukaryotic organisms:				
Mammalian cells:				
Mouse L5178Y lymphoma cells ($TK^{+/-}$ locus)	Gene mutation	-	-	Conaway et al. 1984
Mouse L5178Y lymphoma cells	Gene mutation	+/-	+/-	API 1987b
Human (peripheral lymphocytes)[a]	Sister chromatid exchange	No data	-	Gochet et al. 1984

[a]White spirits used

- = negative result; +/- = inconclusive result

cytotoxic (API 1987b). Refer to Table 2-3 for a further summary of these results. Based on the available genotoxicity data, Stoddard solvent and white spirits do not appear to pose a genotoxic threat in animals. However, the available data are much too scant to allow for definitive conclusions regarding the genotoxicity of Stoddard solvent/white spirits in humans.

Cancer. There is only one chronic inhalation study of humans (Siemiatycki et al. 1987), which reported negative findings, and one chronic dermal study in mice (EPA 1984c), but neither provide conclusive results on the carcinogenic potential of Stoddard solvent for humans exposed at hazardous waste sites. In the positive mouse carcinogenesis skin-painting study, a mixture containing 90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether was used. This study indicates an area of potential concern, even though the carcinogenesis cannot be attributed to a particular component. However, a test using Stoddard solvent alone is needed to verify whether the findings of this study can be attributed to Stoddard solvent. It is also possible that the skin irritant effects of Stoddard solvent could have contributed to promotion of effects initiated by other components of the mixture. Benzene and toluene, which are known to be carcinogenic substances, are found only in very trace amounts in Stoddard solvent.

There are no existing national or international guidelines concerning potential carcinogenicity specifically pertaining to Stoddard solvent.

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 Stoddard solvent 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 Stoddard solvent 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 Stoddard Solvent

No biomarkers are available to specifically identify or quantify exposure to Stoddard solvent. However, hydrocarbon levels in the blood can be used to document exposure to petroleum distillates in general. Components of white spirits have been identified in human blood, fat, and alveolar air using gas chromatography-mass spectrometry (Pedersen et al. 1984). It may be possible to identify Stoddard solvent in this way, comparing the measured sample to the spectrometrical pattern of a known Stoddard solvent standard.

Minimal information is available on the half life of Stoddard solvent in the body. One study showed that levels of aliphatic and aromatic components in alveolar air dropped substantially within 20 minutes of exposure (Astrand et al. 1975). However, measurable amounts remained in the blood for at least 100 minutes post-exposure. In the second study, the rate of inhalation absorption of the alkane components was fairly constant over the different exposure intervals (5 days, 6 hours/day) that were measured. The mean blood concentration of white spirits was 2 mg/L on day 1 and 2.54 mg/L on day 5, showing accumulation of white spirits in the blood, and indicating a much longer half-life of about 2 days (Pedersen et al. 1984, 1987).

One study of humans exposed to white spirits found that levels of dimethylbenzoic acid in the urine correlated to earlier exposure during the workday (Pfaffli et al. 1985). Another study on humans exposed to up to 2,500 mg/m^3 of Stoddard solvent found that aliphatic and aromatic components remained in the blood roughly 1.5 hours after the termination of exposure (Astrand 1975). For more information on biomarkers specifically associated with minor components of Stoddard solvent such as benzene or toluene, see the ATSDR toxicological profiles on these substances (ATSDR 1989, 1990).

2.5.2 Biomarkers Used to Characterize Effects Caused by Stoddard Solvent

Since the effects of Stoddard solvent are not unique to this chemical, no specific biomarkers are available to characterize the effects caused by Stoddard solvent. Headaches, fatigue, incoordination, and skin irritation are general effects which may be encountered following exposure to Stoddard solvent. It is expected that these effects would occur for short periods of time. Other effects, such as bronchitis and pulmonary congestion or emphysema may occur over a longer period of time. However, the durations of the health effects are not well documented in the data. If Stoddard solvent is aspirated into the lungs following oral exposure, it is possible that pulmonary damage may occur, as it does with other petroleum distillates, such as kerosene (Haddad and Winchester 1990). Symptoms such as coughing, choking, or gagging might appear, along with clinical signs such as fever. Chemical pneumonitis may be revealed by chest x-rays. The abnormal chest x-rays may be present 30 minutes to 72 hours after aspiration. However, there are numerous chemicals that may induce these effects. Therefore, it would be difficult to identify Stoddard solvent as the cause based on these symptoms in cases of unidentified chemical exposure.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Although workers are often exposed to a variety of solvents with Stoddard solvent, there are no available studies specifically characterizing the interactions of Stoddard solvent with other chemicals. Since Stoddard solvent may have adverse effects on the nervous system, it may compound the effects of other chemicals that cause central nervous system depression, such as alcohol, barbiturates, benzodiazapines, or medical anesthetics.

Guinea pigs with a diet high in vitamin C survived a high exposure to Stoddard solvent vapors better than those with a diet low in vitamin C (Jenkins et al. 1971); however, it is not known how vitamin C levels might affect humans exposed to Stoddard solvent.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to Stoddard solvent than will most persons exposed to the same level of Stoddard solvent 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."

There is no information on populations that may be unusually susceptible to Stoddard solvent. However, individuals with pre-existing neurological conditions are likely to be a population of concern.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to Stoddard solvent. 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 Stoddard solvent. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Little information is available on mitigation specific for Stoddard solvent itself. However, it is a petroleum distillate, and information on related products is available. Since the absorption from the gastrointestinal tract is likely to be poor, the use of activated charcoal or cathartics would probably not be useful (Litovitz and Greene 1988). Further data is required to determine if activated charcoal will remove the aromatic components of Stoddard solvent. Gastric emptying by either lavage or emesis is a controversial treatment since there is the danger of pulmonary aspiration and subsequent pneumonitis (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Litovitz and Greene 1988). Although the inhalation route is the most probable route of exposure, the only known method to reduce exposure, or to mitigate possible effects from an acute exposure, is to remove the person from the contaminated area (Stutz and Janusz 1988). Excessive inhalation of solvents often leads to central nervous system depression and may require assisted ventilation. The acute effects of central nervous system depression, such as seizures, are often treated with naloxone and glucose. If pulmonary distress is present, positive end expiratory pressure may be used therapeutically (Haddad and Winchester 1990). Washing with soapy water is suggested following dermal contact, and ocular washing is recommended following eye exposure. There are no effective methods to enhance elimination and no known antidotes. Corticosteroids and antibiotics are also not effective treatments (Ellenhorn and Barceloux 1988; Litovitz and Greene 1988). The mechanism of action of Stoddard solvent on the target organ (i.e., the brain) is not known. Since Stoddard solvent can be stored in adipose tissue, the effects may continue for a few days after exposure has occurred.

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 Stoddard solvent 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 Stoddard solvent.

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 will be proposed.

2.9.1 Existing Information on Health Effects of Stoddard Solvent

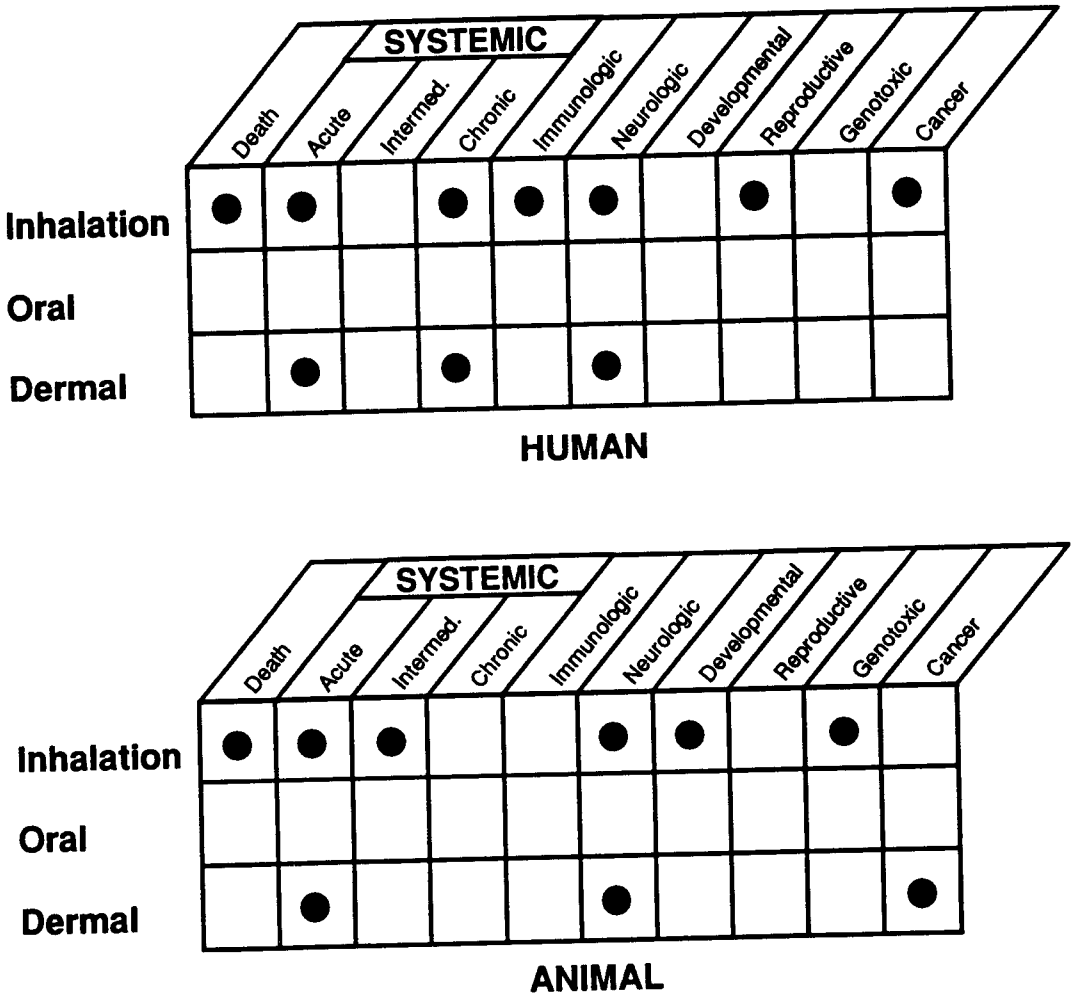
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to Stoddard solvent are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of Stoddard solvent. Each dot in the figure indicates 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" information (i.e., data gaps that must necessarily be filled).

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The available data indicate that following a 6-hour exposure, there is a lack of systemic or neurological effects in humans exposed to low levels (610 mg/m^3) via the inhalation route (Pedersen and Cohr 1984a, 1984b). Humans and animals exposed to airborne, completely vaporized Stoddard solvent at higher levels for acute periods had eye irritation (Carpenter et al. 1975a, 1975b; Hastings et al. 1984) and neurological disturbances (Gamberale et al. 1975). An MRL was derived from the finding of impaired reaction time in humans exposed to 4,000 mg/m^3 for 50 minutes (Gamberale et al. 1975). Further information on levels that would be expected to cause effects following acute, intermediate, or chronic exposure in the air would be useful. No data on oral exposure were available for any duration in any species. Acute dermal exposure resulted in skin irritation in humans (Nethercott et al. 1980) and animals (Anderson et al. 1986). The data were not sufficient to derive an MRL for the oral or dermal routes of exposure. Data from all routes of exposure, for all end points, would be useful in determining levels that may be harmful to humans at hazardous waste sites. Specifically, data are needed to establish a NOAEL for functional neurological tests in humans. Such information would provide a dose-response relationship for the LOAEL used in the MRL derivation for this effect.

More information is needed to follow up on the potential musculoskeletal toxicity following acute human exposure to Stoddard solvent (Pedersen and Cohr 1984b).

FIGURE 2-2. Existing Information on Health Effects of Stoddard Solvent



Intermediate-Duration Exposure. No studies are available regarding intermediate-duration human exposure by any route. Intermediate-duration rat studies reveal damage to the male rat kidney (Carpenter et al. 1975a, 1975b; Phillips 1983; Rector et al. 1966; Viau et al. 1984). It has not been ascertained whether the hyaline droplets observed in the rat renal studies were composed of α_{2u}-globulin instead of other resorbed proteins. This needs to be determined to ensure that Stoddard solvent is indeed acting by inducing male rat-specific α_{2u}-globulin nephropathy and not by another mechanism which might have more relevance to humans. It would be helpful to know whether human lipocalin proteins bind Stoddard solvent components or metabolites and if lipocalin renal catabolism is affected. Since the renal damage may be exclusive to male rats, no human MRLs have been derived from data regarding this end point. Other end points were studied in two major 90-day experiments and a 6-week experiment that used several species (Carpenter et al. 1975a, 1975b; Rector et al. 1966). No adverse systemic effects were found at exposures of up to 1,900 mg/m^3, but there were unexplained deaths in guinea pigs at 363 mg/m^3, so no MRL could be derived from this end point. No data are available from animals for the oral or dermal routes. Further information for all routes would be necessary to develop intermediate-duration MRLs.

Chronic-Duration Exposure and Cancer. The incidence of death was investigated in a single retrospective cohort study among 14,457 workers at an aircraft maintenance facility following exposure to very low levels of Stoddard solvent as well as numerous other chemicals for at least 1 year (Spirtas et al. 1991). An exposure index was developed by evaluating patterns of use that indicated comparative differences in exposure to various chemicals based on occupation. However, exposures could not be quantitated from these methods. The study did not show a statistically significant increase in mortality. Adverse neurological effects have been reported in humans following inhalation or dermal (Daniell et al. 1988; Mergler et al. 1988) exposure. No adverse reproductive effects were noted (Tuohimaa and Wichmann 1981). However, the study was limited because a small population size was used and by the accuracy of the exposure assessment, mixed solvent exposure, and variability of sperm parameters. Observations of systemic effects have been made in humans following chronic exposure (Beving et al. 1991; Flodin et al. 1984; Hane et al. 1977; van der Laan 1980). No studies are available regarding chronic-duration animal exposures by the inhalation or oral routes. Since none of the human studies provide quantitative data suitable for the derivation of an MRL, further studies for all routes and end points would be useful in determining possible effects in humans living near hazardous waste sites.

