

TOXICOLOGICAL PROFILE FOR  
STYRENE

Agency for Toxic Substances and Disease Registry  
U.S. Public Health Service

September 1992

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## FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

- (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

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

*Foreword*

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

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

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



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## CONTENTS

FOREWORD . . . . .	iii
LIST OF FIGURES . . . . .	ix
LIST OF TABLES . . . . .	xi
1. PUBLIC HEALTH STATEMENT . . . . .	1
1.1 WHAT IS STYRENE? . . . . .	1
1.2 HOW MIGHT I BE EXPOSED TO STYRENE? . . . . .	2
1.3 HOW CAN STYRENE ENTER AND LEAVE MY BODY? . . . . .	2
1.4 HOW CAN STYRENE AFFECT MY HEALTH? . . . . .	2
1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO STYRENE? . . . . .	3
1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? . . . . .	4
1.7 WHERE CAN I GET MORE INFORMATION? . . . . .	4
2. HEALTH EFFECTS . . . . .	5
2.1 INTRODUCTION . . . . .	5
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE . . . . .	5
2.2.1 Inhalation Exposure . . . . .	6
2.2.1.1 Death . . . . .	6
2.2.1.2 Systemic Effects . . . . .	6
2.2.1.3 Immunological Effects . . . . .	18
2.2.1.4 Neurological Effects . . . . .	19
2.2.1.5 Developmental Effects . . . . .	21
2.2.1.6 Reproductive Effects . . . . .	22
2.2.1.7 Genotoxic Effects . . . . .	23
2.2.1.8 Cancer . . . . .	24
2.2.2 Oral Exposure . . . . .	26
2.2.2.1 Death . . . . .	26
2.2.2.2 Systemic Effects . . . . .	27
2.2.2.3 Immunological Effects . . . . .	35
2.2.2.4 Neurological Effects . . . . .	35
2.2.2.5 Developmental Effects . . . . .	36
2.2.2.6 Reproductive Effects . . . . .	36
2.2.2.7 Genotoxic Effects . . . . .	36
2.2.2.8 Cancer . . . . .	37
2.2.3 Dermal Exposure . . . . .	38
2.2.3.1 Death . . . . .	38
2.2.3.2 Systemic Effects . . . . .	38
2.2.3.3 Immunological Effects . . . . .	40
2.2.3.4 Neurological Effects . . . . .	40
2.2.3.5 Developmental Effects . . . . .	40
2.2.3.6 Reproductive Effects . . . . .	40
2.2.3.7 Genotoxic Effects . . . . .	40
2.2.3.8 Cancer . . . . .	40
2.3 TOXICOKINETICS . . . . .	40
2.3.1 Absorption . . . . .	40

