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 (l0-20%). A complete list of the individual components of Stoddard solvent is not available (Air Force 1989b); however, some possible components and common hydrocarbon classes are presented in Chapter 3. Data are available on the health effects of the various components of Stoddard solvent, but discussion of individual constituents is beyond the scope of the profile. 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 smallerchained 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 (l0-20%). 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 have a toxic potential.

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Within the aromatic hydrocarbon group, there are several substances that are known to be toxic, including substituted benzenes, naphthalenes, and substituted 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. However, the toxicity of the mixture is probably not governed by any single component. The toxicity of the mixture depends 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.

2. HEALTH EFFECTS

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; Riley 1984). The animals were exposed to completely vaporized Stoddard solvent, but in real life human inhalation exposures might be primarily to the more volatile components. Data from acute studies in cats, dogs, mice, and rats and from intermediate studies in guinea pigs, rats, and dogs that demonstrate toxicity are shown in Table 2-l and Figure 2-l. One of the intermediate 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.

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

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)	Reference
	ACUTE EXPOSURE								
	Death								
1	Cat mixed breed	2.5-7.5 hr						10000 M (4/4 died)	Carpenter et al. 1975a, 1975b
	Systemic								
2	Human	30 min	Resp	2500	M				Astrand et al. 1975
			Cardio	2500	M				
3	Human	3 d 15min/d	Resp	850		2700	(1/6 throat irritation)		Carpenter et al. 1975a, 1975b
4	Human	30 min	Resp	600	M				Hastings et al. 1984
5	Human	30 min	Resp	2400	M				Hastings et al. 1984
6	Human	6 hr	Gastro	610	M				Pedersen and Cohr 1984a
			Musc/skel	610	M				
			Hepatic	610	M				
			Renal	610	M				

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)			LOAEL Serious (mg/m3)			Reference
7	Human	5 d 6hr/d	Musc/skel			616	M	(increased creatine kinase)				Pedersen and Cohr 1984b
8	Rat Harlan-Wistar	8 hr	Resp	2400	M	4600	M	(bloody nose)				Carpenter et al. 1975a, 1975b
9	Rat CDI	4 d 4hr/d	Resp			214	F	(metaplasia, loss of cilia in trachea and nasal cavity)				Riley et al. 1984
10	Mouse Swiss-Webster	1 min	Resp	4400	M				10000	M	(50% respiratory rate depression)	Carpenter et al. 1975a, 1975b
	Immunological/Lymphoreticular											
11	Human	5 d 6hr/d		616	M							Pedersen and Cohr 1984b
	Neurological											
12	Human	3 d 15min/d		850		2700		(2/6 dizzy)				Carpenter et al. 1975a, 1975b
13	Human	50 min				4000	M	(prolonged reaction time)				Gamberale et al. 1975

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key to figure [a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)			LOAEL Serious (mg/m3)			Reference
14	Human	2 hr		1563 [b]	M							Gamberale et al. 1975
15	Human	30 min		2400	M							Hastings et al. 1984
16	Human	6 hr		610	M							Pedersen and Cohr 1984a
17	Rat Harlan-Wistar	8 hr		4600	M	8200	M	(incoordination)				Carpenter et al. 1975a, 1975b
18	Dog Beagle	8 hr		4000	F				8000	F	(tremors & clonic spasms)	Carpenter et al. 1975a, 1975b
19	Cat Mixed Breed	2.5-7.5 hr							10000	M	(convulsions, slowed light reaction)	Carpenter et al. 1975a, 1975b
	Developmental											
20	Rat CRL: COBS	Gd 6-15 6hr/d		2356								API 1977

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
21	Gn Pig NMRI: (ASH)	90 d 24hr/d				892 M (3/15 died)	Jenkins et al. 1971
						892 F (7/15 died)	
22	Gn Pig FTD: Hartley	90 d 24hr/d				892 M (10/15 died; adequate vitamin C)	Jenkins et al. 1971
						892 M (2/15 died; high vitamin C)	
23	Gn Pig FTD: Hartley	90 d 24hr/d				892 M (9/15 died)	Jenkins et al. 1971
						892 F (4/15 died)	
24	Gn pig NS	90 d 24hr/d				363 (4/15 died)	Rector et al. 1966

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)	Reference
	Systemic								
25	Rat Harlan-Wistar	13 wk 5d/wk 6hr/d	Hemato	1900	M				Carpenter et al. 1975a, 1975b
			Hepatic	1900	M				
			Renal	1100	M	1900	M	(tubular regeneration and debris, dilated tubules, increased BUN)	
			Bd Wt	1900	M				
26	Rat Sprague-Dawley, Fischer 344	8 wk 5d/wk 6hr/d	Renal	4580	F	570	M	(decreased urine concentration, increased glucose and protein in urine, regenerative and dilated tubules)	EPA 1984d
27	Rat Mol:WIST	6 mo 5d/wk 6hr/d	Resp			2290	M	(bloody nasal discharge)	Ostergaard et al. 1993
			Bd Wt			4580	M	(decreased body weight)	
28	Rat Sprague-Dawley, Fisher 344	4, 8 wk 5d/wk 6hr/d	Renal	4580	F	570	M	(regenerative tubular epithelium, dilated tubules, increased urinary glucose and protein levels)	Phillips 1983

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)	Reference
29	Rat Fischer 344	1, 4, 8 wk 5d/wk 6hr/d	Renal	5450	F	1840	M	(regenerative epithelium, tubular nephrosis, dilated tubules, necrotic debris)	Phillips and Cockrell 1984
30	Rat Fischer 344	4, 8 wk 5d/wk 6hr/d	Renal	5450	F	1840	M	(epithelial regeneration, tubular dilation)	Phillips and Egan 1984a
31	Rat Sprague-Dawley	12 wk 5d/wk 6hr/d	Resp	5620					Phillips and Egan 1984b
			Cardio	5620					
			Gastro	5620					
			Hemato	5620					
			Musc/skel	5620					
			Hepatic	5620					
32	Rat Sprague-Dawley	4 wk 5d/wk 6hr/d	Renal	5620	F	1910	M	(regenerative tubular epithelia, dilated tubules)	Phillips and Egan 1984b

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
33	Rat Long Evans, Sprague-Dawley	6 wk 5d/wk 8hr/d	Resp	1353			Rector et al. 1966
			Cardio	1353			
			Hemato	1353			
			Hepatic	1353			
			Renal	1353			
			Bd Wt	1353			
34	Rat Long Evans, Sprague-Dawley	90 d 24hr/d	Resp	619	1271 (bronchitis)		Rector et al. 1966
			Cardio	1271			
			Hemato	1271			
			Renal	1271			
			Bd Wt	1271			
35	Rat Sprague-Dawley	9.5-12 mo 5d/wk 8hr/d	Renal		6500 M (increased LDH excretion)		Viau et al. 1984
36	Rat Sprague-Dawley	5 wk 5d/wk 8hr/d	Renal	6500 F 6500 casM	6500 M (tubular dilation, hyaline droplets, regenerative tubular epithelia)		Viau et al. 1986

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key to figure [a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)		LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)	Reference
37	Gn Pig FTD: Hartley	90 d 24hr/d	Resp	892	M				Jenkins et al. 1971
			Gastro			892	M	(diarrhea)	
			Hepatic	892	M				
			Renal	892	M				
38	Gn Pig NS	6 wk 5d/wk 8hr/d	Resp	596		1353		(congestion)	Rector et al. 1966
			Cardio	1353					
			Hemato	1353					
			Hepatic	1353					
			Renal	1353					
			Bd Wt	1353					
39	Gn Pig NS	90 d 24hr/d	Resp	619		1271		(bronchitis)	Rector et al. 1966
			Cardio	1271					
			Hemato	1271					
			Hepatic	1271					
			Renal	1271					
			Bd Wt	1271					
40	Dog Beagle	13 wk 5d/wk 6hr/d	Hemato	1900	M				Carpenter et al. 1975a, 1975b
			Hepatic	1900	M				
			Renal	1900	M				
			Bd Wt	1900	M				

TABLE 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference
	CHRONIC EXPOSURE						
	Reproductive						
41	Human	1-17 yr		294	M		Tuohimaa and Wichmann 1981

[a]The number corresponds to entries in Figure 2-1.
[b]Time weighted average exposure.