The only available study on cancer in humans is limited by its lack of statistical power (Siemiatycki et al. 1987). The only chronic animal study is a briefly reported dermal study on possible carcinogenic effects in mice that was limited by the use of a mixture containing Stoddard solvent (90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether) (EPA 1984c). A follow-up to this study, using Stoddard solvent alone, would be useful.

Genotoxicity. Most of the available in vitro and in vivo studies indicate that neither Stoddard solvent nor white spirits pose a genotoxic threat (Conaway et al. 1984; Gochet et al. 1984). However, based on these few studies, it would be presumptuous to definitively state that Stoddard solvent/white spirits is not genotoxic to humans. Extensive in vitro investigations, especially Ames testing, are probably not necessary, but more mammalian in vivo and human occupational studies are required before a sound conclusion can be reached.

Reproductive Toxicity. The only available human study shows no adverse effects on the sperm of men exposed for a chronic period (Tuohimaa and Wichmann 1981). Further intermediate screening tests assessing in vitro sperm fertilization ability would be useful in determining that this substance poses no reproductive risk. More information on FSH levels is needed in order to confirm that the changes are exposure-related and not a result of individual variations (Pedersen and Cohr 1984b). Multigenerational animal studies should be performed, only if warranted.

Developmental Toxicity. No human data are available regarding developmental toxicity. The only available animal study reported no skeletal or visceral abnormalities in rats following inhalation exposure (API 1977). This study is not sufficient to determine that humans have no risk of developmental effects. Further animal studies using all routes of exposure would be useful.

Immunotoxicity. The only study available regarding immunological effects showed no changes in immunoglobulins in humans exposed to the alkane components for an acute period via the inhalation route (Pedersen and Cohr 1984b). No intermediate- or chronic-duration studies are available in humans, and no studies are available for animals for any route or duration. However, immunotoxicity may have occurred in an individual who developed glomerulonephritis from chronic dermal and/or inhalation exposure (Daniell et al. 1988). Although this is a renal effect, it may have been induced by an immunotoxic reaction to Stoddard solvent as evidenced by the finding of antibodies to the glomerular basement membrane. Therefore, data are needed to determine whether Stoddard solvent affects the immune system to induce renal toxicity. Further studies for all duration categories in both humans and animals would be useful to determine whether this substance poses an immunological threat via the inhalation, oral, or dermal routes. For example, studies could be conducted to determine whether animals or humans exposed to Stoddard solvent are more susceptible to infection or whether Stoddard solvent induces a dermal sensitivity reaction; macrophage, T and B lymphocyte, and natural killer cell function could be tested in animals and individuals exposed to Stoddard solvent.

Neurotoxicity. Acute-duration human studies via the inhalation route (Carpenter et al. 1975a, 1975b; Gamberale et al. 1975; Hastings et al. 1984; Larsen and Schmunes 1974; Pedersen and Cohr 1984a, 1984b) as well as chronic-duration human studies via the inhalation and dermal routes (Arlien-Soborg et al. 1979; Daniell et al. 1988; Flodin et al. 1984; Gregersen et al. 1984; Hane et al. 1977; Mergler et al. 1988; Mikkelsen et al. 1988; Olson 1982) are available. An acute inhalation MRL was derived from the finding of impaired reaction time in humans exposed to 4,000 mg/m^3 (Gamberale et al. 1975). No oral studies are available for humans. For animals, neurological effects have been studied following acute-duration inhalation exposure only (Carpenter et al. 1975a, 1975b). No animal data are available on neurological effects following intermediate- or chronic-duration inhalation exposure. No animal data are available regarding oral or dermal exposure. Since the nervous system appears to be a target organ in humans, further human and animal studies of exposure via all three routes would be useful in determining safe levels for inhalation, oral, or dermal exposure at hazardous waste sites.

Epidemiological and Human Dosimetry Studies. Although there have been studies of persons exposed to Stoddard solvent or white spirits at the workplace, none have recorded exposure levels. This information would be useful in determining whether the MRLs would indeed protect persons exposed at hazardous waste sites.

Biomarkers of Exposure and Effect. There are no studies available to determine specific biomarkers of exposure or effect. Components of Stoddard solvent can be measured in the blood, fat, and breath. Fat appears to be the best compartment to sample for chronic exposure, since Stoddard solvent is extremely lipid soluble (Pedersen et al. 1984, 1987). However, these chemicals can be found in many types of petroleum distillates and are not specific to Stoddard solvent. Additional research that identifies Stoddard solvent exposure using currently available breathalizer techniques with mass spectroscopy would also be useful.

Similarly, the biomarkers of effects from Stoddard solvent are very general and cannot be used to document exposure. Any further information on biomarkers of exposure or effect would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are very few human studies (Pedersen et al. 1984, 1987; Astrand et al. 1975), and no animal studies, regarding toxicokinetics, although Astrand et al (1975) did study the absorption of Stoddard solvent in humans. Further studies in both animals and humans would be very useful in determining possible adverse health effects at hazardous waste sites. In particular, information on the rate and extent of absorption and mode of excretion would be useful in predicting health effects as well as in determining possible mitigation methods. For example, establishing methods for determining gastrointestinal absorption and molecular weight cutoffs for lipophilic absorption would be useful. Also, better pharmacokinetic data on the three main classes of Stoddard solvent components (i.e., alkanes, cycloalkanes, and aromatics) would help predict the toxic properties of this chemical. Identification of the metabolic products of Stoddard solvent components is also a data need.

Comparative Toxicokinetics. Since there are no studies on animal toxicokinetics, there is no information at all on comparative toxicokinetics. Studies of absorption, distribution, metabolism, or excretion would be appropriate in multiple animal species for interspecies comparisons. Comparisons between the pharmacokinetic properties of petroleum distillates of varying chain lengths and aromatics versus other hydrocarbon classes would also be useful.

Mitigation of Effects. Very little information is available for Stoddard solvent itself, or for petroleum distillates as a class. There are no known antidotes for these substances, and it is unlikely that research to find a specific antidote to Stoddard solvent poisoning would be effective. Since there are no human or animal data on oral exposure to Stoddard solvent, no treatment methods have been attempted. Further studies regarding the effectiveness of gastric lavage and the administration of activated charcoal would be useful. Additional studies regarding which Stoddard solvent components are absorbed in the gastrointestinal tract and whether or not activated charcoal absorbs them would also be beneficial. Further research on alternative treatment methods, such as using negative pulmonary pressure, would be appropriate.

2.9.3 On-going Studies

There are no known on-going studies on Stoddard solvent.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of Stoddard solvent is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of Stoddard solvent is located in Table 3-2.

Stoddard solvent is a petroleum distillate mixture of C_7–C_{12} hydrocarbons containing 30–50% straight and branched chain alkanes, 30–40% cycloalkanes, and 10–20% alkyl aromatic hydrocarbons (Air Force 1989a; McDermott 1975). Stoddard solvent is a refinery blend of differently pretreated oil fractions. Its composition varies somewhat, depending on the refinery and the time of production. Table 3-3 lists some of the major components of several Stoddard solvent formulations. Petroleum distillates are often distinguished by boiling or distilling temperatures. Stoddard solvent has a boiling range of 150–200°C (Scott et al. 1959). The 140 flash Stoddard solvent is composed of C_5–C_{12} hydrocarbons and has a boiling range of 185–207°C (Air Force 1989a). White spirits is a term somewhat synonymous with Stoddard solvent since it has a hydrocarbon range between C_7 and C_{11}. Six types of white spirits have been identified based on origin. Each type consists of the same components, but the percentages vary (Scheffers et al. 1985). Possible contaminants of Stoddard solvent include lead (<1 ppm) and sulfur (3.5 ppm) (Suntech 1978).

There are a number of related chemical mixtures with components that are different from those of Stoddard solvent. For instance, high-flash aromatic naphtha is a generic term for petroleum distillates primarily consisting of C_9 aromatics (70–80%) with C_8 or C_{10} aromatics comprising the rest. Stoddard solvent, in contrast, is only 10–20% aromatic (Clark et al. 1989b; Schreiner et al. 1989). Naphtha is also a general term for petroleum distillates containing predominantly aliphatic hydrocarbons C_5–C_{13} and distilling at 30–238°C (Tenenbein et al. 1984).

Benzine and mineral spirits, other associated mixtures, are similar to but not exactly the same as Stoddard solvent. Benzine consists of C_5–C_9 hydrocarbons (Takeuchi et al. 1975) and boils, on average, at between 154°C and 204°C (Navarte et al.). Benzine and Stoddard solvent distill at about the same temperature range, but their hydrocarbon compositions differ. Mineral spirits have a distillation range of 136–277°C. The distillation range of Stoddard solvent falls within that of mineral spirits (Mehlman and Smart 1982). Therefore, Stoddard solvent may be considered a subset of mineral spirits, but mineral spirits as a whole are not described in this profile.

TABLE 3-1. Chemical Identity of Stoddard Solvent

Characteristic	Information	Reference
Chemical name	Stoddard solvent	Sax and Lewis 1989
Synonym(s)	Dry cleaning safety solvent, naphtha safety solvent, PD-680, petroleum solvent, spotting naphtha, varnoline, white spirits	Air Force 1989; NIOSH 1989; Sax and Lewis 1989
Registered trade name(s)	Texsolve S, Varsol 1	Budavari et al. 1989; Hunter et al. 1992
Chemical formula	Not applicable[a]	
Chemical structure	Not applicable[a]	
Identification numbers:		
CAS registry	8052-41-3	Sax and Lewis 1989
NIOSH RTECS	WJ8925000	NIOSH 1990
EPA hazardous waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	1268 27	NIOSH 1990
HSDB	No data	
NCI	No data	

[a]Stoddard solvent is a mixture of C_7–C_{12} hydrocarbons primarily containing straight and branched chain alkanes (30–50%), cycloalkanes (30–40%), and alkyl aromatic hydrocarbons (10–20%) (Air Force 1989; McDermott 1975). See also Table 3-3.

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 Stoddard Solvent

Property	Information	Reference
Molecular weight	144 (mean)	Carpenter et al. 1975
Color	Clear, colorless	Sax and Lewis 1989
Physical state	Liquid	Sax and Lewis 1989
Melting point	No data	
Boiling point	154–202°C	Air Force 1989
	160–199°C	Coast Guard 1985
Density:		
at 20°C	0.78 g/mL	NIOSH 1990
Odor	Similar to kerosene	NIOSH 1990
Odor threshold	0.9 ppm	Carpenter et al. 1975
Solubility:		
Water	Insoluble	McDermott 1975
Organic solvent(s)	Absolute alcohol, benzene, ether, chloroform, carbon tetrachloride, carbon disulfide	Sax and Lewis 1989
Partition coefficients:		
Log K_{ow}	3.16–7.06	Air Force 1989
Log K_{oc}	700–5.50×10^{6}	Air Force 1989
Vapor pressure at 25°C	4–4.5 mmHg	McDermott 1975
Henry's law constant:		
at 25°C	$4.4\times10^{-4-7.4}$ atm · m^3/mol	Air Force 1989
Autoignition temperature	232°C	Sax and Lewis 1989
Flashpoint	37.8–60.0°C	Air Force 1989;
	38–43°C	Sax and Lewis 1989
Flammability limits:		
% volume in air at 25°C	0.9–6.0	Carpenter et al. 1975
Conversion factors:		
at 25°C and 760 mm	1 mg/L = 174.6 ppm;	Carpenter et al. 1975
		McDermott 1975
Explosive limits		
Lower limit	0.9%	
Upper limit	6%	

TABLE 3-3. Possible Formulations of Stoddard Solvent

Hydrocarbons	White Spirits 1[a]	White Spirits 2[a]	White Spirits 3[a]	Stoddard solvent[b] (regular)	Stoddard solvent[b] (140 flash)	Stoddard solvent[c]	Stoddard solvent[d]	Stoddard solvent[e]
Alkanes (paraffins)	**60.0**	**61.0**	**62.8**	**30–50 (48 average)**	**60.8**	**34.9**	**41.6**	**47.7**
n-nonane	11.3	13.3	1.9					0.9
n-decane	7.6	10.0	9.1					
methylnonanes	4.9	7.9						
2,6-dimethyloctane	2.7	4.1						
n-undecane	2.7	2.4	17.5					
dodecanes			11.6					
terdecanes			2.7					
others	30.8	23.3						
Cycloalkanes (cycloparaffins)	**39.7**	**27.3**		**30–40 (38 average)**	**35.7**		**39.5**	**37.6**
monocycloparaffins	16.3	13.7			24.5	34.9	27.9	26.0
trimethycyclohexane	4.7	7.2						
tert-butylcyclohexane	4.5	4.0						
n-butylcyclopentane	5.0	1.3						
n-butylcyclohexane	2.1	1.2						
other cycloparaffins	23.4	13.1						
dicycloparaffins					11.2	5.0	11.6	11.6
tricycloparaffins						0.4	0.0	
acenaphthenes						0.4		
Aromatics	**0.3**	**11.7**	**17.0**	**10-20 (14.1 average)**	**3.40**		**18.9**	
alkylbenzenes				14.0	3.03	22.0	17.6	14.1
dimethylethylbenzenes	0	3.0						
n-propylbenzene	0	2.0						
ethyltoluenes	0	1.2						
1,2,4-trimethylbenzene	0	0.9						
other aromatics	0.3	4.6				1.1		
other benzenes				0.1	0.07			0.1
indans/tetralins				<1	0.3	1.8	1.3	0.5
indenes						0.1		
naphthalenes						0.2		
acenaphthalenes						0.3		
tricyclicaromatics						0.1		

[a]Adapted from Verkkala et al. (1984)
[b]Adapted from Air Force (1989)
[c]Adapted from API (1976)
[d]Adapted from Suntech Group (1978)
[e]Adapted from Carpenter et al. (1975b); this paper also includes a mass spectral analysis of components by carbon number within a hydrocarbon class, e.g., C_8 alkanes.