2.3.1.1	Inhalation Exposure . . . . .	40
2.3.1.2	Oral Exposure . . . . .	41
2.3.1.3	Dermal Exposure . . . . .	41
2.3.2	Distribution . . . . .	41
2.3.2.1	Inhalation Exposure . . . . .	41
2.3.2.2	Oral Exposure . . . . .	42
2.3.2.3	Dermal Exposure . . . . .	42
2.3.3	Metabolism . . . . .	43
2.3.4	Excretion . . . . .	45
2.3.4.1	Inhalation Exposure . . . . .	45
2.3.4.2	Oral Exposure . . . . .	46
2.3.4.3	Dermal Exposure . . . . .	46
2.4	RELEVANCE TO PUBLIC HEALTH . . . . .	46
2.5	BIOMARKERS OF EXPOSURE AND EFFECT . . . . .	55
2.5.1	Biomarkers Used to Identify and/or Quantify Exposure to Styrene . . . . .	55
2.5.2	Biomarkers Used to Characterize Effects Caused by Styrene . . . . .	57
2.6	INTERACTIONS WITH OTHER CHEMICALS . . . . .	57
2.7	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . . .	58
2.8	MITIGATION OF EFFECTS . . . . .	58
2.9	ADEQUACY OF THE DATABASE . . . . .	60
2.9.1	Existing Information on Health Effects of Styrene . . . . .	60
2.9.2	Data Needs . . . . .	60
2.9.3	On-going Studies . . . . .	66
3.	CHEMICAL AND PHYSICAL INFORMATION . . . . .	69
3.1	CHEMICAL IDENTITY . . . . .	69
3.2	PHYSICAL AND CHEMICAL PROPERTIES . . . . .	69
4.	PRODUCTION, IMPORT, USE, AND DISPOSAL . . . . .	73
4.1	PRODUCTION . . . . .	73
4.2	IMPORT/EXPORT . . . . .	73
4.3	USE . . . . .	73
4.4	DISPOSAL . . . . .	76
5.	POTENTIAL FOR HUMAN EXPOSURE . . . . .	77
5.1	OVERVIEW . . . . .	77
5.2	RELEASES TO THE ENVIRONMENT . . . . .	77
5.2.1	Air . . . . .	77
5.2.2	Water . . . . .	81
5.2.3	Soil . . . . .	81
5.3	ENVIRONMENTAL FATE . . . . .	82
5.3.1	Transport and Partitioning . . . . .	82
5.3.2	Transformation and Degradation . . . . .	83
5.3.2.1	Air . . . . .	83
5.3.2.2	Water . . . . .	84
5.3.2.3	Soil . . . . .	84
5.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT . . . . .	84
5.4.1	Air . . . . .	84
5.4.2	Water . . . . .	85
5.4.3	Soil . . . . .	85
5.4.4	Other Environmental Media . . . . .	85

5.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE . . . . .	87
5.6	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES . . . . .	87
5.7	ADEQUACY OF THE DATABASE . . . . .	87
5.7.1	Data Needs . . . . .	87
5.7.2	On-going Studies . . . . .	90
6.	ANALYTICAL METHODS . . . . .	91
6.1	BIOLOGICAL MATERIALS . . . . .	91
6.2	ENVIRONMENTAL SAMPLES . . . . .	95
6.3	ADEQUACY OF THE DATABASE . . . . .	96
6.3.1	Data Needs . . . . .	96
6.3.2	On-going Studies . . . . .	98
7.	REGULATIONS AND ADVISORIES . . . . .	99
8.	REFERENCES . . . . .	103
9.	GLOSSARY . . . . .	137
APPENDICES		
A.	USER'S GUIDE . . . . .	A-1
B.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS . . . . .	B-1
C.	PEER REVIEW . . . . .	C-1



LIST OF FIGURES

2-1	Levels of Significant Exposure to Styrene - Inhalation . . . . .	12
2-2	Levels of Significant Exposure to Styrene - Oral . . . . .	32
2-3	Metabolic Pathways of Styrene . . . . .	44
2-4	Existing Information on Health Effects of Styrene . . . . .	61
5-1	Frequency of NPL Sites with Styrene Contamination . . . . .	78



## LIST OF TABLES

2-1	Levels of Significant Exposure to Styrene - Inhalation . . . . .	7
2-2	Levels of Significant Exposure to Styrene - Oral . . . . .	28
2-3	Levels of Significant Exposure to Styrene - Dermal . . . . .	39
2-4	Genotoxicity of Styrene <u>In Vitro</u> . . . . .	52
2-5	Genotoxicity of Styrene <u>In Vivo</u> . . . . .	53
2-6	On-going Studies on Styrene . . . . .	67
3-1	Chemical Identity of Styrene . . . . .	70
3-2	Physical and Chemical Properties of Styrene . . . . .	71
4-1	Facilities That Manufacture or Process Styrene . . . . .	74
5-1	Releases to the Environment from Facilities that Manufacture or Process Styrene . . . . .	79
5-2	Samples of Styrene Concentrations in Representative Air in the United States . . . . .	86
6-1	Analytical Methods for Determining Styrene in Biological Materials . . . . .	92
6-2	Analytical Methods for Determining Styrene in Environmental Samples . . . . .	94
7-1	Regulations and Guidelines Applicable to Styrene . . . . .	100



## 1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about styrene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Styrene has been found in at least 52 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for styrene. As EPA evaluates more sites, the number of sites at which styrene is found may change. This information is important for you to know because styrene may cause harmful health effects and because these sites are potential or actual sources of human exposure to styrene.