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; casM = castrated male; d = day(s); F = female; Gastro = gastrointestinal; Gd = gestational day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; m^3 = cubic meter; mg = milligram; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Stoddard Solvent - Inhalation

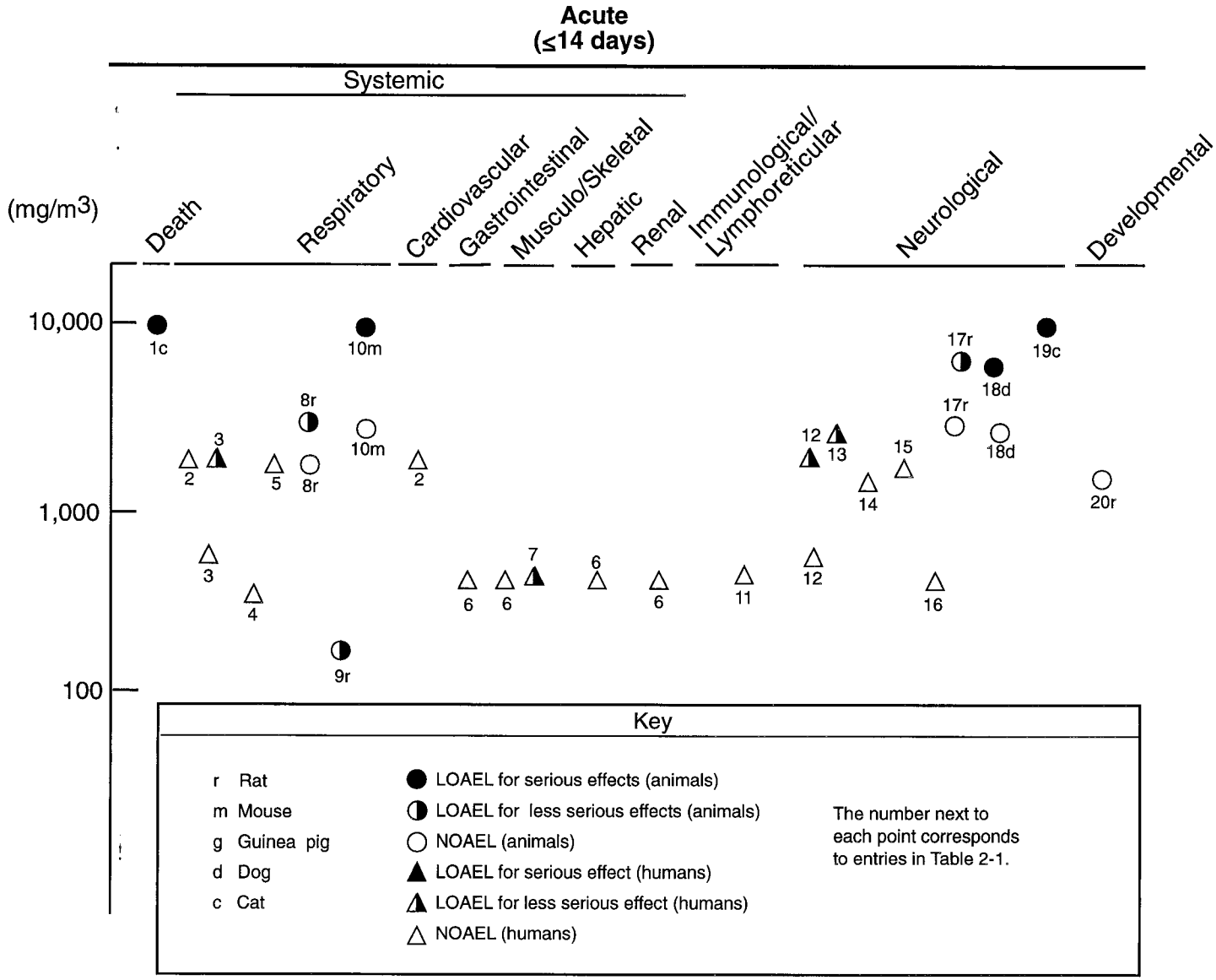
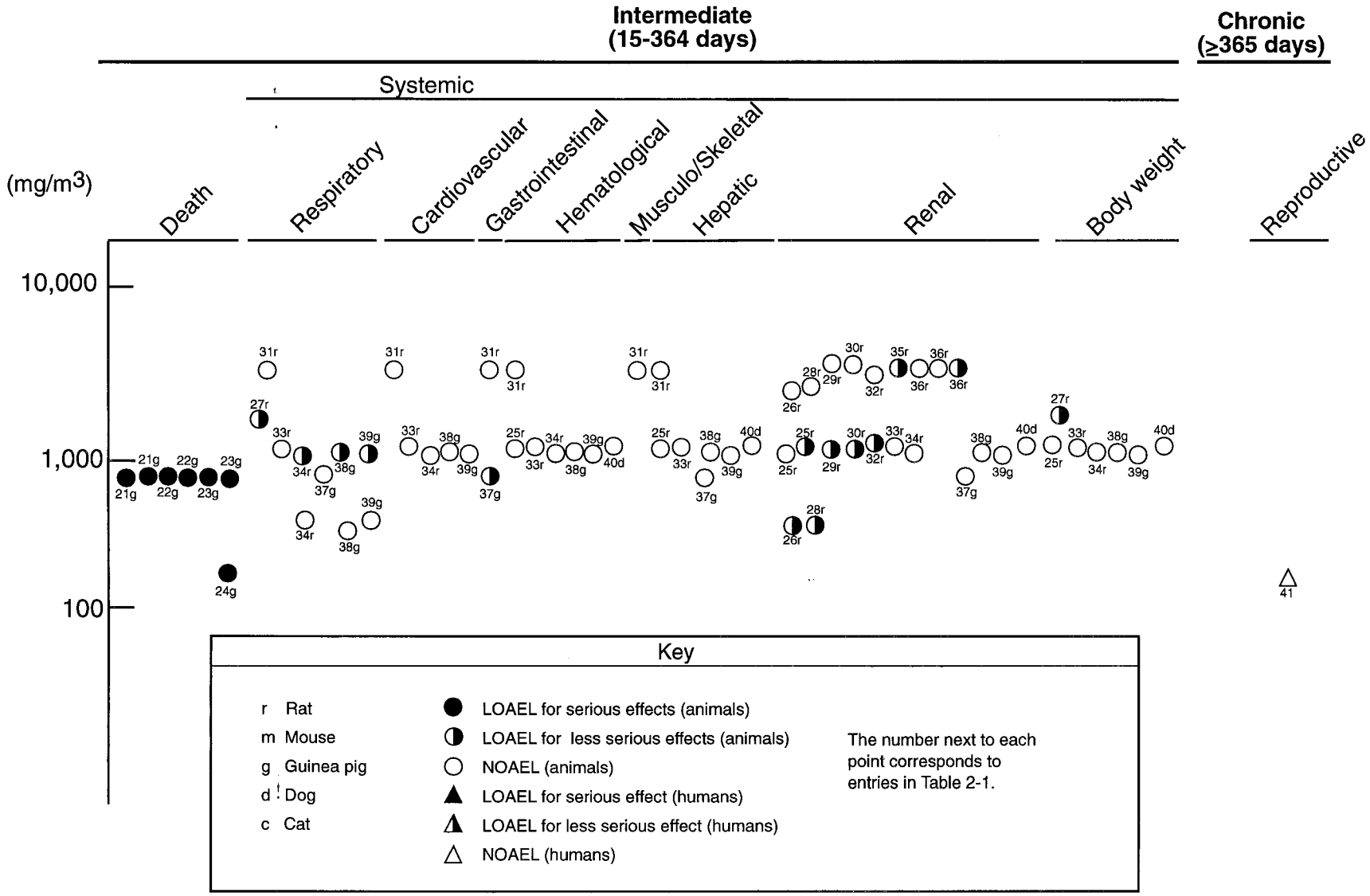


Figure 2-1. Levels of Significant Exposure to Stoddard Solvent – Inhalation (continued)



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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 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% alkames, 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. 19713. 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. Rats

exposed to white spirit (20% aromatics) 6 hours/day, 5 days/week for 6 months showed no compound related mortality at doses up to 4,580 mg/m^3 (Ostergaard et al. 1993). 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

No studies were located regarding dermal effects in humans or animals after inhalation exposure to Stoddard solvent. Ocular effects that occurred after inhalation exposure to Stoddard solvent have resulted from direct contact with the eyes and are discussed in Section 2.2.3.

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

Respiratory Effects. In an experimental study, there was no change in respiratory rate in 10 human males who were exposed to 2,400 mg/m^3 (457 ppm) of completely vaporized Stoddard solvent for 30 minutes (Hastings et al. 1984). Men exposed in an experimental setting to up to 2,500 mg/m^3 (476 ppm) of vaporized white spirits (83% aliphatic and 17% aromatic components) for 30 minutes had no compound-related changes in oxygen uptake or alveolar ventilation measured at rest or during exercise (Astrand et al. 1975). 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). Throat irritation was noted in one out of six volunteers exposed to 2,700 mg/m^3 completely vaporized Stoddard solvent, 15 minutes/day for 3 days (Carpenter et al. 1975a, 1975b). Recovery from this effect was noted 15 minutes post-exposure.

In an acute exposure study, mice exposed to 10,000 mg/m^3 (1,905 ppm) of completely vaporized Stoddard solvent for 1 minute had a 50% reduction in respiratory rate, which was not seen at 4,400 mg/m^3 (Carpenter et al. 1975a, 1975b). Recovery tests were not performed. Exposure of rats to around their nostrils, while 4,600 mg/m^3 completely vaporized Stoddard solvent for 8 hours produced bloody exudate no effects were observed in animals exposed to 2,400 mg/m^3 ed to 214 (Carpenter et al. 1975a, 1975b). Rats exposmg/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. Other histopathological changes included loss of cilia, hyperplasia of basal cells, and squamous metaplasia in the trachea and nasal cavity (Riley et al. 1984). According to the authors, these histopathological changes are not indicative of lung injury, but represent insult to the upper respiratory tract. This study was limited because only one dose was tested.