DRAFT FOR PUBLIC COMMENT

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Stoddard solvent is a chemical mixture containing hydrocarbons that range from C_7 to C_{12} with the majority of hydrocarbons in the C_9–C_{11} range (Air Force 1989a; Rothman and Emmett 1988). The hydrocarbons composing Stoddard solvent are 30–50% alkanes, 30–40% cycloalkanes, and 10–20% aromatics (Air Force 1989a; McDermott 1975). Stoddard solvent is produced from straight-run distillate of paraffinic or mixed base crude oil (Air Force 1989a; Rothman and Emmett 1988) and must meet the specifications of the American Society for Testing and Materials designation for Type I mineral spirits (Stoddard solvent) (ASTM 1988). In 1990, the production volume of Stoddard solvent was 38,325,834 pounds, down from a volume of 74,851,222 pounds in 1986 (EPA 1992). The U.S. companies that produce and/or distribute Stoddard solvent are Ashland Chemical, Inc.; R.E. Carroll, Inc.; Chemcentral Corporation; Coyne Chemicals; Exxon Chemical Company; Holtrachem, Inc.; MacArthur Petroleum and Solvent Company, Inc.; Unocal Chemicals; and Van Waters and Rogers, Inc. (Hunter et al. 1992; Van and Deyrup 1992). Since Stoddard solvent is not required to be reported under SARA Section 313, there are no data for this compound in the 1990 Toxics Release Inventory (TRI90 1992).

4.2 IMPORT/EXPORT

No information regarding the import or export of Stoddard solvent was located.

4.3 USE

Stoddard solvent is a multipurpose petroleum solvent (McDermott 1975). Industrial uses include paint vehicles; thinning agent for paints, coatings, and waxes; printing inks; adhesives; and as a solvent in liquid photocopier toners (Air Force 1989a; McDermott 1975). Stoddard solvent is commonly used at air fields as a degreaser for precision engine parts in machine and automotive repair shops.

4.4 DISPOSAL

Disposal of Stoddard solvent should be in accordance with government regulations for the disposal of petroleum distillates (IRPTC 1985; MSDS-CCOHS 1992). Stoddard solvent has been designated as a hazardous waste by the Department of Transportation and, as such, should not be poured down domestic sewage drains. Carefully controlled incineration is one recommendation for proper disposal. Authorized disposal services should perform or oversee the relegation procedure (MSDS-CCOHS 1992). Recycling, of course, is an alternative to disposal, and since recycling is a suggested waste management technique for petroleum distillates, it should apply to Stoddard solvent as well (IRPTC 1985).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Stoddard solvent is a mixture of hydrocarbons; its environmental fate is dependent on the physical and chemical properties of the individual components. These hydrocarbons consist primarily of linear and branched alkanes, cycloalkanes, and aromatics, including trace amounts of benzene and olefins.

Stoddard solvent may be released to the environment during its use as a solvent in dry cleaning plants or as an industrial degreasing agent. It may also enter water or soil as a result of spills during use or transportation or from leaking shipping and storage containers such as 55-gallon drums. The lower molecular weight alkanes and aromatics tend to volatilize and undergo photodegradation in the atmosphere, while higher molecular weight alkanes and cycloalkanes tend to be sorbed to organic matter in soil or water. Lower molecular weight alkanes may also be sorbed to organic matter if volatilization is not rapid. The higher molecular weight aromatic components may dissolve in surface waters, or they may dissolve in soil water and leach into the groundwater. Biodegradation is expected to be the primary fate process for Stoddard solvent in soil and water. The rate and extent of biodegradation are dependent on the ambient temperature, the presence of a sufficient number of microorganism capable of metabolizing these hydrocarbons, and the concentration of Stoddard solvent in or on the soil or water.

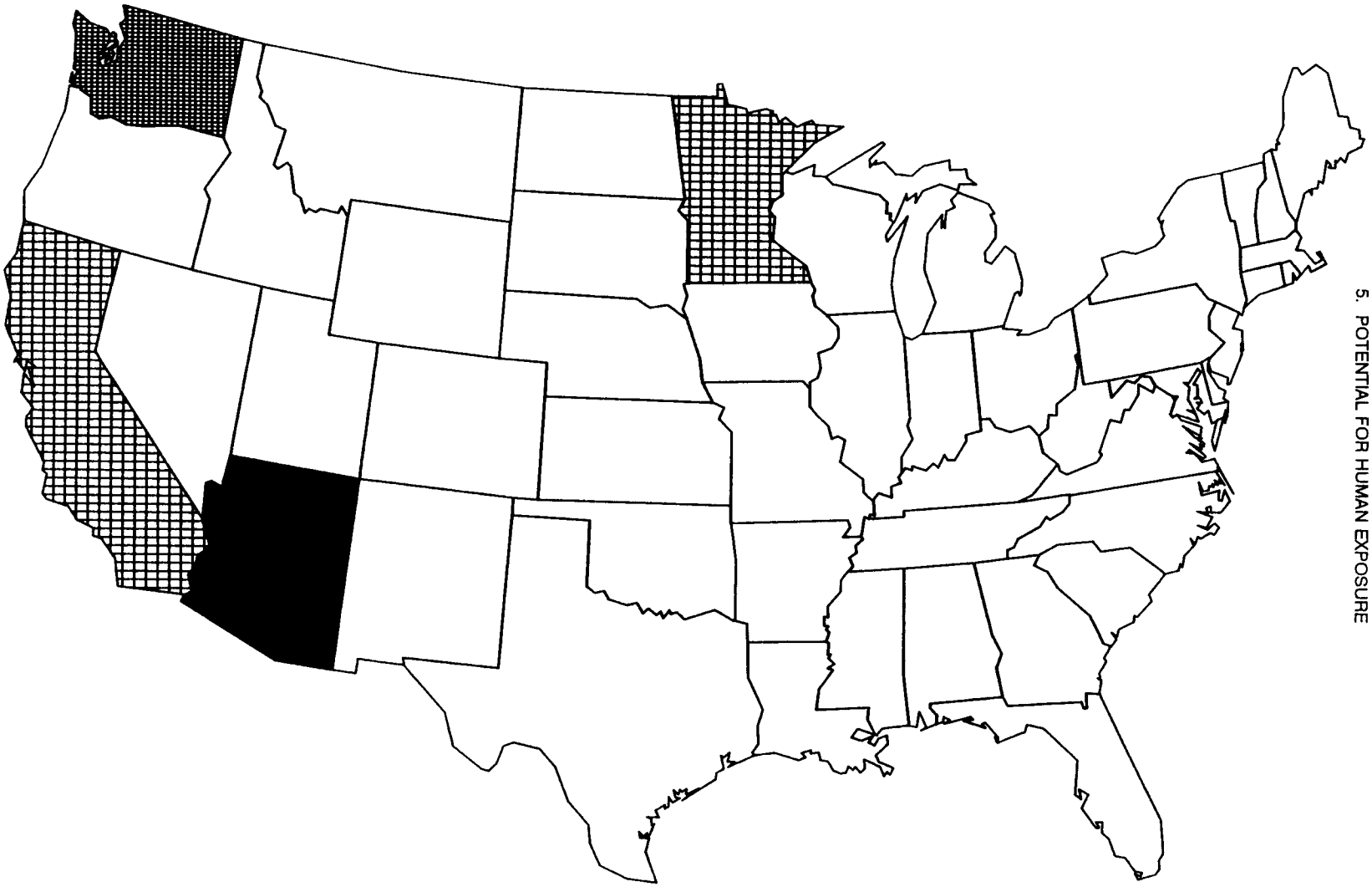
Exposure of the general population to Stoddard solvent may result primarily from inhalation or dermal contact when it is used for such commercial purposes as dry cleaning, degreasing in machine shops, and in paints. Individuals living in areas where Stoddard solvent may have contaminated the soil may be exposed if it has entered their homes through volatilization from the soil, has been transported in flowing groundwater, or if they play or otherwise come in direct contact with contaminated soil. Inhalation of the volatile components of Stoddard solvent is likely to be the main route of occupational exposure for individuals employed in dry cleaning plants where it is used as a cleaning solvent, machine shops where it is used as a degreasing agent, and other industries where Stoddard solvent is used for a variety of purposes. Dermal exposure is also possible if machine parts that have been degreased in Stoddard solvent have not been rinsed or protective clothing is not worn.

Stoddard solvent has been identified in at least 7 of the 1,300 hazardous waste sites on the EPA National Priorities List (NPL) (HAZDAT 1992). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Stoddard solvent may be released to the atmosphere in the exhaust emissions of dry cleaning plants. Emissions from one plant were determined to be 2,100 ppm (measured as propane) (EPA 1980). Fugitive emissions from other industrial or domestic uses may contribute to levels of Stoddard solvent in the environment, including contributions to general volatile organic carbon levels. In addition, surface water contamination may occur as a result of direct spills of Stoddard solvent onto surface waters, runoff from spills to soil, or from improper disposal, such as pouring Stoddard solvent down drains. Accidental spills of Stoddard solvent to various media are reported to the Emergency Response Notification System maintained by EPA (ERNS 1992). Total spill data for Stoddard solvent are:

FIGURE 5-1. FREQUENCY OF NPL SITES WITH STODDARD SOLVENT CONTAMINATION *



*Derived from HAZDAT 1992

DRAFT FOR PUBLIC COMMENT

Year	Media	Quantity spilled (pounds)
1991	Land	2,020
	Water	8,580
1992	Land	33
	Water	0

No spills were reported to air, groundwater, at facilities, or for other types of releases.

Releases of Stoddard solvent are not required to be reported under SARA Section 313; consequently, there are no data for this compound in the 1990 Toxics Release Inventory (TRI90 1992). There are 7 NPL sites where Stoddard solvent is present in waste materials or containers. It is unknown whether there have been releases to the environment from these sites (HAZDAT 1992).

5.2.1 Air

No information was located on releases of Stoddard solvent to the atmosphere.

5.2.2 Water

Stoddard solvent may be released to surface waters as a result of spills, in runoff from industrial facilities where it is used as a solvent, or from the intentional disposal of excess solvent down drains.

Stoddard solvent is not listed in the Contract Laboratory Program Statistical Database (CLPSD) of chemicals detected in groundwater and surface water samples taken only at NPL sites; however, while Stoddard solvent, as a hydrocarbon mixture, is not included as a target chemical, some components, such as alkanes, benzenes, and naphthalenes have been detected in groundwater and surface water samples (CLPSD 1989).

5.2.3 Soil

Stoddard solvent is not listed in the CLPSD of chemicals detected in soil samples taken only at NPL sites; however, while Stoddard solvent, as a hydrocarbon mixture, is not included as a target chemical, some components, such as alkanes, benzenes, and naphthalenes have been detected in soil samples (CLPSD 1989).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The transport and partitioning of Stoddard solvent is dependent on the environmental fate of its hydrocarbon components. Based on Mackay's equilibrium partitioning model using low concentrations (below aqueous solubility) of Stoddard solvent, sorption to organic matter in soil or water is a major partitioning process for all hydrocarbon classes (alkanes, cycloalkanes, and aromatics) with partitioning to the soil-vapor phase being relatively unimportant. The aromatic constituents of Stoddard solvent, particularly the alkyl benzenes, are water soluble and may dissolve in infiltrating water with a minimum of volatilization. As such, the model indicates, they may be transported through soil into the underlying groundwater, although sorption to soil organic matter will retard this leaching process. For saturated deep soils that contain no soil air and little

organic matter, the model predicts that aromatic hydrocarbons will be dissolved in the soil-water phase and subsequently, will be transported to underlying groundwater (Air Force 1989a).

If a release of Stoddard solvent exceeds the sorptive capacity of the soil the equilibrium partitioning model is no longer applicable. Large quantities of Stoddard solvent may move through the soil with gravity as bulk fluid and enter the groundwater. At the soil/groundwater interface, the soluble components can dissolve in the water, while insoluble components with specific gravities of less than 1 will float on top of the water table and move horizontally along the soil/water interface (Air Force 1989a). In addition, horizontal movement of Stoddard solvent through the soil, particularly through cracks and fissures in the soil material, is possible if the concentration is large enough to exceed the sorptive capacity of the soil or if the release has occurred below the surface of the soil (for example from a leaking underground storage tank).

Alkanes with low water solubility are unlikely to be dissolved in water moving through soil and consequently are likely to be sorbed to organic matter in the soil; however, it is expected that these compounds will volatilize more quickly than they will bind to organic matter. Aliphatic hydrocarbons with higher water solubilities are likely to be dissolved in water and may be transported through soil more rapidly, although the rate at which this transport occurs may be hindered to some extent by sorption to organic matter or volatilization (Air Force 1989a).

The potential for bioaccumulation of Stoddard solvent in either aquatic or terrestrial ecosystems is dependent on the bioaccumulation potential of the individual hydrocarbon components. Water soluble aliphatics and aromatics may be expected to have low bioconcentration factors based on their octanol water partition coefficients. Although no information is available on the bioconcentration of Stoddard solvent directly, aquatic organisms have been found to bioconcentrate some of the hydrocarbons found in fuel oils, many of which are also found in Stoddard solvent. Mussels exposed to fuel oil no. 2 were found to have significantly increased concentrations of alkanes, cycloalkanes, and aromatics in their tissue on the first day of exposure although by day 5, the n-alkanes were barely detectable and by day 21, concentrations of a mixture of alkanes and cycloalkanes had decreased to 30% of the day 1 concentrations. The half-life of naphthalenes with C-2 and C-3 moieties were 0.9 and 1.5 days, respectively (Farrington et al. 1982).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Volatilization from soil and surface waters with subsequent rapid photooxidation in the atmosphere is expected to be an important fate process for Stoddard solvent based on its vapor pressure of 3.0 mmHg (at 20°C) and also, by analogy, based on the environmental fate of jet fuel 4 (JP-4) which contains similar classes of hydrocarbons (Air Force 1989a, 1989b). This is particularly true for the alkane constituents of Stoddard solvent with low water solubilities. Low ambient temperatures tend to inhibit the volatilization process. Other constituents of Stoddard solvent, such as alkylbenzenes, are less volatile and more water soluble and, consequently, are more likely to be degraded by other processes such as sorption or biodegradation.