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

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

### 1.1 WHAT IS STYRENE?

Pure styrene is a colorless liquid that evaporates easily and has a sweet smell. However, styrene often contains other chemicals that give it a sharp, unpleasant smell. Styrene dissolves in some liquids, but dissolves only slightly in water.

Styrene is used mostly to make rubber and plastics. Billions of pounds of styrene are produced for this purpose each year in the United States. Products produced from styrene include packaging, insulation (electrical and thermal), fiberglass, pipes, automobile parts, drinking cups and other "fooduse" items, and carpet backing. These products mainly contain styrene linked together in long chains (polystyrene). However, most of these products also contain a residue of unlinked styrene. Styrene is also present in combustion products such as cigarette smoke and automobile exhaust.

Low levels of styrene occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats. Styrene can be found in air, soil, and water after release from the manufacture, use, and disposal of styrene-based products.

## 1. PUBLIC HEALTH STATEMENT

Styrene is quickly broken down in the air, usually within 1-2 days. Styrene evaporates from shallow soils and surface water. Styrene that remains in soil or water may be broken down by bacteria. More information about the chemical and physical properties of styrene can be found in Chapter 3. More information about styrene's occurrence and what happens to it in the environment can be found in Chapter 5.

### 1.2 HOW MIGHT I BE EXPOSED TO STYRENE?

The major way you can be exposed to styrene is by breathing air containing it. Styrene is found in city air and indoor air. Styrene is released into the air from industries that make and use styrene. It is also released from automobile exhaust, cigarette smoke, building materials, and consumer products (polystyrene products such as packaging materials, toys, housewares and appliances that may contain residual amounts of unlinked styrene). Accidental spills and hazardous waste disposal sites are also sources of styrene in air. Usually indoor air that has less movement contains higher levels of styrene than does outdoor air. Rural or suburban air generally contains lower concentrations of styrene than city air.

Styrene is not usually found in drinking water. When it is found in water, the main source is usually industrial waste discharge from factories and coal gasification plants. Also styrene may leach into groundwater around hazardous waste sites. Soil may become contaminated with styrene by spills, landfilling with wastes, and industrial discharges. Styrene can be a natural part of some foods, or can be transferred to food from polystyrene packaging material. For more information on human exposure to styrene see Chapter 5.

### 1.3 HOW CAN STYRENE ENTER AND LEAVE MY BODY?

Styrene can enter your body through your lungs if you breathe contaminated air or through your stomach and intestines if you eat or drink contaminated food or water. Styrene can also pass through the skin into your body. Studies on humans show that styrene enters the body tissues quickly after it is breathed in or taken in by mouth. Because styrene is not usually found in drinking water, the most common way it will enter your body is if you breathe air containing it. Ingestion of styrene contaminated foods is another way styrene can enter the body. Once styrene is in the body, it changes quickly to other chemical forms and leaves the body through the urine and exhaled air within a few days to a few weeks. Chapter 2 has more information on how styrene enters and leaves the body.

### 1.4 HOW CAN STYRENE AFFECT MY HEALTH?

Illness or injury has been reported in people, especially workers, who breathe large amounts of styrene for short periods of time. The most common health problems involve the nervous system. These health effects include depression, concentration problems, muscle weakness, tiredness, and nausea. People exposed to styrene may also have irritation of the eyes, nose, and throat. There have been no reports of death as a result of styrene exposure.

## 1. PUBLIC HEALTH STATEMENT

Recovery from the ill effects of short-term exposure is rapid after styrene exposure ends. The health effects for people exposed to styrene for longer periods of time are not known except for limited information on the harmful effects on the nervous system in occupationally-exposed workers.

Some studies of female workers exposed to elevated air concentrations of styrene have suggested that styrene may cause lower birth weights and produce an increased risk of spontaneous abortions. However, these studies are not completely reliable because the studies often involved exposure to chemicals other than styrene.