In an intermediate exposure study rats, rabbits, guinea pigs, dogs, and monkeys that were exposed to I,27 1 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. No respiratory effects were noted in rats exposed to 5,620 mg/m^3 of completely vaporized C_{10}-C_{11} isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) (Phillips and Egan 1984b). Rats exposed to 2,290 mg/m^3 for 6 months (6 hours/day, 5 days/week) to white spirit (20% aromatics) showed a bloody nasal discharge (Ostergaard et al. 1993).

Cardiovascular Effects. Men exposed in an experimental setting to up to 2,500 mg/m^3 (476 ppm) 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).

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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 for 6 weeks (5 days/week, 8 hours/day) (Rector et al. 1966). The data for rabbits, dogs, and monkeys are limited by the use of three animals or less. No cardiovascular effects were noted in rats exposed to 5,620 mg/m^3 of completely vaporized C$_{10}$-C$_{11}$ isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) (Phillips and Egan 1984b).

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.

Transient diarrhea was noted in some guinea pigs exposed to 892 mg/m^3 of vaporized mineral spirits continuously for 90 days (Jenkins et al. 1971). No gastrointestinal effects were noted in rats exposed to 5,620 mg/m^3 of completely vaporized C$_{10}$-C$_{11}$ isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) (Phillips and Egan 1984b).

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 decreases 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 persons exposed to a variety of solvents, including white spirits (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).

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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 for 6 weeks (5 days/week, 8 hours/day) (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 (5 days/week, 6 hours/day) exposed rats and dogs to higher levels of completely vaporized Stoddard solvent (1,900 mg/m^3) (Carpenter et al. 1975a, 1975b). No hematological effects were noted in rats exposed to 5,620 mg/m^3 of completely vaporized C_{10}-C_{11} isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) (Phillips and Egan l984b).

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 animal studies were located that showed musculoskeletal effects. Rats exposed to 5,620 mg/m^3 of completely vaporized C_{10}-C_{11} isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) did not show any clinical or histopathological changes in musculoskeletal parameters (Phillips and Egan 1984b). Rats that were exposed to white spirits at concentrations of 2,290 or 4,580 mg/m^3 showed significant increases in serum creatinine, but since no dose response was evident, the results were not definitive (Ostergaard et al. 1993).

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

a group of patients exposed to a variety of solvents, including white spirits, who had mostly normal liver parameters, except for elevated glutamyl transferase levels (Flodin et al. 1984). In a prospective cohort 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), but the authors did not attribute this to the exposure. No consistent liver histopathology was seen in rats or guinea pigs exposed to 1,353 mg/m^3 intermittently (8 hours/day, 5 days/week) for 6 weeks (Rector et al. 1966) or in rats exposed to 5,620 mg/m^3 of C_{10}-C_{11} isoparaffins for up to 12 weeks (6 hours/day, 5 days/week) (Phillips and Egan 1984b). Serum indicators of liver function were normal in rats and dogs exposed intermittently (13 weeks, S/days week, 6 hours/day) to 1,900 mg/m^3 of completely vaporized Stoddard solvent (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 β-2-microglobulin levels as compared to pre-exposure levels (Pedersen and Cohr 1984a). β-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 Eaan 1980). However, another case-control study showed a significantly greater exposure of patients with glomerulonephritis to petroleum products, in particular, to greasing/degreasing agents (Yaqoob et al. 1992), but the sample population was small and specific agents were not identified. In a case report, patients 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 (Daniel1 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). Rats exposed to white spirit (2,290 or 4,580 mg/m^3) for 6 hours/day over a 6-month period showed increases in blood urea nitrogen (BUN)

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2 weeks after treatment ended. However, possible renal effects indicated by these results are equivocal as there was no dose response noted (Ostergaard et al. 1993).

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 6 hours/day, 5 days/week for 13 weeks 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 showed slight increases in blood urea nitrogen levels, but statistical analyses were not performed and no histopathological changes in the kidneys were noted that could be attributed to exposure (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). Similar results were reported in a study in male rats that were exposed to 570 or 4,580 mg/m^3 of Varsol 1 vapor (6 hours/day, 5 days/week) for 8 weeks (EPA 1984d), although these effects were not observed in females even at high dose. 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 blood urea nitrogen (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% cycloalkanes, mainly C_{11}-C_{12}; boiling range, 155-193°C) and C10-C11 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 (EPA 1991a). 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 bulin 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 in nephropathy syndrome is characterized by the following lesions (Alden 1986; EPA 1991a; Lehman-McKeeman 1993; 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; singlecell 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-(Olson et al. 1990). Comparison of urine obtained from men showed that the total protein content of human urine is only 1% of that obtained from male rats (Olson et al. 1990). Furthermore, primarily high molecular weight protein ($\geq$75 kDa) was found in men, while low molecular weight protein (12-66 kDa), which includes $\alpha_{2\mu}$-globulin, was predominant in rat urine (Olson et al. 1990). To completely dismiss the possibility of human risk, members of the human lipocalin family, which had been filtered and resorbed in the kidney, could be assayed to determine their ability to bind

similar xenobiotics or metabolites, as well as to determine whether any binding that occurred inhibited catabolism.

Ocular Effects. No studies were located regarding systemic ocular effects in humans or in animals after inhalation exposure to Stoddard solvent. Ocular effects that have been observed in humans and in animals after inhalation exposure were probably due to direct contact of the vapor with the eyes rather than to a systemic effect due to inhalation exposure. For details of these studies, see Section 2.2.3.

Body Weight Effects. No studies were located regarding body weight 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. Normal body weight gain was also noted in rats and guinea pigs following intermittent exposure 8 hours/day, 5 days/week for 6 weeks to up to 1,353 mg/m^3 mineral spiritscompletely (Rector et al. 1966). No adverse effects on body weight were seen in rats or dogs exposed to 1,900 mg/m3 vaporized Stoddard solvent 6 hours/day, 5 days/week for 13 weeks (Carpenter et al. 1975a, 1975b). Decreased body at weight was noted in rats exposed to white spirit (20% aromatic) for 6 months (6 hours/day, 5 days/week) levels of4,580 mg/m^3, but the percent change was not quantified (Ostergaard et al. 1993).

2.2.1.3 Immunological and Lymphoreticular 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 further studies were located regarding lymphoreticular effects in humans after inhalation exposure to Stoddard solvent.

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

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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, numerical ability, or manual dexterity when compared with preand post-exposure self controls. 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 at 0, 600, 1,800, and 2,400 mg/m^3 had no dose-related changes in hand-eye coordination, reaction time/decision making or video game visual motor skill/band-eye coordination challenges. When results were compared to control values from unexposed men, there was a statistically significant difference observed in both the eye-hand coordination test and the video game visumotor test at 600 mg/m^3. Since the results at higher exposure levels were not different from controls, 2,400 mg/m^3 was considered to be the tentative level at which no effect was observed (Hastings et al. 1984). Similarly, perceptual speed, numerical ability, manual dexterity, reaction time, and short-term memory were not altered by exposure to white spirits for 30 minutes at 625 mg/m^3, followed by 30 minutes at 1,250 mg/m^3, followed by 30 minutes at 1,875 mg/m^3, followed by 30 minutes at 2,500 mg/m^3. Testing began after only 10 minutes of the 2,500 mg/m^3 exposure, and the time-weighted average exposure when testing ended was 1,563 mg/m^3 (Gamberale et al. 1975). Twelve human volunteers exposed to 610 mg/m^3 of Varnoline (57% alkanes, 25% cycloalkanes, 1% alkenes, and 17.8% alkylbenzenes) or two other white spirit formulations (99% paraffins or 52% paraffins and 48% cycloalkanes) 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 (Pedersen and Cohr 1984a).

Neurological effects have been described in several case reports (Bruhn et al. 1981; Daniel1 et al. 11988; 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; Mikkelsen et al. 1988; Olson 1982) in

which workers were chronically exposed to Stoddard solvent, white spirit, or other solvents 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), dementia (Mikkelsen 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; Hane et al. 1977), discoordination (Mikkelsen et al. 1988), and fatigue (in 38/50; Arlien-Soborg et al. 1979; in 28/65; Gregersen et al. 1984; Hane et al. 1977). The reversibility of headaches and fatigue was not addressed in studies by Arlien-Soborg et al. (1979), Gregersen et al. (1984), and Hane (1977). 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. Significant decreases on test performances of visual-biological ability and psychomotor coordination were noted among a group of 52 housepainters in Sweden, when compared to a group of 52 non-solvent-exposed referents (Hane et al. 1977). Information regarding dermal-exposure toxicity is also discussed for some studies (Daniel1 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 that was not observed at 4,600 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 before their death (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. Rats exposed to white spirit (20% aromatics) (6 hours/day, 5 days/week, for 6 months) showed no changes in histopathology of the brain or in brain weight, motor or neurobehavioral activity, although a transient narcotic effect was noted. However, neurochemical analyses showed significant increases in noradrenaline, dopamine, and 5-hydroxytryptamine levels in certain regions of the brain at 2,290 and 4,580 mg/m^3. No effects on motor activity were noted on weekends between weekday exposures. The

study was limited in that neurobehavioral testing occurred 2 months after exposure and only two doses were tested (Ostergaard et al. 1993). Stoddard solvent does not contain the short-chained alkanes hydrocarbons that are known to cause anesthesia (Haydon et al. 1977). 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-l and plotted in Figure 2-1.