5.3.2.2 Water

The C_5–C_9 hydrocarbon components of Stoddard solvent released to surface waters are primarily lost by evaporation to the atmosphere. Larger hydrocarbon components are most likely to undergo biodegradation. Microorganisms capable of degrading these hydrocarbons have been found in surface waters (Air Force 1989a). In aquatic environments, C_{10}–C_{25} n-alkanes are preferentially degraded by microorganisms, although

biodegradation decreases as the hydrocarbons become more complex from aliphatics to cycloalkanes. In situations where biodegradation is a rare occurrence for a single bacterial species, cometabolism may occur (Edgerton et al. 1987).

In aqueous environments, photooxidation of trisubstituted benzenes and naphthalenes may be quite rapid, while alkanes, benzenes, and monosubstituted benzenes are relatively resistant to photooxidation (Air Force 1989a).

5.3.2.3 Soil

Stoddard solvent released to soil surfaces will undergo "weathering" over time that will result in changes in the concentrations of the constituent hydrocarbons. Low molecular weight hydrocarbons (such as C_5–C_9 alkanes and aromatics) are more likely to evaporate from soil surfaces rather than be biodegraded. Loss of higher molecular weight aliphatic and aromatic constituents of Stoddard solvent will occur by both slow evaporation and by biodegradation. Soil microorganisms may preferentially degrade certain components of Stoddard solvent, with the rate of biodegradation being fastest for low molecular weight aromatics. Biodegradation is slower for aliphatic hydrocarbons that are branched or cyclic or that contain 10 or more carbons. The length of time required to achieve total degradation of Stoddard solvent may be substantial as demonstrated by the degradation of another petroleum distillate, fuel oil no. 2, which was degraded by 86–90% after 1 year (Air Force 1989a; Raymond et al. 1975, 1976).

Stoddard solvent, applied to soil at a toxic concentration of 100 gallons per acre, reduced the number of soil microorganisms by more than half (Persidsky and Wilde 1956), indicating that high concentrations of Stoddard solvent may have a detrimental effect on the ability of soil bacteria to degrade it.

In order to determine the potential hazard to operators of landfill sites where solvents may be disposed, the evaporation of white spirits (Stoddard solvent) from a simulated landfill site (using pulverized domestic waste) was studied. Evaporation of Stoddard solvent from the landfill was compared with its evaporation from a holding lagoon (using a liquid pool of the solvent). The volatile components of Stoddard solvent initially evaporated rapidly from both sites, although the rate of evaporation was much greater from the waste site. After 6 hours, the loss of solvent from the waste was still twice that from the pool of liquid, suggesting that land application may pose a greater initial hazard to site operators from fumes than would disposal by lagooning; ideally however, other disposal methods, such as incineration, are preferred (Jones and McGugan 1977).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Stoddard solvent is not monitored in air as a hydrocarbon mixture; its volatile components, such as low molecular weight alkanes and aromatics, are more likely to be monitored as individual compounds in the air.

Stoddard solvent, used in industrial paints for dump trucks, was present in the paint booth at concentrations between 7.0 and 12.0 ppm as determined by personal sampling apparatus; however, this was considerably below the threshold limit value (time-weighted average) of 100 ppm for occupational safety (Bradley and Bodsworth 1983).

The use of hazardous wastes as fuel for industrial and commercial boilers may result in significant population exposures to hazardous air emissions, particularly when compared with disposal in incinerators regulated under the Resource Conservation and Recovery Act (RCRA) which must achieve a removal efficiency of at least 99.99%. Using EPA's population exposure and air dispersion models, the potential population exposure was measured for five combustion scenarios (one commercial incinerator and four boilers with varying capacities and destruction efficiencies) using Stoddard solvent and the trimethylbenzene component of Stoddard solvent as potential industrial waste streams. Modeling results showed that the greatest exposure to emissions and the highest emission concentrations were generated by a 15-million British thermal unit (Btu) boiler operating at 97.0% destruction capacity. Under this scenario, the highest concentrations of Stoddard solvent and trimethylbenzene to which people would be exposed were 103 $\mu g/m^3$ and 15.4 $\mu g/m^3$, respectively. By comparison, a 75-million Btu incinerator operating at 99.99% destruction and removal efficiency would expose people to concentrations several orders of magnitude less (exact number unspecified) (Coyle and Potenta 1983).

5.4.2 Water

No information was located on levels of the Stoddard solvent as a hydrocarbon mixture monitored in surface or groundwater. Although some hydrocarbon components of Stoddard solvent have been detected in water samples it is not evident whether the source was a release of Stoddard solvent or some other hydrocarbon mixture or compound.

5.4.3 Soil

No monitoring studies for Stoddard solvent as a hydrocarbon mixture in soil were located.

5.4.4 Other Environmental Media

No monitoring studies for Stoddard solvent in other environmental media were located.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

According to the National Occupational Exposure Survey conducted from 1981 to 1983 by NIOSH, 1,922,235 employees (including 230,356 females) in 404 plants were potentially exposed to Stoddard solvent in the workplace (NOES 1992). Most exposure was for persons employed as cleaners or janitors. It is expected that workers who use Stoddard solvent as a degreasing agent or who work in dry cleaning establishments or print shops where it is used as a solvent may have significant exposure potential.

Transport of Stoddard solvent through soil and into groundwater may result in general population exposure through the ingestion of contaminated drinking water. Inhalation exposure may also result from the volatilization of Stoddard solvent components from contaminated soil, including the diffusion of volatile components through soil and into the basements of buildings (Air Force 1989a).

Use of Stoddard solvent in dry cleaning may result in the occupational exposure of workers in these establishments (Air Force 1989a). The use of Stoddard solvent (mineral spirits) in commercial paints may result in inhalation exposure, particularly if the paint is applied with a sprayer (Fidler et al. 1987), as well as dermal exposures if protective clothing is not worn (Air Force 1989a).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

No studies were located regarding populations with potentially high exposures; however, it is possible that persons living or working near facilities that use Stoddard solvent may receive exposure to the more volatile components.

Use of Stoddard solvent for painting and in printing inks increases the likelihood of exposure by painters and others who work in areas where Stoddard solvent is used. In addition, people who use commercial products such as degreasers and paints which contain Stoddard solvent may also be exposed by inhaling solvent vapors or by dermal contact with the product. Use of a respirator and good ventilation can reduce exposure to the solvent vapors and protective clothing will help prevent dermal contact.

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 Stoddard solvent 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 Stoddard solvent.

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 will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. More information on the exact identity and properties of each of the various formulations that are called Stoddard solvent would make it easier to distinguish the toxicity and environmental effects caused by Stoddard solvent and to trace its fate based on levels of distinguishing components, if any. Identification of components or ratios between different components that may be used to distinguish Stoddard solvent from other hydrocarbon mixtures in waste streams or other applications would be useful. Data needs associated with some of the specific compounds that are components of Stoddard solvent (e.g., toluene and naphthalene) are presented in the ATSDR toxicological profiles for these chemicals (ATSDR 1990, 1991).

Production, Import/Export, Use, and Release and Disposal. Data on the potential for human exposure are limited (Air Force 1989a; NOES 1992). Further information on current uses, production volumes, and releases of Stoddard solvent from industrial uses or as a result of its disposal would be helpful in assessing the potential risk of exposure to this compound.

Environmental Fate. Stoddard solvent partitions to the various environmental compartments according to the physical/chemical properties of its individual components. Major fate processes include volatilization of low molecular weight alkanes and aromatics with photooxidation in the atmosphere, sorption to soil and water organic matter for cycloalkanes and longer-chain alkanes, and dissolution of aromatic hydrocarbon constituents in water (Air Force 1989a). Biodegradation in soils may be significant for the aliphatic and aromatic

hydrocarbon components of Stoddard solvent that are not primarily lost by evaporation (Air Force 1989a). The behavior of Stoddard solvent upon release to the environment has not been well characterized. Limited information is available on the environmental fate of the three hydrocarbon classes (linear and branched alkanes, cycloalkanes, and aromatics) that comprise Stoddard solvent, although further study on the interactions of these classes, particularly over time, would be useful in assessing the persistence and degradation of Stoddard solvent in the environment. In addition, fate information derived from the use of an equilibrium partitioning model should be experimentally verified.

Bioavailability from Environmental Media. Since the factors characterizing the absorption of Stoddard solvent are not known for humans or animals, the bioavailability is also unknown. There are no data on whether Stoddard solvent released to soil or water will be absorbed by humans or animals through contact with contaminated media. It is expected that the alkylbenzene components of Stoddard solvent, being more water soluble than the alkanes and cycloalkanes, will be more readily available for adsorption from contaminated waters. In addition, there are also no data to indicate whether plants grown on contaminated soil or fish living in contaminated water are likely to absorb Stoddard solvent or its constituents and thus enter the food chain. More data on possible rates and extent of absorption through the inhalation, oral, and dermal routes would be useful in determining bioavailability from environmental media.

Food Chain Bioaccumulation. No information was found on the bioaccumulation potential of Stoddard solvent in either terrestrial or aquatic ecosystems; however, the individual components making up the mixture may bioaccumulate depending on their individual properties. In general, lower molecular weight alkanes do not tend to bioaccumulate, aromatics may have a moderate tendency to bioaccumulate, and the higher molecular weight alkanes, such as cycloalkanes, tend to bioaccumulate; although this may not be true for all compounds within a class (Air Force 1989a). Research on the biomagnification of Stoddard solvent would not be useful because it is not available to the food chain as a mixture; however, further research on the biomagnification potential of major components of Stoddard solvent may be helpful in assessing the risk associated with eating foods grown in contaminated soil.

Exposure Levels in Environmental Media. There are very limited exposure data for air concentrations of Stoddard solvent in areas where it is used as an industrial paint solvent (Bradley and Bodsworth 1983). More data on levels in air resulting from other uses or storage or disposal would be useful. Data on levels in contaminated surface water, groundwater, and soil are needed to assess the potential risk from these likely sources of exposure.

Exposure Levels in Humans. There is a total lack of monitoring information on levels of Stoddard solvent in the workplace or for the general population based on determination of the component ratios of hydrocarbons. Monitoring surveys that examine levels of Stoddard solvent in the workplace and for the populations living or working in the vicinity of manufacturing or industrial use sites, or near disposal, dump, or leakage sites would be useful in determining approximate levels of exposure for these populations, although there may be difficulties in distinguishing exposure to Stoddard solvent versus other hydrocarbon mixtures, e.g., fuel oils or naphthas. Such distinctions may be based on ratios of hydrocarbon components and determination of actual use of Stoddard solvent.

Exposure Registries. No exposure registries for Stoddard solvent were located. This substance is not currently one of the compounds 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 On-going Studies

No on-going studies were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring Stoddard solvent 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 Stoddard solvent. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect Stoddard solvent 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 are 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 are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Stoddard solvent is a mixture of aliphatic and aromatic hydrocarbons. The primary method used to detect hydrocarbons in biological materials is gas chromatography (GC) either alone or in combination with a mass spectrometer (MS) for quantification. GC has been used to detect white spirits (99% C_8–C_{12} aliphatics) in expiratory air from the lungs, blood, and human adipose tissue. See Table 6-1 for a summary of these methods. In general, hydrocarbon components, whether of Stoddard solvent or other hydrocarbon mixtures such as fuel oils, have relatively simple sample preparation procedures which consist of adsorption of the volatile hydrocarbons to an adsorption column or charcoal, followed by elution and injection into the gas chromatograph. Capillary columns that have been successfully used include charcoal (Pedersen et al. 1984), Chromosorb G (Astrand et al. 1975), and Porapak or Chemipak (Kimura et al. 1988). The percent error associated with detecting white spirits by these methods is between 4% for adipose tissue (Pedersen et al. 1984) and 8.3% for air and blood (Astrand et al. 1975). Wide-bore capillary columns have also been used (Hara et al. 1988) for GC/MS analysis combined with flame ionization detectors (FID). This method determined levels of several volatile organic compounds in the blood, urine, and stomach contents. The sensitivity and precision of this method was generally good (93–100% recovery).

6.2 ENVIRONMENTAL SAMPLES

As with biological materials, detection of Stoddard solvent in environmental samples is based on the detection of component hydrocarbons. See Table 6-2 for a summary of the analytical methods used to determine Stoddard solvent hydrocarbons in environmental samples.

The primary method for detecting volatile components of Stoddard solvent in air is GC using a flame ionization detector (FID) (NIOSH 1984; Otson et al. 1983). Stoddard solvent in air may be determined by absorption to an appropriate column such as charcoal, desorption in a solvent (carbon disulfide is recommended), and subsequent quantification. Recovery tends to be rather poor (18–80%) because of the slow volatilization of Stoddard solvent. Precision, however, is good--greater than 10% relative standard deviation when the recovery is greater than 80% (Otson et al. 1983).

No analytical methods specific for Stoddard solvent in water or soil samples were located; however, determination of Stoddard solvent may be assumed to be similar to the detection of comparable hydrocarbon mixtures. Detection of Stoddard solvent in water is dependent on the identification and quantification of the specific hydrocarbon components of the solvent. The primary method, GC either alone or in combination with MS, may be used for the identification of the major hydrocarbon components, i.e., n-alkanes, branched alkanes, cycloalkanes, benzene, and alkylbenzenes. Separation of the aliphatic and aromatic fractions may be achieved by liquid-solid column chromatography followed by dilution of the eluates with carbon disulfide. Aqueous

DRAFT FOR PUBLIC COMMENT

TABLE 6-1. Analytical Methods for Determining Stoddard Solvent in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Add internal standard; extract with n-pentane; centrifuge; freeze; decant solvent; concentrate; inject to GC	GC/MS	50 pg	NR	Kimura et al. 1988
Blood	Mix sample with internal standard; add salt solution; equilibrate; aspirate headspace vapor and inject to GC	GC/MS	50 pg (toluene)	NR	Kimura et al. 1991
Stomach contents, blood, urine	Extract sample with ethyl acetate; condense; inject to GC	GC/FID/MS	0.2 μg/mL	93–100	Hara et al. 1988

FID = flame ionization detector; GC = gas chromatograph(y); MS = mass spectrometry; NR = not reported

TABLE 6-2. Analytical Methods for Determining Stoddard Solvent in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorb to solid sorbent tube (e.g., charcoal); desorb in CS_2; equilibrate; inject aliquot to GC	GC/FID	0.1 mg/5–10-mL sample	96–106	NIOSH 1984
Air	Adsorb to charcoal tube; extract with CS_2; inject extract to GC	GC/FID	0.05 mg/mL	78–91; 106	Otson et al. 1983
Water	Strip sample in sparger with helium; adsorb effluent gas to adsorption tube; thermally desorb to GC	GC/FID/MS	10 µg/L	89.7–95.7	Bianchi et al. 1991
Water (purgeable aromatics)	Purge sample with inert gas; adsorb vapor in trap; heat trap; backflush to GC	GC/PID	0.2 µg/L	92–96	EPA 1991c

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil (other solid materials)	Extract sample with CCl_4; inject extract	GLC	NR	NR	Midkiff and Washington 1972
Soil	Extract sample with CCl_4; centrifuge; remove water and humic materials with Na_2SO_4 and Al_2O_3; inject extract	GC/FID	NR	NR	Galin et al. 1990a
Sediment	Add internal sample to sample; extract with KOH in methanol; partition into petroleum ether; concentrate; purify and isolate hydrocarbon fractions using TLC or column chromatography	GLC/FID	NR	NR	Gearing et al. 1980

Al_2O_3 = aluminum oxide; CCl_4 = carbon tetrachloride; CS_2 = carbon disulfide; FID = flame ionization detector; GC = gas chromatography; GLC = gas liquid chromatography; KOH = potassium hydroxide; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NR = not reported; PID = photoionization detector; TLC = thin layer chromatography

samples may be extracted with trichlorotrifluoroethane, while solid samples may be extracted by Soxhlet extraction or sonication methods (Air Force 1989a). Purgeable (volatile) aromatics may be determined with a purge-and-trap apparatus. This method requires a trap with a Tenax/Chromosorb absorbent and the use of GC with a photoionization detector (PID) (EPA 1991c), an ion trap detector (ITD), or FID (Thomas and Delfino 1991). A modification of the purge-and-trap method uses ambient temperature, has the advantage of being applicable to a variety of waters, requires virtually no sample preparation (no solvents are required for desorbing the hydrocarbons), and has an analysis time of approximately 30 minutes (Bianchi et al. 1991). While this method may be used for determining the presence of industrial solvent mixtures in water, it cannot distinguish between various sources of this contamination, e.g., gasoline, kerosene, Stoddard solvent.

Although no analytical methods were identified for determining the presence of Stoddard solvent in soil samples, methods do exist for detecting other hydrocarbon mixtures, such as kerosene, and these may be applicable to Stoddard solvent. Two methods that have been used for petroleum distillates include GC/FID (Galin et al. 1990) and gas liquid chromatography (GLC) with FID (Midkiff and Washington 1972). Soil samples are extracted with carbon tetrachloride. Recovery, sensitivity, and levels of detection data were not reported. Quantification of oils and grease, by gross weight only, in soils and sludges may be accomplished by extraction with a Soxhlet apparatus using either trichlorotrifluoroethane (APHA 1985) or methylene chloride (Martin et al. 1991) as the solvent, although this method is qualitative, not quantitative, and cannot be used to identify the type of oil or grease bound to the soil.

While no analytical methods were located that are specific for detecting Stoddard solvent in sediment, as with water and soil, methods that detect other hydrocarbon mixtures may be applicable. For example, quantification of fuel oil hydrocarbons from sediments is a relatively involved process. Following extraction, the saturated and olefinic hydrocarbon fraction is separated from the aromatic hydrocarbon fraction using thin-layer chromatography or column chromatography. Fractions are subsequently analyzed by GLC (Gearing et al. 1980).

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 Stoddard solvent 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 Stoddard solvent.

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 will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. There are no known methods for determining biomarkers of exposure or effect. Any information of this type, including the possible identification of a trace compound(s) for Stoddard solvent as well as information on its metabolites in humans, would be useful for determining whether an individual has been exposed to Stoddard solvent. It has been

suggested that elevated levels of dimethylbenzoic acid in the urine may be indicative to exposure to Stoddard solvent (Pfaffli et al. 1985), but further study of the use of this compound as a biomarker is needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Although no specific methods were located for measuring Stoddard solvent in soil or water, methods do exist for measuring particular hydrocarbon components of Stoddard solvent, such as 2,6-dimethyloctane, based on analysis with GC. In addition, it may be possible to identify Stoddard solvent based on characteristic ratios of hydrocarbon components, but such ratios have not be established. An analytical method does exist for determining Stoddard solvent in air using GC/FID (NIOSH 1984; Otson et al. 1983). The precision of the method is good, but recovery is poor. Some methods for detecting hydrocarbon fractions for other hydrocarbon mixtures (e.g., gasoline, fuel oils) in environmental media may be applicable to Stoddard solvent (Bianchi et al. 1991; Gearing et al. 1980; Midkiff and Washington 1972) but should be subjected to further analysis to determine their precision, recovery, and selectivity when used for Stoddard solvent. In addition, methods should be developed to distinguish between contamination from Stoddard solvent versus other petroleum distillates. At present, knowledge on the exact hydrocarbon components and their ratios in various hydrocarbon mixtures (e.g., gasoline, kerosene, Stoddard solvent, paint thinners, etc.) is scarce, and more precise numbers would facilitate in determining the exact hydrocarbon mixture present in the environmental sample. This would be particularly useful for determining hydrocarbon wastes and contamination at hazardous waste sites where several such mixtures may be present.

6.3.2 On-going Studies

No on-going studies were located for Stoddard solvent.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding Stoddard solvent in air, water, and other media are summarized in Table 7-1.

The acute inhalation MRL for Stoddard solvent is 1.4 mg/m^3/day.

There is no EPA reference dose (RfD) or reference concentration (RfC) for Stoddard solvent.

Stoddard solvent contains volatile organic compounds (VOC) and may be regulated under the Clean Air Act guidelines for reduction of VOC emissions from solvents (Clean Air Act 1990).

Under the Hazardous Materials Transportation Act, Stoddard solvent 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 Stoddard Solvent

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification for occupational exposures in petroleum refining	Group 2A[a]	IARC 1989
NATIONAL			
Regulations:			
a. Air:			
AFOSH	PEL TWA	100 ppm	Air Force 1989
	STEL (15 minutes)	150 ppm	Air Force 1989
OSHA	PEL TWA	100 ppm	OSHA 1989a (29 CFR 1910.1000); OSHA 1989b
b. Other:			
DOT	Hazardous Material Transportation Act: Stoddard solvent is designated as hazardous materials which are subject to requirements for packaging, shipping, and transporting.	Yes	DOT 1989a (49 CFR 172.101; Appendix Appendix A); DOT 1989b
Guidelines:			
a. Air:			
ACGIH	TLV TWA	100 ppm	ACGIH 1990
NIOSH	TWA	85 ppm (350 mg/m^3)	NIOSH 1992
	Ceiling REL (15 minutes)	438 ppm (1,800 mg/m^3)	NIOSH 1992
b. Other:			
EPA	Clean Air Act: Reduction in emissions of volatile organic compounds from solvents	Yes	Clean Air Act 1990
STATE:			
Regulations and Guidelines:			
a. Air:	Acceptable Ambient Air Concentrations		NATICH 1991
Connecticut	(8 hours)	7.00×10^3 µg/m^3	
Florida-Pinellas	(8 hours)	5.25×10^3 µg/m^3	
Florida-Pinellas	(24 hours)	1.26×10^3 µg/m^3	
Maryland		0.00	
North Dakota	(8 hours)	5.25 mg/m^3	
Nevada	(8 hours)	1.25×10^1 mg/m^3	
Oklahoma	(24 hour)	3.50×10^4 µg/m^3	
Texas	(30 minutes)	3.50×10^3 µg/m^3	
Texas	(Annual)	3.50×10^2 µg/m^3	
Virginia	(24 hours)	8.80×10^3 µg/m^3	
Vermont	(Annual)	1.25×10^4 µg/m^3	

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
	Regulations on hydrocarbon emissions (petroleum distillates)	Yes	CELDS 1991
Connecticut Kansas Wisconsin			
	Regulations on VOC emissions	Yes	CELDS 1991
Alabama Arizona Florida Maine Maryland Michigan New Jersey South Carolina Virginia Texas Washington, D.C.			
b. Water:			
Alaska	Aquatic life criterion for total hydrocarbons in marine and surface waters	15 µg/L	State of Alaska 1989
	Aquatic life criterion for aromatic hydrocarbons in marine and surface waters	10 µg/L	State of Alaska 1989
Arkansas	Average or maximum allowable quantity of oil or grease discharged into surface waters	10 mg/L (average) 15 mg/L (maximum)	State of Arkansas 1991
Florida	Average or maximum allowable quantity of oil or grease discharged into Class V waters (navigation, industrial use)	10 mg/L	State of Florida 1992
	Average or maximum allowable quantity of oil or grease discharged into all other surface waters	5 mg/L	State of Florida 1992
Massachusetts	Maximum discharge concentration of oil or grease of petroleum origin in surface waters	15 mg/L	Commonwealth of Massachusetts 1990
Nebraska	Maximum petroleum oil concentration in surface waters	10 mg/L	State of Nebraska 1990
South Dakota	Water quality standard for all petroleum products in surface waters	10 mg/L	State of South Dakota 1992
Virginia	Water quality standard for petroleum hydrocarbons in groundwater	1 mg/L	Commonwealth of Virginia 1990
Wyoming	Water quality standard for all surface water classes	10 mg/L	State of Wyoming 1990

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
c. Other:			
Colorado Maryland Massachusetts Wisconsin	Regulations on the transport of flammable/hazardous liquids (petroleum distillates or VOCs)	Yes	CELDS 1991
Maine	Regulations on the disposal of special wastes including diesel fuels	Yes	CELDS 1991
California	Regulations on leaking underground fuel tanks	Yes	CELDS 1991

[a]Group 2A = probably carcinogenic to humans. This classification applies only to occupational exposures in petroleum refining

ACGIH = American Conference of Governmental Industrial Hygienists; AFOSH = Air Force Office of Health and Safety; DOT = Department of Transportation; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; LC_{50} = lethal dose, 50% kill; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; STEL = Short-Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; VOC = volatile organic compound

8. REFERENCES

*ACGIH. 1990. Threshold limit values and biological exposure indices for 1990-1991. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

*Air Force. 1989. Stoddard solvent. In: The installation restoration program toxicology guide. Volume 4. Contract no. DE-AC05-84OR21400. Wright-Patterson Air Force Base, OH: Air Force Systems Command, Aerospace Medical Division, Harry G. Armstrong Aerospace Medical Research Laboratory. DOE interagency agreement no. 1891-A076-A1. 67-1 - 67-25.

*Alden CL. 1986. A review of unique male rat hydrocarbon nephropathy. Toxicol Pathol 14:109-11.

*Anderson C, Sundberg K, Groth O. 1986. Animal model for assessment of skin irritancy. Contact Dermatitis 15:143-151.

Andrews LS, Snyder R. 1991. Toxic effects of solvents and vapors. In: Amdur MO, Doull J, Klaassen CD, eds. Casarett and Doull's Toxicology: The basic science of poisons. 4th ed. New York, NY: Pergamon Press, 681-685.

*Annobil SH. 1988. Skin bullae following kerosene poisoning. Ann Trop Pediatr 8(1):45-47.

*APHA. 1985. Standard methods for the examination of water and wastewater. 16th ed. Washington, DC: American Public Health Association.

*API. 1976. Detectability and irritability of hydrocarbons in human subjects. Final report to American Petroleum Institute. Contract no. U-15-14-PS-5. Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH.

*API. 1977. Teratology study in rats. Stoddard solvent final report. Washington, DC: American Petroleum Institute.

*API. 1979a. Inhalation/teratology study in rats: Fuel oil. Washington, DC: American Petroleum Institute. Document no. FYI-AX-0183-0230.

*API. 1979b. Teratology study in rats: Diesel fuel. Washington, DC: American Petroleum Institute. Document no. FYI-AX-0183-0230.

*API. 1982. Mutagenicity study of thirteen petroleum fractions. Project no. U-150-14 (EA-1). Washington, DC: American Petroleum Institute.

*API. 1987a. Acute inhalation toxicity evaluation of a petroleum derived hydrocarbon in rats - API 84-02 and API 85-01 with heavy thermal cracked naphtha with cover letter dated 05/19/87. Project no. 22235-14. Washington, DC: American Petroleum Institute.

*API. 1987b. Mutagenicity of API 8501, Stoddard solvent (CAS 8052-41-3) in a mouse lymphoma mutation assay. Final report. Washington, DC: American Petroleum Institute.

---

*Cited in text

*Arlien-Söborg P, Bruhn P, Gyldensted C, et al. 1979. Chronic painters' syndrome: Chronic toxic encephalopathy in house painters. Acta Neurol Scand 60:149-156.

*ASTM. 1988. 1988 Annual book of ASTM standards: volume 6.03. Paints - Fatty oils and acids, solvents, miscellaneous; aromatic hydrocarbons. Philadelphia, PA: American Society for Testing and Materials. Designation:D 235-87.

*Astrand I, Kilbom A, Ovrum P. 1975. Exposure to white spirit: I. Concentration in alveolar air and blood during rest and exercise. Scand J Work Environ Health 12:15-30.

*ATSDR. 1989. Toxicological profile for benzene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1990. Toxicological profile for toluene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1991. Toxicological profile for naphthalene and 2-methylnaphthalene. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

*ATSDR. 1993. Draft toxicological profile for gasoline; Draft toxicological profile for jet fuels JP-4 and JP-7; Draft toxicological profile for fuel oils. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Baker RW, Yoshioka N, Mohr JM, et al. 1987. Separation of organic vapors from air. J Membr Sci 31:259-272.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

*Beck LS, Hepler DI, Hansen KL. 1983. The acute toxicology of selected petroleum hydrocarbons. In: MacFarland HN, Holdsworth LE, MacGregor JA, et al., eds. Proceedings on the 1st Symposium on the Toxicology of Petroleum Hydrocarbons, Washington, DC, May 1982. 1-12.