2.2.1.5 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 at 24 and 96 hours after the initiation of 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.

2.2.1.6 Developmental Effects

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

Offspring of 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. 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.

2.2.1.7 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

Human data are available 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 Hodgkin's lymphoma and squamous cell carcinoma of the lung. However, squamous cell carcinoma of the lung was of "borderline" significance since the OR was determined to be 1.2 (90% CI: 1.0-1.5). 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 (90%) around the odds ratio estimates were too wide to suggest a correlation. A case-referent study using cases of Hodgkin's disease and non-Hodgkin's lymphoma among Swedish workers exposed to white spirits implied a slight increase in crude odds ratios, but the study was limited by an insufficient number of cases (Persson et al. 1993).

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 and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals following inhalation exposure to Stoddard solvent.

2.2.3 Dermal Exposure

Because of the lack of quantifiable exposure data for other effects, only studies showing ocular effects after dermal exposure are suitable for presentation in a table on levels of significant exposure. See Table 2-2. Ocular effects noted in this section occurred after inhalation exposure to Stoddard solvent. However, these ocular effects are probably due to direct contact with the eyes rather than as a systemic effect due to inhalation exposure. See Section 2.2.1.2.

TABLE 2-2. Levels of Significant Exposure to Stoddard Solvent - Dermal

Species/ (strain)	Exposure/ duration/ frequency/ (specific route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	3 d 15min/d	Ocular	140 mg/m^3	2700 mg/m^3 (slight eye irritation)		Carpenter et al. 1975a, 1975b
Human	30 min	Ocular	600 M mg/m^3			Hastings et al. 1984
Human	30 min	Ocular	1800 M mg/m^3	2400 M mg/m^3 (eye irritation)		Hastings et al. 1984
Rat Harlan-Wistar	8 hr	Ocular	2400 M mg/m^3	4600 M mg/m^3 (eye irritation)		Carpenter et al. 1975a, 1975b
Dog Beagle	8 hr	Ocular	4000 F mg/m^3	8000 F mg/m^3 (eye irritation)		Carpenter et al. 1975a, 1975b
INTERMEDIATE EXPOSURE						
Systemic						
Rat Mol:WIST	6 mo 5d/wk 6hr/d	Ocular		2290 M mg/m^3 (lacrimation)		Ostergaard et al. 1993

d = day(s); F = female; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; m^3 = cubic meter; mg = milligram; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; wk = week(s)

2. HEALTH EFFECTS

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 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 and review articles on industrial hygiene list Stoddard solvent or Varsol as a possible eye, skin, nose, and throat irritant (Birmingham 1988; 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).

Ocular Effects. Humans exposed to 600 mg/m3 or up to 1,800 mg/m3 of completely vaporized Stoddard solvent for 30 minutes in separate experiments in a controlled laboratory setting showed no

eye irritation as indicated by eye blinks but individuals exposed to 2,400 mg/m^3 exhibited eye irritation as measured by eye blink rate (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).

Eye irritation was also seen in rats during acute inhalation 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). Lacrimation was noted in rats exposed by inhalation for 6 months (5 days/week, 6 hours/day) to 2,290 mg/m^3 white spirit (20% aromatics) (Ostergaard et al. 1993). Although these effects were reported after inhalation exposure to Stoddard solvent, they are probably due to direct contact of the vapor with the eyes rather than to a systemic effect.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular 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 (Daniel1 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 fn 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 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

A case-referent study using cases of Hodgkin’s disease and non-Hodgkin’s lymphoma among Swedish workers exposed to white spirit implied a slight increase in crude odds ratios, but the study was limited by an insufficient number of cases (Persson et al. 1993).

2. HEALTH EFFECTS

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 1984~). 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. Some toxicokinetic data that are specific to the three classes of Stoddard solvent components (i.e., alkanes, cycloalkanes, and aromatics) are available.

Studies in humans and animals have shown that Stoddard solvent and white spirits are readily absorbed through the lungs. In general, it can be expected that Stoddard solvent components such as the aromatics, which have higher blood/gas solubility ratios, would be more completely absorbed through the lungs that those with lower ratios (Klaassen 1991). Aliphatic components of white spirit have been shown to have only limited blood solubility, while aromatic components were relatively soluble (Astrand et al. 1975). No studies were located that reported the absorption of Stoddard solvent after oral exposure in either humans or animals. However, from studies of other petroleum distillates, it is expected that certain components of Stoddard solvent (smaller alkanes or aromatics) might be more readily absorbed than other components such as longer (C_{10}-C_{16}). alkane chains. Neither human nor animal studies evaluating the absorption of Stoddard solvent after dermal exposure were located, but dermal absorption in rats is known to have occurred after application of white spirits. Aromatic components would be expected to have greater dermal absorption than aliphatic components.

White spirits has been found to accumulate in the blood and subcutaneous fat of humans following inhalation exposure. The uptake of aliphatic components in blood was lower than the uptake of aromatic components (Astrand et al. 1975). It is believed that white spirits can enter the brain of humans since neurological effects have been reported; however, no human data are available to verify

this. White spirits has been shown to accumulate in the rat brain after inhalation exposure (Lam et al. 1992). There is no information available on the distribution of Stoddard solvent following oral or dermal exposure.

Elevated levels of dimethylbenzoic acid, a metabolite of trimethylbenzene (a constituent of Stoddard solvent) were identified in the urine of humans exposed to a mist of white spirits (Pfaffli et al. 1985). Correlations were found between exposure concentrations of 1,2,4-trimethylbenzene and urinary concentrations of its metabolite, 3,4-dimethylhippuric acid (Fukaya et al. 1994). No other studies were located regarding metabolism following exposure to Stoddard solvent.

Although no studies were found that reported the excretion of Stoddard solvent after inhalation or oral exposure in humans and animals, or after dermal exposure in humans, it is expected that volatile components or metabolites of Stoddard solvent that have low blood solubility would be most easily excreted in exhaled breath (Klaassen and Rozman 1991). Aromatic components, which have high blood/gas solubility ratios, would be expected to be excreted primarily in urine. After dermal exposure to white spirits, rats were found to excrete dimethylbenzoic acid isomers in the urine (Verkkala et al. 1984).

The mechanism of action on the target organ (i.e., the brain) of humans is not known.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Following acute inhalation exposure of humans to white spirits (600 mg/m^3 in a laboratory setting), white spirits were 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 samplesindicated 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±211 mg/hour). Thus, the rate of inhalation absorption was fairly constant over the different exposure intervals measured here. Mean blood concentration was 2 mgL 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 2,000 mg/m^3 of white spirits (83% aliphatic and 17% aromatics) for 30 minute intervals per concentration during rest in the laboratory bad 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 sequence of another experiment in the same study consisted of 30-minute exposure periods interrupted by three 30-minute exercise periods. Pre-exercise concentrations of alveolar air in subjects exposed to 1,250 mg/m^3 of white spirits for 30 minutes at rest were 256 mg/m^3 of aliphatic components and 27.8 mg/m^3 of aromatic components; arterial blood concentrations were 1.7 mg/kg for the aliphatics and 0.2 mg/kg for the aromatics (Astrand et al. 1975). After exercise, alveolar air concentrations increased to approximately 513 mg/m^3 (aliphatics) and 40 mg/m^3 (aromatics); arterial blood concentrations increased to 3.5 mg/kg (aliphatics) and 0.9 mg/kg (aromatics) (Astrand et al. 1975). Thus, the aromatics appear to be more soluble in blood and more efficiently absorbed through the lungs. Due to increased respiration that occurs during exercise, more of the solvent is taken up at this time than during sedentary periods.

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 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 foollowing dermal exposure to Stoddard solvent in humans or animals. However, daily applications of white spirits (absorbed dose 690.8 mg/kg) for 6 weeks on the tail of rats were associated with axonal prenodal swellings (Verkkala et al. 1984) indicating that dermal absorption had occurred. This study also reported that several products (dimethylbenzoic acid isomers) of trimethylbenzene metabolism were found in the urine of treated rats, providing further evidence of dermal absorption. 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.l 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 nonexposure. 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. A 3-week inhalation study in Wistar rats exposed for 6 hours/day, 5 days/week at levels of 2,290 and 4,580 mg/m^3 found that white spirits (20% aromatics) accumulated in the brain (3.4 and 10.2 mg/kg wet weight, respectively) (Lam et al. 1992). This study also measured the distribution of aromatic and aliphatic components; aliphatics seemed to accumulate more than aromatics. In the brain, aromatic compounds of white spirits increased proportionately with the exposure level (2.1 times), while metabolic elimination aromatic aliphatic compounds increased 3.6 times. This may be due to an increased metabolic elimination of the components (Zahlsen et al. 1992). No studies using Stoddard solvent or white spirits were available in which distribution to any other organs was measured.