Beliles RP, Mecler FJ. 1982. Inhalation teratology of jet fuel A, fuel oil and petroleum naphtha in rats. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Proceedings of the symposium: The toxicology of petroleum hydrocarbons. Washington, DC: American Petroleum Institute, 233-238.

*Beliles RP, Mecler FJ. 1983. Inhalation teratology of jet fuel A, fuel oil and petroleum naphtha in rats. In: MacFarland HN, ed. Proceedings of the Symposium on the toxicology of petroleum hydrocarbons, Washington, DC, May 1982. Washington, DC: American Petroleum Institute, 233-238.

Beving H, Malmgren R, Olsson P. 1988. Changed fatty acid composition in platelets from workers with long term exposure to organic solvents. Br J Ind Med 45:565-567.

*Beving H, Tornling G, Olsson P. 1991. Increased erythrocyte volume in car repair painters and car mechanics. Br J Ind Med 48:499-501.

8. REFERENCES

*Bianchi AP, Varney MS, Phillips J. 1991. Analysis of industrial solvent mixtures in water using a miniature purge-and-trap device with thermal desorption and capillary gas chromatography-mass spectrometry. J Chromatogr 557(1-2):429-439.

Biles RW, McKee RH. 1983. Toxicological testing for hazard identification in synthetic fuel technology. Dev Toxicol Environ Sci 11:13-21.

Bjerre A. 1989. Assessing exposure to solvent vapour during the application of paints, etc.--model calculations versus common sense. Ann Occup Hyg 33:507-517.

*Bocskei Z, Groom CR, Flower DR, et al. 1992. Pheromone binding to two rodent urinary proteins revealed by X-ray crystallography. Nature 360:186-188.

*Borghoff SJ, Short BG, Swenberg JA. 1990. Biochemical mechanism and pathobiology of α_{2u}-globulin nephropathy. Annu Rev Pharmacol Toxicol 30:349-367.

*Bradley A, Bodsworth PL. 1983. Environmental control of a large paint booth. Ann Occup Hyg 27:223-224.

Bratton L, Haddow JE. 1975. Ingestion of charcoal lighter fluid. J Pediatr 87:633-636.

Braunstein LE. 1940. Subacute yellow atrophy of the liver due to solvent. Journal of the American Medical Association 114:136-138.

*Bruhn P, Arlien-Söborg P, Gyldensted C, et al. 1981. Prognosis in toxic encephalopathy: A two-year follow-up study in 26 house painters with occupational encephalopathy. Acta Neurol Scand 64:259-272.

Buckley JD, Robison LL, Swotinsky R, et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: A report from the children's cancer study group. Cancer Res 49:4030-4037.

*Budavari S, O'Neil MJ, Smith A, et al., eds. 1989. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. Eleventh edition. Rahway, NJ: Merck & Co., Inc., 976.

*Carpenter CP, Kinkead ER, Geary DL Jr, et al. 1975a. Petroleum hydrocarbon toxicity studies: I. Methodology. Toxicol Appl Pharmacol 32:246-262.

*Carpenter CP, Kinkead ER, Geary DL Jr, et al. 1975b. Petroleum hydrocarbon toxicity studies: III. Animal and human response to vapors of Stoddard solvent. Toxicol Appl Pharmacol 32:282-297.

*CELDS. 1991. Computer-Environmental Legislative Data Systems. University of Illinois, Urbana, IL. June 20, 1991.

Chelton CF, Zakraysek N, Lautner GM, et al. 1983. Evaluation of the performance and response of the Bacharach TLV sniffer and H-nu photoionization gas analyzer to common hydrocarbon solvents. Am Ind Hyg Assoc J 44:710-715.

Cherry N, Waldron HA. 1983. The neuropsychological effects of solvent exposure. The Colt Foundation, New Lane, Havant, Hampshire, PO9 2LY, United Kingdom, 205.

Churchill DN, Fine A, Gault MH. 1983. Association between hydrocarbon exposure and glomerulonephritis: An appraisal of the evidence. Nephron 33:169-172.

Clark CR, Walter MK, Ferguson PW, et al. 1988. Comparative dermal carcinogenesis of shale and petroleum-derived distillates. Toxicol Ind Health 4:11-22.

Clark CR, Ferguson PW, Katchen MA, et al. 1989a. Comparative acute toxicity of shale and petroleum derived distillates. Toxicol Ind Health 5:1005-1016.

*Clark DG, Butterworth ST, Martin JG, et al. 1989b. Inhalation toxicity of high flash aromatic naphtha. Toxicol Ind Health 5:415-28.

*Clean Air Act. 1990. Washington, DC: The Bureau of National Affairs, Inc. PL 101-549. 71:1159,1175-1188.

*CLPSD. 1989. Contract Laboratories Program Statistical Database. U.S. Environmental Protection Agency, Washington, DC. July, 1989.

*Commonwealth of Massachusetts. 1990. Massachusetts Surface Water Quality Standards. Boston, MA: Massachusetts Surface Water Quality Standards, Division of Water Pollution Control. Massachusetts 314 CMR 4.00.

*Commonwealth of Virginia. 1990. Commonwealth of Virginia State Water Control Board Regulations. Richmond, VA: Commonwealth of Virginia State Water Control Board Regulations, Water Quality Standards.

*Conaway CC, Schreiner CA, Cragg ST. 1984. Mutagenicity evaluation of petroleum hydrocarbons. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Advances in modern environmental toxicology. Vol. 6: Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, Inc., 89-107.

*Coruh M, Inal H. 1966. Kerosene poisoning in children with special reference to lung complication. Turk J Pediatr 8(1):36-42.

*Coyle JJ, Potenta EJ. 1983. Population exposure to hazardous air pollutants from waste combustion in industrial boilers and RCRA regulated incinerators. In: Frederick ER, ed. Proceedings, measurement, and monitoring of non-criteria (toxic) contaminants in air specialty conference, 1983. Chicago, IL: Air Pollution Control Association, 138-149.

*Daniell WE, Couser WG, Rosenstock L. 1988. Occupational solvent exposure and glomerulonephritis: A case report and review of the literature. J Am Med Assoc 259:2280-2283.

*Dice WH, Ward G, Kelley J, et al. 1982. Pulmonary toxicity following gastrointestinal ingestion of kerosene. Ann Emerg Med 11:138-142.

Dick RB. 1988. Short duration exposures to organic solvents: The relationship between neurobehavioral test results and other indicators. Neurotoxicol Teratol 10:39-50.

8. REFERENCES

*Dossing M, Arlien-Soborg P, Petersen LM. 1983. Liver damage associated with occupational exposure to organic solvents in house painters. Eur J Clin Invest 13:151-158.

*DOT. 1989a. Hazardous materials table. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101 Appendix A.

*DOT. 1989b. Hazardous materials table and hazardous materials communications regulations. Department of Transportation. Federal Register 54:39501-39505.

*Edgerton SA, Coutant RW, Henley MV. 1987. Hydrocarbon fuel spill dispersion on water: A literature review. Chemosphere 16(7):1475-1487.

*Ellenhorn MJ, Barceloux DG, eds. 1988. Medical toxicology: Diagnosis and treatment of humans poisoning. New York, NY: Elsevier.

Enzminger JD, Ahlert RC. 1987. Environmental fate of polynuclear aromatic hydrocarbons in coal tar. Environmental Technology Letters 8:269-278.

*EPA. 1980. Demonstration of carbon adsorption technology for petroleum dry cleaning plants. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. ISS EPA-600/2-80-145, order no. PB80-221039.

EPA. 1982a. Mixed solvent vapor exposure, with cover letter. Washington, DC: U.S. Environmental Protection Agency. U.S. EPA/OPTS public files 878210808. Microfiche no. OTS0206238.

EPA. 1982b. Product environmental data. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0206107.

EPA. 1982c. Product environmental data. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0206116.

EPA. 1984a. Response to EPA document 8EHQ-0584-0517 with attached summary of histopathological findings of a lifetime skin painting study in mice. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0509708.

*EPA. 1984b. Review of toxicity information on varsol 40 (Varsol 1). Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0000313-0.

*EPA. 1984c. Summary of histopathology findings for dermal carcinogenesis lifetime skin painting study of solvent-cutback type rust preventative. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. Document no. 88-8400629.

EPA. 1986a. A copy of a study on the genetic toxicity of Rust-Ban 392 and excerpts from the final report with cover letter dated 06/20/86. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0509708-1.

EPA. 1986b. Oral toxicity, dermal toxicity, dermal irritation, eye irritation and dermal sensitization studies performed with API 83-15, 85-01 & 83-20 (final report) with letter. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0000371-5.

*EPA. 1986c. Quality criteria for water. Washington, DC: U.S. Environmental Protection Agency. EPA 440/5-86-001.

EPA. 1987. 28-Day dermal toxicity study of API 85-01 in the rabbit (draft final report) with cover letter dated 02/25/87. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. NTIS/OTS0000533-0.

*EPA. 1989. Pesticides required to be reregistered: List C. U.S. Environmental Protection Agency. Federal Register 54 (104): 30846-30855.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066A.

*EPA. 1991a. α_{2U}-globulin: Association with chemically-induced renal toxicity and neoplasia in the male rat. Review draft. Washington, DC: U.S. Environmental Protection Agency. EPA/624/3-91/019A.

*EPA. 1991b. C9 aromatic hydrocarbon fraction. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 799.2175.

*EPA. 1991c. Method 602 - Purgeable aromatics; Method 610 - Polynuclear aromatic hydrocarbons; Method 625 - Base/neutrals and acids. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136, Appendix A.

*EPA. 1992. Toxic Substances Control Act Inventory 1990 [Chemical Update System Database]. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Information Management Division.

*ERNS. 1992. Emergency Response Notification System. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. December 21, 1992.

*Farrington JW, Davis AC, Frew NM, et al. 1982. No. 2 fuel oil components in Mytilis edulis: Retention and release after an oil spill. Mar Biol 66:15-26.

*Fidler AT, Baker EL, Letz RE. 1987. Estimation of long term exposure to mixed solvents from questionnaire data: A tool for epidemiological investigations. Br J Ind Med 44:133-141.

*Flodin U, Edling C, Axelson O. 1984. Clinical studies with psychoorganic syndromes among workers with exposure to solvents. Am J Ind Med 5:287-295.

*Galin T, Gerstl Z, Yaron B. 1990. Soil pollution by petroleum products: III. Kerosene stability in soil columns as affected by volatilization. J Contam Hydrol 5(4):375-385.

*Gamberale F, Annwall G, Hultengren M. 1975. Exposure to white spirit: II. Psychological functions. Scand J Work Environ Health 1:31-39.

*Gearing PJ, Gearing JN, Pruell RJ, et al. 1980. Partitioning of no. 2 fuel oil in controlled estuarine ecosystems: Sediments and suspended particulate matter. Environ Sci Technol 14(9):1129-1136.

*Gochet B, de Meester C, Leonard A, et al. 1984. Lack of mutagenic activity of white spirit. Int Arch Occup Environ Health 53:359-364.

Goodfield MJ, Saihan EM. 1988. Contact urticaria to naphtha present in a solvent. Contact Dermatitis 18:187.

Grasso P. 1988. Neurotoxic and neurobehavioral effects of organic solvents on the nervous system. State Art Rev Occup Med 3:525-539.

*Gregersen P. 1988. Neurotoxic effects of organic solvents in exposed workers: Two controlled follow-up studies after 5.5 and 10.6 years. Am J Ind Med 14:681-702.

*Gregersen P, Angelsoe B, Nielson TE, et al. 1984. Neurotoxic effects of organic solvents in exposed workers: An occupational, neuropsychological, and neurological investigation. Am J Ind Med 5:201-225.

*Haddad LM, Winchester JF, eds. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1177-1183.

Hagmar L, Bellander T, Hoegstedt B, et al. 1988. Biological effects in a chemical factory with mutagenic exposure: I. Cytogenetic and hematological parameters. Int Arch Occup Environ Health 60:437-444.

Halder CA, Holdsworth CE, Cockrell BY, et al. 1985. Hydrocarbon nephropathy in male rats: Identification of the nephrotoxic components of unleaded gasoline. Toxicol Ind Health 1:67-88.

*Hane M, Axelson O, Blume J, et al. 1977. Psychological function changes among house painters. Scand J Work Environ Health 3:91-99.

Hansen MK, Larsen M, Cohr K-H. 1987. Waterborne paints: A review of their chemistry and toxicology and the results of determinations made during their use. Scand J Work Environ Health 13:473-485.

*Hara K, Kageura M, Hieda Y, et al. 1988. Application of wide-bore capillary gas chromatography to analyze volatile compounds in body fluids. Jpn J Legal Med 42(2):142-146.

Hashimoto DM, Kelsey KT, Seitz T, et al. 1991. The presence of urinary cellular sediment and albuminuria in newspaper pressworkers exposed to solvents. J Occup Med 33:516-526.

*Hastings L, Cooper GP, Burg W. 1984. Human sensory response to selected petroleum hydrocarbons. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Advances in modern environmental toxicology. Vol. VI: Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, Inc., 255-270.

Hauser SP. 1988. [Naphtha-B 100 to 140--petroleum. Documentation no. 12.] Schweiz Rundsch Med Prax 77:152-154. (German)

*HAZDAT. 1992. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

Holmberg PC, Nurminen M. 1980. Congenital defects of the central nervous system and occupational factors during pregnancy: Case-referent study. Am J Ind Med 1:167-176.

*Hunter D, Kislin AH, Kiesche E, et al., eds. 1992. Buyer's guide: Special issue. Chemical Week 149:500, 589.

*IARC. 1989. Occupational exposures in petroleum refining. IARC monographs on the evaluation of carcinogenic risks to humans. Occupational exposures in petroleum refining. Vol. 45: Crude oil and major petroleum fuels, Lyon, France: World Health Organization, International Agency for Research on Cancer, 39-117.