Distributions of some possible components of Stoddard solvent have also been examined. A toxicokinetic study on the distributions of C_9-C_{10}, alkanes, aromatics, and cycloalkanes in blood, brain, liver, kidney, and perirenal fat was performed in rats after inhalation exposure 12 hours/day for up to 3 days at 100 ppm (Zahlsen et al. 1992). The compounds tested included *n*-nonane and *n*-decane (alkanes), trimethylbenzene and t-butylbenzene (aromatics), and trimethylcyclohexane and t-butylcyclohexane (cycloalkanes). It was reported that aromatics generally showed higher blood concentrations than alkanes and cycloalkanes. C_9 cycloalkanes showed higher brain concentrations than the corresponding aromatics and alkanes, while brain concentrations of C_{10} alkanes were slightly greater than C_{10} cycloalkane concentrations, which in turn were greater than C_{10} aromatic concentrations (Zahlsen et al. 1992). Fat contained the highest concentrations of each of the hydrocarbons examined; concentrations of aromatics and cycloalkanes in fat were higher than concentrations of alkanes. The concentrations of aromatics in fat decreased on each successive day of exposure, which could be an indication of a higher rate of metabolic elimination (Zahlsen et al. 1992). C_9 alkanes were found in particularly low concentrations in the liver compared to levels found in the brain and kidney. Although C_9 alkane levels were similar in the brain and kidney, C_{10} alkane levels were found to be slightly higher in the brain. Concentrations of trimethylcyclohexane and trimethylbenzene were higher in kidney tissue than were concentrations of the alkanes (Zahlsen et al. 1992).

Rats exposed by inhalation to 1,000 ppm of trimethylbenzene, *n*-nonane, or trimethylcyclohexane (12 hours/day for up to 14 days) reported that after the first day of exposure, trimethylbenzene showed

the greatest blood concentration (537 µmol/L) followed by *n*-nonane (174 µmol/L) and trimethylcyclohexane (130 µmol/L) (Zahlsen et al. 1990). However, *n*-nonane showed the highest brain concentration (1,416 µmol/kg), while concentrations of trimethylcyclohexane (1,109 µmol/kg) and trimethylbenzene (998 µmol/kg) were somewhat similar. This finding was in contrast to the later Zahlsen et al. (1992) study in which C_9 cycloalkanes showed higher brain concentrations than alkanes. In perirenal fat, the highest concentrations were of trimethylbenzene (49,190 µmol/kg on day l), followed by *n*-nonane (15,980 µmol/kg on day 3) and trimethylcyclohexane (6,860 to 9,550 µmol/kg throughout exposure) (Zahlsen et al. 1990). The concentrations in perirenal fat in the later Zahlsen et al. (1992) study again were different from these earlier results; concentrations of aromatics were greater than those of cycloalkanes, which were greater than those of alkanes. It is possible that the results of these studies differ due to saturation of metabolic pathways, since the concentrations used in the two studies differed by 10-fold. In the Zahlsen et al. (1990) study, although there was some overall decrease in the concentrations of all three compounds in blood, brain, and fat over the total period of exposure, the decreases were most prominent following exposure to trimethylbenzene and, to a lesser extent, trimethylcyclohexane. These data suggest that these two compounds may be capable of the induction of their own metabolic conversion (Zahlsen et al. 1990).

2.3.2.2 Oral Exposure

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

2.3.2.3 Dermal Exposure

No studies were located regarding distribution following dermal exposure to Stoddard solvent 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. It assumed that being

in a mixture does not affect the metabolism of trimethylbenzene or any of the other constituents of Stoddard solvent 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. A correlation between exposure to 1,2,4-trimethylbenzene, a component of white spirits, at the TLV-TWA (25 ppm), and the urinary concentration of 3,4-dimethylhippuric acid (3/4-DMHA) was reported in ceramics workers (Fukaya et al.1994). Rats were dosed by gavage with t-butylcyclohexane (800 mg/kg), another component of white spirits, andseven compounds were identified as urinary metabolites (Henningsen et al. 1987). The primary metabolite was trans-4-t-butylcyclohenanol, with lesser amounts of 2^{c}-hydroxy-4^{t}-t-butylcyclohexanol, 2-methyl-2-cyclohexylpropanoic acid,2^{c}-hydroxy-4^{c}-t-butylcyclohexanol, 2-methyl-2-cyclohexyl-1,3-propanediol, 2t-hydroxy-4t-butylcyclohexanol, and Cis-4-t-butylcyclohexanol also being detected. Rats that had a white spirit formulation (690.8 mg/kg) applied to their tails 5 days/week for 6 weeks were reported to have excreted several products (dimethylbenzoic acid isomers) of trimethylbenzene metabolism in their urine.

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 of Stoddard solvent 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 of Stoddard solvent following dermal exposure in humans. Rats exposed to daily applications of white spirits (absorbed dose of 690.8 mg/kg) 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). No other metabolic parameters have been measured.

2.3.5 Mechanisms of Action

Little is known regarding the specific mechanisms of action by which Stoddard solvent exerts its toxic effects. Generally, it is believed that the aromatic components of Stoddard solvent would be more readily and completely absorbed through the lungs and skin than would long-chained aliphatic components. The mechanism of action of Stoddard solvent on the central nervous system is not known. Exposure to white spirit increased levels of the neurotransmitters noradrenaline, dopamine, and 5-hydroxytryptamine in the brain of exposed rats, although the biological significance of these changes is not understood (Lam et al. 1992). Stoddard solvent does not contain the shorter chain alkanes that have been known to cause anesthesia (Haydon et al. 1977). Inhalation exposure of rats to white spirits for 3 weeks (6 hours/day, 7 days/week) resulted in a significant increase in the rate of reactive oxygen species (ROS) generation in the hippocampus (Lam et al. 1994). Since the brain contains large amounts of polyunsaturated fatty acids, proteins, and catecholamines, all of which are targets for ROS, increased rates of ROS in the brain following white spirit exposure might provide evidence that the mechanism for neurotoxicity involves ROS interaction with lipid peroxidation, protein oxidation, and DNA (Lam et al. 1994).

Although renal toxicity has been reported after exposure to Stoddard solvent in rats, it has not been reported in humans, rabbits, guinea pigs, dogs, or monkeys. A mechanism of action has been proposed for the renal effects observed in male rats. The carrier protein $\alpha_{2\mu}$-globulin is synthesized in large quantities by these animals and is used to transport pheromones into the urine (Boeskei et al. 1992). After glomerular filtration with their ligand, these carrier proteins are resorbed in massive quantities in the PZ section of the proximal convoluted tubule and catabolized in lysosomes (EPA 1991a; Kimura et al. 1991a). It is proposed that Stoddard solvent exerts its toxic effect by binding to $\alpha_{2\mu}$-globulin; after resorption in the proximal tubule, it is believed to accumulate in lysosomes, where it resists degradation and causes the pathological changes that characterize $\alpha_{2\mu}$-globulin nephropathy

syndrome. Since synthesis of the carrier protein, $\alpha_{2\mu}$-globulin, is under androgenic control, this hypothesis would explain why neither female rats nor castrated male rats have been found to be afflicted with $\alpha_{2\mu}$-globulin nephropathy. A more detailed discussion of this mechanism can be found in Section 2.2.1.2.

Humans are not believed to be susceptible to proximal tubule damage by the mechanism, since they do not produce the $\alpha_{2\mu}$-globulin protein. Analogous human proteins could possibly undergo the same interactions as $\alpha_{2\mu}$-globulin if they were produced in similar quantities. But because humans are not known to synthesize and resorb other lipocalin proteins in such massive quantities as rats do with $\alpha_{2\mu}$-globulin, it is unlikely that Stoddard solvent would cause such profound toxicity if an interaction did occur. No reports were located that show proximal tubule damage in persons exposed to Stoddard solvent. Epidemiology studies of persons with glomerulonephritis showed no differences in exposure to organic solvents between cases and controls (van der kaan 1980), and patients exposed to white spirits exhibited normal renal function (Flodin et al. 1984). However, one case study of a man chronically exposed to Stoddard solvent reported the development of glomerulonephritis (Daniell et al.1988). This case is discussed more fully in Section 2.3.2. Thus, it is possible that there may be other mechanisms of action for renal toxicity in humans.

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 exposuresituations. 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. It is likely that most exposure at hazardous waste sites would occur to the vapor of 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 adversefindings in the controls. Adverse respiratory effects have not been seen in humans. It is possible that aspiration ofStoddard 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.

Minimal Risk Levels for Stoddard Solvent

An MRL could not be derived for acute inhalation exposure (14 days or less) to Stoddard solvent. The best study in the acute database was a no-observed-adverse-effect level (NOAEL) at a time weighted average of 1,560 mg/m^3 in sedentary male human volunteers exposed to completely vaporized white spirits for 2 hours. This study was not suitable for MRL derivation because the results from a 2-hour exposure could not be reliably extrapolated to a continuous 14-day exposure. These humans showed no neurological effects from exposure to the white spirits (presumably the 83% aliphatic, 17% aromatic components described in Astrand et al. 1975) (Gamberale et al. 1975). In this study, central nervous system function was evaluated in multiple tests including perceptual speed, simple reaction time, short-term memory, numerical ability, and manual dexterity. A lowest-observed-adverse-effect level (LOAEL) was seen in the same study when humans were exposed to 4,000 mg/m^3 for 50 minutes. The subjects had a prolonged simple reaction time compared to control results in the same volunteers during a non-exposure period.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).

2. HEALTH EFFECTS

There were no human or animal studies suitable for developing MRLs for intermediate- or chronicduration exposures to Stoddard solvent in the air. However, more serious health effects would be predicted with longer duration exposure. 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 amethodology 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. 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. However, death is unlikely unless there is an extremely high exposure, since Stoddard solvent contains very little of the smaller carbon chains (C_8 and below) which are known to be highly volatile and highly toxic (Andrews and Snyder 1986). 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. Concentrations of 10,000 mg/m^3 Stoddard solvent were lethal to cats (Carpenter et al. 4975a, 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). 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).

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). Possible indications of musculoskeletal effects were noted, however, as increased creatinine kinase levels after an exposure to 616 mg/m^3 of vaporized white spirits (99% alkanes, no aromatics) (Pedersen and Cohr 1984b).

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 to 2,400 mg/m^3 (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 upper respiratory irritant effects in rats from acute exposure (Carpenter et al. 1975a, 1975b; 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 woulid be aspirated into the lungs and might then cause pneumonitis (Coruh and Inal 1966; Majeed et al. 1981; Nouri and Al-Rahim 1970). Exposure of rats to 214 mg/m^3 of white spirits for 4 days caused loss of cilia and squamous metaplasia in the trachea and nasal cavity (Riley et al. 1984). However, the study was limited by use of only one dose group in addition to the controls. No other significant adverse respiratory effects were seen in other animal studies (Carpenter et al. 1975a, 1975b; Rector et al. 1966).

Cardiovascular Effects. No compound-related changes in cardiovascular parameters were noted after men were exposed to up to 2,500 mg/m^3 of vaporized mineral spirits for a 30-minute period (Astrand et al. 1975), and no changes in blood pressure were noted in painters exposed for 4-42 years to paints and solvents (Hane et al. 1977). No histopathological changes were noted in the hearts of rats, rabbits, guinea pigs, dogs, or monkeys exposed to 1,271 mg/m^3 of vaporized mineral spirits for an intermediate-duration exposure (Rector et al. 1966). Although Stoddard solvent exposure does not appear to cause any effect on the cardiovascular system, sufficient data do not exist to make an unequivocal determination.

Gastrointestinal Effects. No adverse gastrointestinal effects were noted after inhalation of 610 mg/m^3 vaporized white spirits by human volunteers for 6 hours (Pedersen and Cohr 1984a), andnausea was reported in one of nine workers exposed to Stoddard solvent when cleaning machines (Larsen and Schmunes 1974). No studies were located regarding gastrointestinal effects in animals after inhalation exposure to Stoddard solvent. While it appears that Stoddard solvent might cause nausea in certain individuals, sufficient data do not exist to make an unequivocal determination regarding gastrointestinal effects.

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Hematological Effects. Studies of house painters and car repair workers exposed to mixed solvents have shown decreased red blood cell counts and hemoglobin concentrations as well as increased mean erythrocyte and platelet volumes in these workers (Beving et al. 1991; Hane et al. 1977). However, normal hematological values were noted in 128 persons exposed to a variety of solvents including white spirits (Flodin et al. 1984) and, in other case reports, and no causal relationship could be established between persons with aplastic anemia and exposure to Stoddard solvent (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 up to 1,353 mg/m^3 of vaporized mineral spirits for 6 weeks or to 1,271 mg/m^3 for 90 days (Rector et al. 1966) or in rats and dogs exposed to 1,900 mg/m^3 of vaporized Stoddard solvent for 13 weeks (Carpenter et al. 1975a, 1975b). Since there are hmited and conflicting data regarding the hematological effects of exposure to Stoddard solvent, an unequavocal conclusion about these end points cannot be made.

Musculoskeletal Effects. The only indicator of musculoskeletal compromise was an increase in creatine kinase after exposure of human volunteers to 616 mg/m^3 of vaporized white spirits for 5 days (Pedersen and Cohr 1984b). No changes in serum creatine kinase was noted after exposure of volunteers to 610 mg/m^3 for one 6-hour period (Pedersen and Cohr 1984a). Rats that were exposed to 2,290 mg/m^3 or 4,580 mg/m^3 white spirits showed increases in serum creatinine, but no dose response was evident (Ostergaard et al. 1993). Although Stoddard solvent exposure does not appear to cause any musculoskeletal effects, sufficient data do not exist to make an unequivocal determination.

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. Men exposed to 610 mg/m^3 for 6 hours showed no changes in serum liver products (Pedersen and Cohr 1984a). Painters exposed to white spirits and other solvents for chronic periods showed elevated levels of serum alanine aminotransferase but had normal liver biopsies (Dossing et al. 1983). Persons exposed to a variety of solvents, including white spirits, showed elevated glutamyl transferase levels (Flodin et al. 1984). A group of painters showed normal serum transaminase levels compared to unexposed controls (Hane et al. 1977). No histopathological or blood chemical indicators of liver damage were noted in guinea pigs exposed to up to 1,271 mg/m^3 of vaporized white spirits for 90 days (Jenkins et al. 1971; Rector et al. 1966), in rats or guinea pigs exposed to 1,353 mg/m^3 for 6 weeks (Rector et al. 1966), or in rats and dogs exposed to 1,900 mg/m^3 Stoddard solvent for 90 days (Carpenter et al. 1975a 1975b).

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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 $\alpha_{2\mu}$-globulin, which is synthesized in large quantities in the liver (Bocskei et al. 1992). X-ray crystallography has demonstrated that $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-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. 1994a).

Unfortunately, the $\alpha_{2\mu}$-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-$\alpha_{2\mu}$-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 $\alpha_{2\mu}$-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 thekidney; association of the hyaline droplets with the protein $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-globulin nephropathy. Aging male rats show chronic progressive nephropathy symptoms that are similar to $\alpha_{2\mu}$-globulin nephropathy, so it is important to run concurrent controls when assessing renal toxicity. $\alpha_{2\mu}$-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 nonrodent 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 $\alpha_{2\mu}$-globulin interaction as the mechanism for Stoddard solventinduced 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 $\alpha_{2\mu}$-globulin left (Borghoff et al. 1990). The pathological sequence is consistent with $\alpha_{2\mu}$-globulin nephropathy. Hyaline droplets enclosed in isosomes 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 $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-globulin -induced damage is typically confined to the proximal tubule.

Glomerulonephritis has also been raised as a possible renal effect due to Stoddard solvent exposure, but the evidence is equivocal. A case-control study showed a significantly greater exposure of patients with glomerulonephritis to petroleum products (Yaqoob et al. 1992). Another case-control study of

patients with end-stage renal failure showed that approximately 60% of those with glomerulonephritis had significant exposure to hydrocarbons compared with 25% of patients with nonglomerulonephritis renal failure (Finn et al. 1980); however, the use of hospital inpatients as the control group rather than employed workers may have biased this study toward a positive outcome (Phillips 1984). In both of these studies, however, patients may have been exposed to multiple hydrocarbon products. A patient with glomerulonephritis who was exposed to Stoddard solvent by both inhalation and dermal contact up to 6 hours/day for a year was reported by Daniel1 et al. (1988). However, both another case report and a case-control study showed no increase in glomerulonephritis with organic solvent exposure (Flodin et al. 1984; van der Laan 1980). A review of the literature (Bombassei and Kaplan 1992) identified a number of other studies claiming an association between hydrocarbon exposure and antiglomerular basement membrane antibody-mediated disease (Goodpasture's syndrome) or other types of glomerulonephritis.

If all the renal damage caused by Stoddard solvent in rats is due to $\alpha_{2\mu}$-globulin interactions, then it probably does not pose a large risk of nephrotoxicity to humans. Since humans do not have $\alpha_{2\mu}$-globulin, the issue becomes whether analogous human proteins could possibly undergo the same interactions as $\alpha_{2\mu}$-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 $\alpha_{2\mu}$-globulin, it is unlikely that Stoddard solvent would cause such remarkable toxicity even if an interaction did occur (Olson 1990). 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 Effects. Dermal irritation is an effect that has been reported after exposure to Stoddard solvent. 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.

Ocular Effects. 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 through direct contact at concentrations of 2,700 mg/m^3 (Carpenter et al. 1975a, 1975b) and 2,400 mg/m^3 (Hastings et al. 1984).

Body Weight Effects. Although no human studies were located regarding body weight changes, studies in rats, rabbits, guinea pigs, monkeys, and dogs exposed by inhalation to Stoddard solvent or mineral spirits for intermediate durations were found to have normal body weight gain (Carpenter et al. 1975a, 1975b; Rector et al. 1966). One study, in which rats were exposed to white spirits (4,580 mg/m^3) for 6 months, did report decreased body weight, but the change was not quantified (Ostergaard et al. 1993). Although Stoddard solvent exposure does not appear to cause any effect on body weight, sufficient data do not exist to make an unequivocal determination.