Iregren A, Gamberale F. 1990. Human behavioral toxicology central nervous effects of low-dose exposure to neurotoxic substances in the work environment. Scand J Work Environ Health 16:17-25.

*IRPTC. 1985. Treatment and disposal methods for waste chemicals: IRPTC file. Geneva, Switzerland: United Nations Environment Programme, International Register of Potentially Toxic Chemicals, 222.

Jakobsen BM, Hass U, Juul F, et al. 1986. Prenatal toxicity of white spirits inhalation in the rat [Abstract]. Teratology 34:415.

*Jenkins LJ Jr, Coon RA, Lyon JP, et al. 1971. Effect on experimental animals of long-term inhalation exposure to mineral spirits: II. Dietary, sex and strain influences in guinea pigs. Toxicol Appl Pharmacol 18:53-59.

*Jones CJ, McGugan PJ. 1978. An investigation of the evaporation of some volatile solvents from domestic waste. Journal of Hazardous Materials 2:235-252.

*Kainz RJ, White LE. 1984. Depressant effects associated with the inhalation of uncombusted diesel vapor. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Advances in modern environmental toxicology. Volume VI: Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, Inc.

Kastl J, Horacek J. 1982. [Primary myogenic skin tumours (multiple piloleiomyoma, subcutaneous leiomyosarcoma).] Cesk Dermatol 57:205-207. (Czech)

*Kimura K, Nagata T, Hara K, et al. 1988. Gasoline and kerosene components in blood: A forensic analysis. Hum Toxicol 7(4):299-305.

*Kimura H, Odani S, Nishi S, et al. 1991a. Primary structure and cellular distribution of two fatty acid-binding proteins in adult rat kidneys. J Biol Chem 266:5963-5972.

Kimura K, Nagata T, Kudo K, et al. 1991b. Determination of kerosine and light oil components in blood. Biol Mass Spectrom 20(8):493-497.

*Klaassen CD. 1991. Distribution, excretion, and absorption of toxicants. In: Amdur MO, Doull J, Klaassen CD, eds. Casarett and Doull's Toxicology: The basic science of poisons. 4th ed. New York, NY: Pergamon Press, 56-57.

*Knave B, Olson BA, Elofson S, et al. 1978. Long term exposure to jet fuel: II. A cross-sectional epidemiologic investigation on occupationally exposed industrial workers with special reference to the nervous system. Scand J Work Environ Health 4:19-45.

Koh D, Foulds IS, Aw TC. 1990. Dermatological hazards in the electronics industry. Contact Dermatitis 22:1-7.

Kopecni MM, Tarana MV, Cupic SD, et al. 1989. Gas chromatographic determination of phenols in waste water-oil emulsions. J Chromatogr 462:392-397.

*Kumar A, Sparks BD, Majid A. 1986. Recovery of organics from tailings pond sludge using coke for agglomeration. Separation Science and Technology 21:315-326.

Kurppa K, Vainio H. 1983. Study design liver disease and house painters exposure to organic solvents. Eur J Clin Invest 13:113-114.

Kurppa K, Holmberg PC, Hernberg S, et al. 1983. Screening for occupational exposures and congenital malformations: Preliminary results from a nationwide case-referent study. Scand J Work Environ Health 9:89-93.

Kyyronen P, Taskinen H, Lindbohm ML, et al. 1989. Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. J Epidemiol Community Health 43:346-351.

*Larsen LB, Schmunes E. 1974. Occupational health case report--no. 6: Stoddard solvent. J Occup Med 16:276-278.

Lebowitz H, Brusick D, Matheson D, et al. 1979. Commonly used fuels and solvents evaluated in a battery of short-term bioassays [Abstract]. Environ Mutagen 1:172-173.

Linz DH, de Garmo PL, Morton WE, et al. 1986. Organic solvent-induced encephalopathy in industrial painters. J Occup Med 28:119-125.

*Litovitz T, Greene AE. 1988. Health implications of petroleum distillate ingestion. State Art Rev Occup Med 3:555-567.

*Litton Bionetics. 1978. Teratology study in rats: Unleaded gasoline. Final report submitted to American Petroleum Institute, Washington, DC. Litton Bionetics, Inc., Kensington, MD.

*Majeed HA, Bassyouni H, Kalaawy M, et al. 1981. Kerosene poisoning in children: A clinico-radiological study of 205 cases. Ann Trop Pediatr 1(2):123-130.

*Mann MD, Pirie DJ, Wolfsdorf J. 1977. Kerosene absorption in primates. J Pediatr 91(3):495-498.

*Martin JH, Siebert AJ, Loehr RC. 1991. Estimating oil and grease content of petroleum-contaminated soil. Journal of Environmental Engineering 117(3):291-299.

*McDermott HJ. 1975. Hygienic guide series: Stoddard solvent (mineral spirits, white spirits). Am Ind Hyg Assoc J 36:553-558.

McKee RH, Hinz JP. 1987. Evaluation of the subacute and subchronic toxicity of inhaled hydrotreated naphtha in the rat. Fundam Appl Toxicol 9:120-130.

McKee RH, Biles RW, Kapp RW, et al. 1984. The acute toxicity of coal liquefaction-derived materials. J Appl Toxicol 4:198-205.

McKee RH, Hinz JP, Traul KA. 1986. Evaluation of the teratogenic potential and reproductive toxicity of coal-derived naphtha. Toxicol Appl Pharmacol 84:149-158.

McKee RH, Schmitt S, Wong Z, et al. 1990a. The reproductive and developmental toxicity of high flash aromatic naphtha. Toxicologist 10:41.

McKee RH, Wong ZA, Schmitt S, et al. 1990b. The reproductive and developmental toxicity of high flash aromatic naphtha. Toxicol Ind Health 6:441-460.

*Mehlman MA, Smart CL. 1982. A comparative toxicological evaluation of paint solvents. In: Englund A, Ringen K, Mehlman MA, eds. Occupational health hazards of solvents. Princeton, NJ: Princeton Scientific Publishers, 53-67.

Melke D. 1987. [Measuring chemical pollutants in the air at the work site of watchmakers.] Z Gesamte Hyg 33:640-641. (German)

Mellgren SI, Formoe T, Sundby R. 1988. Vibratory threshold in workers exposed to organic solvents [Abstract]. Neurology 38(Suppl. 1):222.

*Mergler D, Belanger S, de Grosbois S, et al. 1988. Chromal focus of acquired chromatic discrimination loss and solvent exposure among printshop workers. Toxicology 49:341-348.

*Midkiff CR Jr, Washington WD. 1972. Gas chromatographic determination of traces of accelerants in physical evidence. J Assoc Off Anal Chem 55(4):840-845.

*Mikkelsen S, Jorgensen M, Browne E, et al. 1988. Mixed solvent exposure and organic brain damage: A study of painters. Acta Neurol Scand Suppl 78:1-143.

*Mosconi G, Migliori M, Greco V, et al. 1988. Kerosene "burns": A new case. Contact Dermatitis 19(4):314-315.

*MSDS-CCOHS. 1992. Mineral spirits. Material Safety and Data Sheet-Canadian Center for Occupational Health and Safety. May 13, 1992.

*Narvarte J, Saba SR, Ramirez G. 1989. Occupational exposure to organic solvents causing chronic tubulointerstitial nephritis. Arch Intern Med 149:154-158.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

8. REFERENCES

*NATICH. 1991. National Air Toxics Information Clearinghouse. Data base report on state, local, and EPA air toxics activities. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Washington, D.C.: August 13, 1991.

*NESCAUM. 1989. Evaluation of the health effects from exposure to gasoline and gasoline vapors. Final report. Northeast States for Coordinated Air Use Management.

*Nethercott J, Pierce JM, Likwornick G, et al. 1980. Genital ulceration due to Stoddard solvent. J Occup Med 22:549-552.

Niemela R, Pfaffli P, Harkonen H. 1987. Ventilation and organic solvent exposure during car washing. Scand J Work Environ Health 13:424-430.

Nierenberg DW, Horowitz MB, Harris KM, et al. 1991. Mineral spirits inhalation associated with hemolysis, pulmonary edema, and ventricular fibrillation. Arch Intern Med 151:1437-1440.

NIOSH. 1977. Criteria for a recommended standard... Occupational exposure to refined petroleum products. Washington DC: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHEW (NIOSH) publication no. 77-192.

*NIOSH. 1984. Manual of analytical methods. 3rd ed. Eller PM, ed. Cincinnati, OH: National Institute for Occupational Safety and Health. Publication no. 84-100, method 1550.

*NIOSH. 1990. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) publication no. 90-117.

*NIOSH. 1992. NIOSH recommendations for occupational safety and health: Compendium of policy documents and statements. Cincinnati, OH: National Institute for Occupational Safety and Health. DHHS(NIOSH) publication no. 92-100.

*NOES. 1992. National Occupational Exposure Survey. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies.

*Nouri L, Al-Rahim K. 1970. Kerosene poisoning in children. Postgrad Med J 46(532):71-75.

*Olson BA. 1982. Effects of organic solvents on behavioral performance of workers in the paint industry. Neurobehav Toxicol Teratol 4:703-708.

*Olson MJ, Johnson JT, Reidy CA. 1990. A comparison of male rat and human urinary proteins: Implications for human resistance to hyaline droplet nephropathy. Toxicol Appl Pharmacol 102:524-536.

Ono Y, Takeuchi Y, Hisanaga N, et al. 1982. Neurotoxicity of petroleum benzine compared with n-hexane. Int Arch Occup Environ Health 50:219-229.

8. REFERENCES

*OSHA. 1989a. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

*OSHA. 1989b. Air contaminants. Occupational Safety and Health Administration. Federal Register 54:2920-2960.

*Otson R, Williams DT, Bothwell PD. 1983. Charcoal-tube technique for simultaneous determination of selected organics in air. Am Ind Hyg Assoc J 44:489-494.

Overby ST, DeBano LF. 1990. New technique for measuring volumetric shrinkage in soils. Soil Science Society of America Journal 54:1797-1799.

*Pedersen LM, Cohr K-H. 1984a. Biochemical pattern in experimental exposure of humans to white spirit: 1. The effects of a 6 hours single dose. Acta Pharmacol Toxicol 55:317-324.

*Pedersen LM, Cohr K-H. 1984b. Biochemical pattern in experimental exposure of humans to white spirit: 2. The effects of repetitive exposures. Acta Pharmacol Toxicol 55:325-330.

Pedersen LM, Rasmussen JM. 1982. The hematological and biochemical pattern in occupational organic solvent poisoning and exposure. Int Arch Occup Environ Health 51:113-126.

*Pedersen LM, Larsen K, Cohr C-H. 1984. Kinetics of white spirits in human fat and blood during short-term experimental exposure. Acta Pharmacol Toxicol 55:308-316.

*Pedersen LM, Rasmussen S, Cohr C-H. 1987. Further evaluation of the kinetics of white spirits in human volunteers. Pharmacol Toxicol 60:135-139.

*Persidsky DJ, Wilde SA. 1956. Effect of eradicants on the microbiological properties of nursery soils. Wisconsin Academy of Sciences, Arts and Letters 44:65-73.

Petrone RL. 1988. Cancer mortality among petroleum solvent exposed Oklahoma dry cleaners. Diss Abstr Int [B] 48:1955.

*Pfaffli P, Harkonen H, Savolainen H. 1985. Urinary dimethylbenzoic-acid excretion as an indicator of occupational exposure to white spirit. Journal of Chromatography, Biomedical Applications 337:146-150.

*Phillips RD. 1983. Effect of Stoddard solvent on kidney function and structure of Fischer 344 and Sprague-Dawley rats. In: Proceedings of the 13th Conference on environmental toxicology, Wright-Patterson Air Force Base, Nov. 16-18, 1982. Springfield, VA: Air Force Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, 328-336.

*Phillips RD, Cockrell BY. 1984. Kidney structural changes in rats following inhalation exposure to C10-C11 isoparaffinic solvent. Toxicology 33:261-273.

Phillips RD, Egan GF. 1981. Teratogenic and dominant lethal investigation of two hydrocarbon solvents [Abstract]. Toxicologist 1:15.

*Phillips RD, Egan GF. 1984a. Effect of C10-C11 isoparaffinic solvent on kidney function in Fischer 344 rats during eight weeks of inhalation. Toxicol Appl Pharmacol 73:500-510.

*Phillips RD, Egan GF. 1984b. Subchronic inhalation exposure of dearomatized white spirits and C10-C11 isoparaffinic hydrocarbon in Sprague-Dawley rats. Fundam Appl Toxicol 4:808-818.

Polakowska B. 1986. [Functional disorders of the nervous system of female workers in the rubber industry exposed to benzine vapors.] Med Pr 37:42-46. (Polish)

*Poklis A, Burkett CD. 1977. Gasoline sniffing: A review. Clin Toxicol 11:35-41.

*Porter HO. 1990. Aviators intoxicated by inhalation of JP-5 fuel vapors. Aviat Space Environ Med 61(7):654-656.

*Prager D, Peters C. 1970. Development of aplastic anemia and the exposure to Stoddard solvent. Blood 35:286-287.

Quinet B, Begue P, Baron S. 1987. [Specificities of pediatric poisoning.] J Pharm Clin 6:421-428. (French)

Radujkov Z, Ristic L, Mihajlov A, et al. 1982. [The incidence of hyperlipoproteinemia in workers involved in the manufacture of naphtha and gas.] Med Pregl 35:27-31. (Serbo-Croatian)

Ramirez G. 1990. Occupational exposure to organic solvents [letter; comment]. Arch Intern Med 150:919.

Ratnoff WD, Gress RE. 1980. Familial occurrence of polycythemia vera: Report of a father and son, with consideration of the possible etiologic role of exposure to organic solvents, including tetrachloroethylene. Blood 56:233-236.

*Raymond RL, Hudson JO, Jamison VW. 1975. Assimilation of oil by soil bacteria. Proceeding of the American Petroleum Institute, Refining Department 54:429-455.

*Raymond RL, Hudson JO, Jamison VW. 1976. Oil degradation in soil. Appl Environ Microbiol 31(4):522-535.