Immunological and Lymphoreticular 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 for 6 hours/day over a 5-day period (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. Acute inhalation exposure to Stoddard solvent or white spirits has caused nervous system effects. A NOAEL was seen in sedentary male humans exposed to a time-weighted average of 1,563 mg/m^3 of completely vaporized white spirits for 2 hours (Gamberale et al. 1975). These humans showed no neurological effects from exposure to the white spirits (presumably the 83% aliphatic, 17% aromatic components described in Astrand et al. 1975) (Gamberale et al. 1975). In this study, central nervous system function was evaluated in multiple tests including perceptual speed, simple reaction time, short-term memory, numerical ability, and manual dexterity. A lowest-observedadverse-effect level (LOAEL) was seen in the same study when humans were exposed to 4,000 mg/m^3 for 50 minutes. The subjects had a prolonged simple reaction time compared to controlresults in the same volunteers during a non-exposure period. 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).

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Other studies support the hypothesis that the central nervous system (CNS) is the most sensitive target for acute exposure to Stoddard solvent. 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 both the eye-hand coordination test and the video game visumotor 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 to be the tentative level at which no effect was observed. 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 or two other white spirit formulations (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 Gamberale et al. (1975) 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 8,200 mg/m^3, but not to 4,600 mg/m^3, was observed (Carpenter et al. 1975a, 1975b). Since the incoordination was seen during cage-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 Gamberale et al. (1975) study. Furthermore, much higher acute inhalation doses have caused much more blatant nervous system effects.

Cerebral atrophy, discoordination, dementia, headaches, memory deficits, and fatigue were reported in humans from chronic exposure to several solvents, including Stoddard solvent (Daniel1 et al. 1988; Flodin et al. 1984; Gregersen et al. 1984; Hane et al. 1977; Mikkelsen et al. 1988; Olson.1982). These chronic effects may or may not be due to Stoddard solvent since other chemicals were also present during exposure; however, these data imply that effects become more severe with prolonged exposure time. 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 short-chained

alkanes that are known to cause anesthesia (Haydon et al. 1977). Mice exposed to propylbenzene, a component of Stoddard solvent, at 2,000-8,000 ppm for 20 minutes showed a range of neurobehavioral effects including a loss of righting reflex, decreased arousal, and reaction to sensory stimuli and psychomotor impairment (Tegeris and Balster 1944). 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).

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 ($p<0.05$) serum levels of folliclestimulating hormone (Pedersen and Cohr 1984b). The possible reproductive outcome of this change isnot 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 had several limitations including a small test population, the degree of accuracy of the exposure assessment, exposure to mixed solvents, 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.

Developmental Effects. No human studies on developmental effects from Stoddard solvent exposure 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). Certain other petroleum distillates (gasoline or fuel oils) have also shown very few adverse developmental effects (API 1979a, 1979b; Beliles and Mecler 1983; API 1978).

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 any concentration at either incubation period (Gochet et al. 1984). Refer to Table 2-3 for a further summary of these results.

In vivo animal studies involving either Stoddard solvent or white spirits provide no evidence of genotoxicity. Neither inhaled (50 mg/m^3 in five periods of 5 minutes each, separated by 5-minute noexposure intervals) 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). 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, for a further analysis of the composition) (API 1978a; 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* (API 1978a; Conaway et al. 1984; Gochet et al. 1984) and mouse L5178Y lymphoma cells (API 1978a, 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 cytotoxic (API 198713). Please refer to Table 2-4 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.

Concerns have been raised about the genotoxicity of the individual components of Stoddard solvent. Frequency of mutations induced by methylazoxymethanol (MAM), a complete carcinogen in several species, was increased ($p<0.05$) in V79 Chinese hamster cells by *n*-decane, while treatment with this alkane alone did not cause mutagenesis (Lankas et al. 1978). This suggests that *n*-decane may be a

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

Species (test system)	End point	Results	Reference
Mammalian cells:			
Rat (bone marrow)	Chromosome aberrations	–	API 1978a; 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; API = American Petroleum Institute

TABLE 2-4. 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, TA1535, TA100, TA98, TA1538, TA1537)[a]	Gene mutation	–	–	Gochet et al. 1984
S. typhimurium (TA1535, TA1537, TA1538, TA98, TA100)	Gene mutation	–	–	API 1978a; Conaway et al. 1984
Eukaryotic organisms:				
Mammalian cells:				
Mouse L5178Y lymphoma cells ($TK^{+/-}$ locus)	Gene mutation	–	–	API 1978a; 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; API = American Petroleum Institute

promoter. Further study is needed to determine whether the effects observed with individual components would also occur in the Stoddard solvent mixture.

Cancer. There is one chronic inhalation exposure study of humans (Siemiatycki et al. 1987), which presented epidemiological data that reported an odds ratio greater than 1 for prostate cancer, Hodgkin's lymphoma, and squamous cell carcinoma of the lung. However, the study was limited due to exposure to mixed substances and an arbitrary statistical selection criteria for analysis. A mouse skin-painting study (EPA 1984c) demonstrated carcinogenesis using a mixture containing 90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether. This study indicates an area of potential concern, even though the carcinogenesis cannot be attributed to a particular component. Thus, neither study provides conclusive results on the carcinogenic potential of Stoddard solvent for humans exposed at hazardous waste sites. A test using Stoddard solvent alone is needed to verify whether the findings of EPA 1984c can be attributed to Stoddard solvent.

It is also possible that the skin irritant effects of Stoddard solvent could have contributed to the promotion of effects initiated by other components of the mixture. The alkylbenzenes present in Stoddard solvent are not believed to be carcinogenic, based upon negative or weakly positive genotoxicity test results (Andrews and Snyder 1991). However, further animal testing is needed to confirm a lack of carcinogenicity. A dermal study in mice showed that dodecane was a tumor promotor (Site 1966). Benzo[a]pyrene and benzo[a]anthracene were reported to be 1,000 times more potent in producing tumors when dodecane was used as a diluent than when it was not used (Bingham and Falk 1969).

Promotion activity of n-dodecane was also demonstrated in dermal tests using Swiss mice, although dermal carcinogenicity tests were negative (Saffiotti and Shubic 1963). Decane was reported to enhance the carcinogenicity of benzo[a]pyrene after application to mouse skin (Van Duuren and Goldschmidt 1976). Several studies have shown that some n-alkane components of Stoddard solvent are promoters of carcinogenicity (Site 1966; Saffioti and Shubik 1965; Van Duuren and-Goldschmidt 1976). Other studies raise questions about whether some of the *n*-alkane components may also be cocarcinogens (Bingham and Falk 1969; Horten et al. 1957, 1966, 1976; Van Duuren and Goldschmidt 1976). Further study is needed to determine whether the effects observed with these individual components would also occur in the Stoddard solvent mixture.

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There are no existing national guidelines concerning potential carcinogenicity that specifically pertain to Stoddard solvent. The International Agency for Research on Cancer (IARC) has determined that some petroleum distillates are probably carcinogenic to humans for occupational exposure in petroleum refining (IARC 1989); however, petroleum solvents as a group have not yet been evaluated.

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.

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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 (Pedersen et al. 1984, 1987). Following repeated exposure (600 mg/m^3) to white spirits (6 hours/day for 5 days), only 23% of the concentration in body fat was removed over a 60-hour period of non-exposure (Pedersen et al. 1984).

Studies of certain components of Stoddard solvent indicate that their metabolites may be useful indications of exposure, provided the interaction of the components in the mixture does not interfere with their metabolism. A correlation between exposure to 1,2,4-trimethylbenzene (a component of white spirits) and a urinary concentration of 3,4-dimethylhippuric acid (a metabolite of 1,2,4-trimethylbenzene) was reported in workers exposed at the TLV-TWA (25 ppm) (Fukaya et al. 1994). Another study of humans exposed to white spirits found that levels of dimethylbenzoic acid, another metabolite of trimethylbenzene, in the urine correlated to earlier exposure during the workday (Pfaffli et al. 1985). A study of 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). Fischer-344 rats dosed by gavage with 800 mg/kg of t-butylcyclohexane, a component of white spirits, were found to have seven metabolites in their urine (Henningsen et al. 1987). The primary metabolite was trans-4-t-butylcyclohexanol.

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; their onset is relatively fast and some of the effects are reversible when the person is removed from the exposure situation. 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 after aspiration. Radiological changes are usually detected up to several days after exposure, but can remain evident for several weeks or months (Haddad and Winchester 1990). 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. Individuals with pre-existing neurological conditions are likely to be a population of concern due to the neurological effects noted after exposure to Stoddard solvent and white spirits. Stoddard solvent has been shown to be irritating to the eyes and possibly the respiratory system. Therefore, persons susceptible to eye or respiratory diseases might be unusually susceptible to the effects of Stoddard solvent. Because there is uncertainty about adverse renal effects occurring in humans due to exposure to Stoddard solvent, persons with kidney diseases also may be unusually susceptible to the effects of Stoddard solvent exposure. Glomerulonephritis is known to have a genetic component (Bombassei and Kaplan 1992; Rambausek et al. 1993).

Additionally, persons with higher percentages of body fat might be more likely to store these solvents, since the solvent lipophilicity is a pharmacokinetic characteristic. In general, there would be a potentially greater storage in women, due to their increased relative volume of body fat, than in men (Sato and Nakajima 1987).