*Rector DE, Steadman BL, Jones RA, et al. 1966. Effects on experimental animals of long-term inhalation exposure to mineral spirits. Toxicol Appl Pharmacol 9:257-268.

*Riley AJ, Collings AJ, Browne NA, et al. 1984. Responses of the upper respiratory tract of the rat to white spirits vapor. Toxicol Lett 22:125-132.

*Rothman N, Emmett EA. 1988. The carcinogenic potential of selected petroleum-derived products. State Art Rev Occup Med 3:475-494.

*Savolainen H, Pfaffli P. 1982. Neurochemical effects of extended exposure to white spirits vapour at three concentration levels. Chem Biol Interact 39:101.

*Sax NI, Lewis RJ. 1989. Dangerous properties of industrial materials. Seventh edition. Volume III. New York, NY: Van Nostrand Reinhold Co., 3117.

*Scheffers TML, Jongeneelen FJ, Bragt PC. 1985. Development of effect-specific limit values (ESLVS) for solvent mixtures in painting. Ann Occup Hyg 29:191-199.

Schreiner CA. 1983. Petroleum and petroleum products: A brief review of studies to evaluate reproductive effects. In: Christian MS, Galbraith WM, Voytek P, et al., eds. Advances in modern environmental toxicology. Vol. 3: Assessment of reproductive and teratogenic hazards. Princeton, NJ: Princeton Scientific Publishers, Inc., 29-45.

*Schreiner CA, Edwards DA, McKee RH, et al. 1989. The mutagenic potential of high flash aromatic naphtha. Cell Biol Toxicol 5:169-188.

*Scott JL, Cartwright GE, Wintrobe MM. 1959. Acquired aplastic anemia - an analysis of thirty-nine cases and review of the pertinent literature. Medicine 38:119-172.

Seppalainen AM, Husman K, Martenson C. 1978. Neurophysiological effects of long-term exposure to a mixture of organic solvents. Scand J Work Environ Health 4:304-314.

*Shapiro LE, Sachchidananda J. 1982. Regulation of proteins by thyroid hormone and glucocorticoid: The responses of hepatic α_{2u}-globulin and pituitary growth hormone differ in adult male hypothyroid rats. Endocrinology 8:653-660.

Shirkey HC. 1971. Treatment of petroleum distillate ingestion. Mod Treat 8:580-592.

*Short BG, Burnett VL, Cox MG, et al. 1987. Site-specific renal cytotoxicity and cell proliferation in male rats exposed to petroleum hydrocarbons. Lab Invest 57:564-577.

*Siemiatycki J, Dewar R, Nadon L, et al. 1987. Associations between several sites of cancer and twelve petroleum-derived liquids: Results from a case-referent study in Montreal. Scand J Work Environ Health 13:493-504.

Spencer PS, Schaumburg HH. 1985. Organic solvent neurotoxicity facts and research needs. Scand J Work Environ Health 11(Suppl. 1):53-60.

*Spirtas R, Stewart PA, Lee JS, et al. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility: I. Epidemiological results. Br J Ind Med 48:515-530.

Starek A, Golba W. 1984. [Analysis of naphtha vapors in the air by gas chromatography.] Med Pr 35:373-8. (Polish)

*State of Alaska. 1989. Alaska water quality standards. Juneau, AL: Alaska Administrative Code, Water Quality Standards, Amended 12/89. Alaska Title 18, Chapter 70.

*State of Arkansas. 1991. Regulation no. 2 as amended water quality standards for surface waters of the State of Arkansas. Little Rock, AK: Water Quality Standards for Surface Waters of the State of Arkansas.

*State of Florida. 1992. Florida Water Quality Standards 1992. Tallahassee, FL: Florida Water Quality Standards 17.-3.

8. REFERENCES

*State of Nebraska. 1990. Nebraska water quality standards 1990. Lincoln, NE: Nebraska Water Quality Standards for Surface Waters of the State, revised effective 11/90. Nebraska State, Title 117.

*State of South Dakota. 1992. South Dakota water quality standards 1992. Bismarck, SD: South Dakota Surface Water Quality Standards, 10/92. Chapter 74:03:17.

*State of Wyoming. 1990. Wyoming water quality rules and regulations. Cheyenne, WY: Wyoming Water Quality Standards. Cheyenne, WY: Wyoming Department of Environmental Quality, Water Quality Standards for Wyoming Surface Waters, Chapter I.

Stewart PA, Lee JS, Marano DE, et al. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility: 2. Exposures and their assessment. Br J Ind Med 48:531-537.

Stricoff RS. 1983. Control of occupational health hazards in the dry cleaning industry. Instructor's guide. Washington, DC.: U.S. Department of Health and Human Services, Division of Training and Manpower Development, National Institute for Occupational Safety and Health, 68.

Stubblefield WA, McKee RH, Kapp RW Jr, et al. 1989. An evaluation of the acute toxic properties of liquids derived from oil sands. J Appl Toxicol 9:59-65.

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 360-361.

*Suntech Group. 1978. Written communication (February 23) to C. E. Holdworth, American Petroleum Institute, regarding Stoddard solvent analysis. American Petroleum Institute, Washington, D.C.

*Swenberg JA, Short B, Borghoff S, et al. 1989. The comparative pathobiology of α_{2u}-globulin nephropathy. Toxicol Appl Pharmacol 97:35-46.

*Tagami H, Ogino A. 1973. Kerosine dermatitis: Factors affecting skin irritability to kerosine. Dermatologica 146(2):123-131.

*Takeuchi Y, Mabuchi C, Takagi S. 1975. Polyneuropathy caused by petroleum benzine. Int Arch Arbeitsmed 34:185-198.

*Tenenbein M, deGroot W, Rajani KR. 1984. Peripheral neuropathy following intentional inhalation of naphtha fumes. Can Med Assoc J 131:1077-1079.

*Thomas DH, Delfino JJ. 1991. A gas-chromatographic/chemical indicator approach to assessing ground water contamination by petroleum products. Ground Water Monitoring Review 11(4):90-100.

*TRI90. 1992. Toxic Chemical Release Inventory. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

*Tuohimaa P, Wichmann L. 1981. Sperm production of men working under heavy-metal or organic-solvent exposure. In: Hemminki K, Sorsa M, Vainio H, eds. Occupational hazards and reproduction. Washington, DC: Hemisphere Publishing Corp., 73-79.

8. REFERENCES

*Van H, Deyrup CA, eds. 1992. OPD chemical buyers directory. 79th annual edition. New York, NY: Schnell Publishing Company, Inc., 746.

*van der Laan G. 1980. Chronic glomerulonephritis and organic solvents. Int Arch Occup Environ Health 47:1-8.

van der Wal JF, Moerkerken A. 1984. The performance of passive diffusion monitors for organic vapours for personal sampling of painters. Ann Occup Hyg 28:39-47.

*Van Doren G, Mertens B, Heyns W, et al. 1983. Different forms of α_{2u}-globulin in male and female rat urine. Eur J Biochem 134:175-181.

van Ert MD, Harris RL, Symons MJ, et al. 1980. Worker exposures to chemical agents in the manufacture of rubber tires: Solvent vapor studies. Am Ind Hyg Assoc J 41:212-219.

Vaziri ND, Smith PJ, Wilson A. 1980. Toxicity with intravenous injection of naphtha in man. Clin Toxicol 16:335-343.

*Verkkala E, Pfaffli P, Savolainen H. 1984. Comparison of local neurotoxicity of three white spirits formulations by percutaneous exposure of rat tail nerve. Toxicol Lett 21:293-299.

*Vernot EH, Drew RT, Kane ML. 1990. Acute toxicologic evaluation of unleaded motor gasoline. Acute Toxic Data 1:28. [Abstract]

*Viau C, Bernard A, Lauwerys R. 1984. Distal tubular dysfunction in rats chronically exposed to a 'white spirit' solvent. Toxicol Lett 21:49-52.

*Viau C, Bernard A, Gueret F, et al. 1986. Isoparaffinic solvent-induced nephrotoxicity in the rat. Toxicology 38:227-240.

*WHO. 1982. Environmental health criteria 20: Selected petroleum products. Geneva, Switzerland: United Nations Environment Programme, International Labour Organisation, World Health Organization.

*WHO. 1991. Environmental health criteria 119: Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals. Geneva, Switzerland: United Nations Environment Programme, International Labour Organization, World Health Organization.

*Wolfsdorf J, Kundig H. 1972. Kerosene poisoning in primates. S Afr Med J 46(20):619-621.

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 min 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.

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.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ 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 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Sister Chromatid Exchange (SCE) -- The result of DNA repair when the damaged piece of chromosome is exchanged with the analogous piece on the corresponding sister chromatid.

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 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 nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance 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 substance.

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 (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. 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) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used 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.

The legends presented below demonstrate the application of these tables and figures. A representative example 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 exist, 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.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(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.

(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 define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5). Species The test species, whether animal or human, are identified in this column.

(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 [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(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, one systemic effect (respiratory) was investigated in this study.

(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 0.005 ppm (see footnote "b").

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level 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 healtheffects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(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 epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE 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 levels for particular exposure duration.

(13). Exposure Duration 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 exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported 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 end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates 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 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). 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 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							
3 → Systemic							
4 → 18	5 → Rat	6 → 13 wk 5d/wk 6hr/d	7 → Resp	8 → 3[b]	9 → 10 (hyperplasia)		10 → Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d			11 → 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 5×10^{-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 = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

DRAFT FOR PUBLIC COMMENT

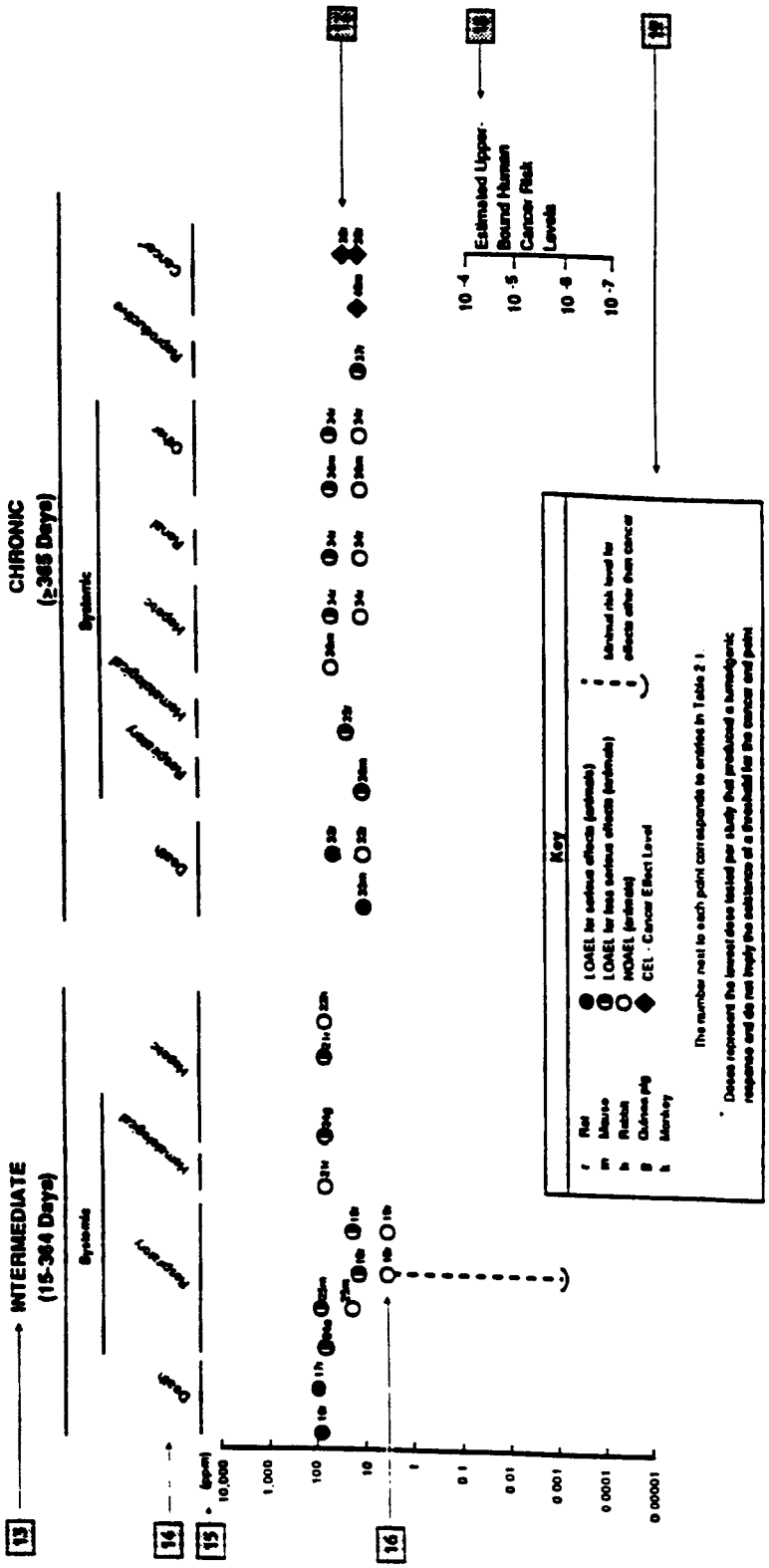


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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 toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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 discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and 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. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint 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 substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" 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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point 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. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used 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 adjusted 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	atmosphere
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
L	liter

LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	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
mmHg	millimeters of mercury
mmol	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
nL	nanoliter
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
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	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
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
WHO	World Health Organization
wk	week
$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
%	percent
α	alpha
ß	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for Stoddard solvent. The panel consisted of the following members: Mr. Lyman Skory, Private Consultant, Skory Consulting, Midland, Michigan; Mr. Edwin Kinkead, Research Scientist, Mantech Environmental Technology, Inc., Wright-Patterson AFB, Ohio; Dr. Martin Alexander, Professor, Soil Microbiology, Cornell University, Ithaca, New York; and Dr. Richard Stewart, Professor, Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI. These experts collectively have knowledge of Stoddard solvent's 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.