2. HEALTH EFFECTS

2.8 METHODS FOR REDUCING TOXIC 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.

2.8.1 Reducing Peak Absorption Follow Exposure

Little information is available on specific methods for reducing absorption after exposure to 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 for alkane and cycloalkane components (Klein and Simon 1986; Litovitz and Greene 1988). Further data are required to determine if either activated charcoal or cathartics 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; Klein and Simon 1986; Litovitz and Greene 1988). Although the inhalation route is the most probable route of exposure, the only known method to reduce 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, it has been suggested that positive end expiratory pressure be used therapeutically (Haddad and Winchester 1990; Klein and Simon 1986). Washing with soapy water is suggested following dermal contact, and ocular washing is suggested following eye exposure.

2.8.2 Reducing Body Burden

There are no effective methods to enhance elimination of Stoddard solvent and no known antidotes. Since inhalation is the most probable route of exposure, removing the person from the contaminated area may help to reduce the body burden (Stutz and Janusz 1988). Stoddard solvent can be stored in

adipose tissue; thus, the effects may continue for a few days after exposure has occurred as Stoddard solvent is released from storage.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of Stoddard solvent on the target organ (i.e., the brain) is not known. Also, no information was located that provided therapeutic measures designed to interfere with a possible mechanism of action for Stoddard solvent. In the kidney, the mechanism of action of Stoddard solvent appears to be specific to male rats, which synthesize $\alpha_{2\mu}$-globulin, a protein not found in humans. This protein is believed to interact with Stoddard solvent and to cause pathological changes in the P_2 proximal tubule epithelium and other renal effects. Because the $\alpha_{2\mu}$-globulin nephropathy is not believed to affect humans, interfering with this particular mechanism of action would not be relevant.

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 may be proposed.

2.9.1 Existing Information on Health Effects of Stoddard Solvent

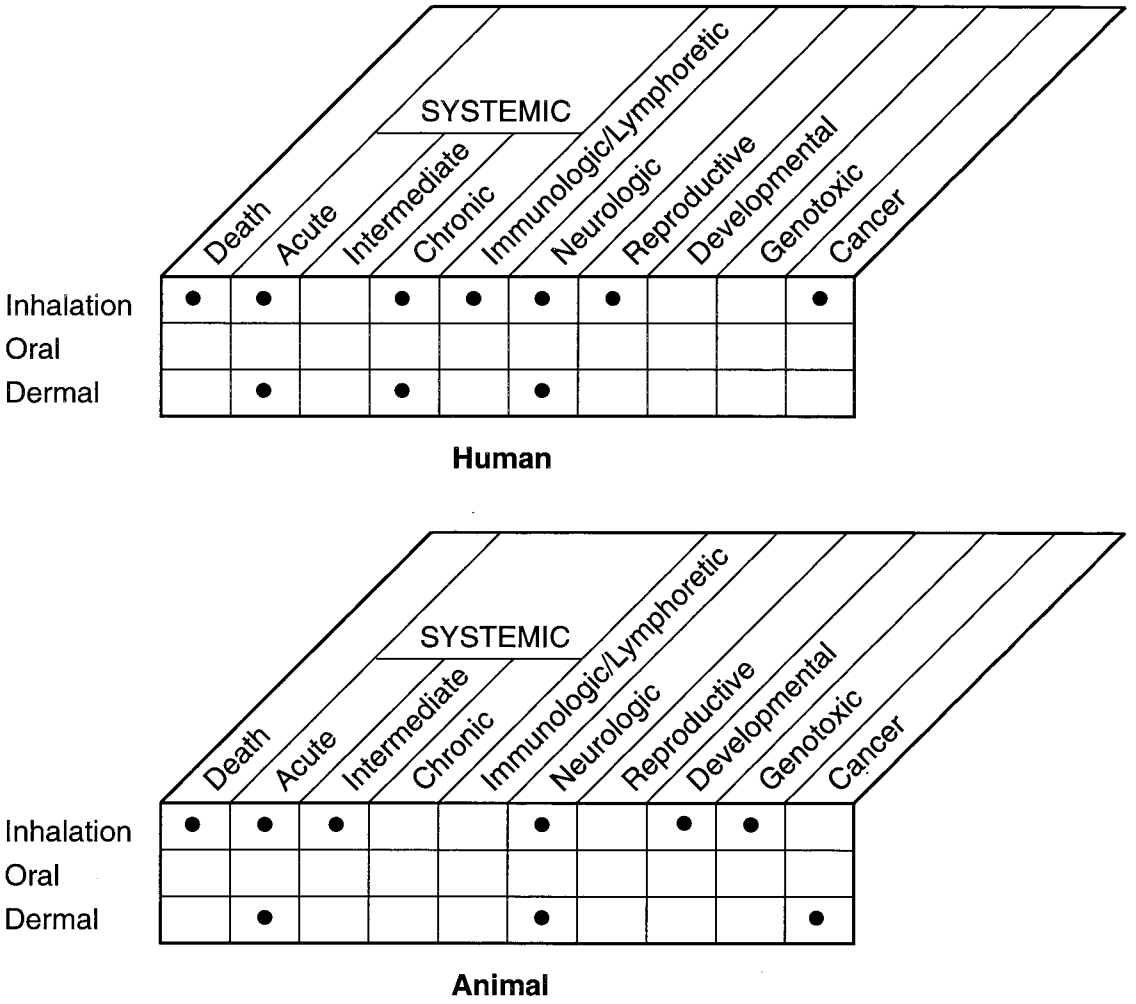
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to Stoddard solvent are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of Stoddard solvent. Each dot in the figure indicates 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). A neurological NOAEL was observed in humans exposed by inhalation to a time-weighted average of 1,563 mg/m^3 for 2 hours (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. Specifically, data are needed to establish a NOAEL for functional neurological tests in humans after inhalation exposure for a duration longer than 2 hours.

More information is needed to follow up on the potential musculoskeletal toxicity, as indicated by increased creatinine kinase levels, following acute human exposure to Stoddard solvent (Pedersen and Cohr 1984b). 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. Furthermore, acute neurological studies of longer durations would be useful since the studies located had exposures of 3 days or less. In particular, studies are needed on upper respiratory/nasal effects observed that have included respiratory depression (Carpenter et al. 1975a, 1975b), metaplasia and cilia1 loss in the nasal cavity

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



● Existing Studies

and trachea (Riley et al. 1984), and nasal irritation (Carpenter 1975a, 1975b; Larsen and Schumes 1974). Renal studies would be useful in elucidating whether the enzyme changes suggesting distal tubular damage, noted after 10 days of exposure in rats, can be verified (Viau et al. 1986). This is the only study suggesting injury to the kidney in a location other than the proximal tubule; however, further studies are needed before distal tubule damage can be ruled out. It would also be useful to have further data from muscular function tests that relate to increased serum creatinine kinase levels (Pedersen and Cohr 1984b).

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 $\alpha_{2\mu}$-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-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 13-week (5 days/week) 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, and, because study interpretation was compromised, 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 l 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 (Daniel1 et al. 1988; Mergler et al. 1988) exposure. No adverse reproductive effects were

noted (Tuohimaa and Wichmann 1981). However, the study was limited due to the small population sample size, questionable accuracy of the exposure assessment, exposure to mixed solvents, 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, particularly more studies addressing glomerulonephritis and atrophy of the brain cortex, including development of animal models. To fully exclude glomerulonephritis as an effect of Stoddard solvent exposure, epidemiological (case-control, cross-sectional, or prospective cohort) studies examining renal outcomes in exposed workers would be particularly useful.

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. Concerns have been raised about the genotoxicity of some individual components of Stoddard solvent. Treatment of V79 Chinese hamster cells by n-decane alone did not cause mutagenesis, but in combination with methylazoxylmethanol (MAM), it appeared to promote mutagenesis (Lankas et al. 1978). Several studies have shown that some n-alkane components of Stoddard solvent are promoters of carcinogenicity (Site 1966; Saffiotti and Shubik 1965; Van Duuren and Goldschmidt 1976). Other studies raise questions about whether some of the n-alkane components may also be co-carcinogens (Bingham and Falk 1969; Horten et al. 1957, 1966, 1976; Van Duuren and Goldschmidt 1976). Carcinogenicity studies utilizing Stoddard solvent mixtures containing these components would be useful.

Genotoxicity. Most of the available in vitro and in viva studies indicate that neither Stoddard solvent nor white spirits pose a genotoxic threat (API 1978a, 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, especially since some individual components of Stoddard solvent are promoters of carcinogenicity. 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.

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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 the effects of inhalation exposure on FSH levels is needed In order to confirm that the decreases in FSH noted in men exposed for an acute period are exposure related and not a result of individual variations or not just extremely transient (Pedersen and Cohr 1984b). Multigenerational animal studies could be considered.

Developmental Toxicity. No human data are available regarding developmental toxicity. The only available animal study reported no skeletal or visceral abnormalities in the offspring of rats following inhalation exposure of the dams (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, P975b; 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; Daniel1 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. The chronic studies reported findings after mixed solvent exposures. A NOAEL was found in humans exposed to a time weighted average of 1,563 mg/m^3 for 2 hours (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. A prospective occupational study that provides exposure levels would be useful in determining standards that would 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 (headaches, fatigue, incoordination, skin irritation, bronchitis, coughing, and abnormal chest x-rays) 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 humanstudies (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 is sparse data 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.

Methods for Reducing Toxic 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 i 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.