Styrene vapor affects the lungs of animals that breathe it. Animal studies have shown that inhalation of styrene can result in changes in the lining of the nose that can last up to 12 weeks after exposure ceases. Longterm animal exposure to high levels of styrene results in damage to the liver but this effect has not been seen in people.

There is little or no information regarding adverse effects in humans following oral or dermal exposure to styrene. However, animal studies indicate that ingestion of styrene can produce effects on the liver, kidney, blood, immune system and nervous system. Dermal exposure has resulted in irritation to the skin and eyes of rabbits. The International Agency for Research on Cancer has determined that styrene is possibly carcinogenic to humans.

Further information on the health effects of styrene in humans and animals can be found in Chapter 2.

### **1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO STYRENE?**

Styrene and its breakdown products can be found in your blood, urine, and body tissues for a short time following exposure to moderate-to-high levels. Because urine samples are easily obtained, urine is often analyzed for the common breakdown products to determine whether a person has been exposed to styrene. However,, the breakdown products can also be found in the urine of persons who have been exposed to chemicals other than styrene. The tests for styrene and its breakdown products in urine require specific methods and equipment and are not usually available at a doctor's office. Because styrene is cleared quickly from the body, the above methods are useful only for detecting exposures that have occurred within 1 day. Testing within 1 day after moderate-to-high exposures allows us to estimate the actual exposure level. Testing urine for styrene and its breakdown products usually does not help predict how severe the resulting health effects may be, Information about tests for detecting styrene in the body is given in Chapters 2 and 6.

## 1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) has determined that 0.1 ppm is the maximum amount of styrene that may be present in drinking water. This level is believed to be low enough to protect an adult from the noncancer effects of styrene, even if exposure occurs for a lifetime. The EPA is currently reviewing the cancer studies on styrene to decide if this chemical is likely to cause cancer in humans.

The Occupational Safety and Health Administration (OSHA) has set a time weighted average (TWA) of 50 ppm styrene as a permissible exposure limit (PEL) and a short-term exposure limit (STEL) of 100 ppm styrene to protect workers during an 8-hour shift over a 40-hour workweek.

More information on governmental regulations for styrene can be found in Chapter 7.

**1.7 WHERE CAN I GET MORE INFORMATION?**

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road, E-29  
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

## 2. HEALTH EFFECTS

### 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of styrene 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 styrene based on toxicological studies and epidemiological investigations.

### 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 (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in this chapter 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 to identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with the carcinogenic effects of styrene in animals are indicated in Figures 2-1 and 2-2.

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 from laboratory animal data to humans.

## 2.HEALTH EFFECTS

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989d), 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

Most information on the effects of inhalation exposure to styrene in humans comes from studies of workers exposed to styrene vapors in the production and use of plastics and resins, especially polystyrene resins. In most cases, the studies involve workplace exposures such as fiberglass boat building factories where the actual levels of styrene are reported as a range of styrene air concentrations. However, there are a few human clinical studies in which exposures are better quantified. Provided below are descriptions of the known effects of inhalation exposure of humans and animals to styrene.

#### 2.2.1.1 Death

There have been no reports of deaths in humans directly associated with exposure to styrene in the workplace (EPA 1988b; Gosselin et al. 1984; NIOSH 1983).

In animals, inhalation studies indicate that the acute toxicity of styrene is low to moderate. An  $LC_{50}$  of 2,770 ppm after 2 hours of exposure was reported in rats, and the  $LC_{50}$  for mice after exposure for 4 hours was 4,940 ppm (Shugaev 1969). All rats and guinea pigs survived after exposure to 1,300 ppm styrene for 30 hours and 16 hours, respectively (Spencer et al. 1942). However, all animals died after 40 hours of exposure.

All reliable LOAEL values and  $LC_{50}$  values for lethality in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

#### 2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular and musculoskeletal effects in humans or animals after inhalation exposure to styrene.

For the following systemic effects resulting from inhalation exposure to styrene, the highest NOAEL values and all reliable LOAEL values in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Styrene - Inhalation

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Rat	3-40+ hr				1300 (LC100)	Spencer et al. 1942
2	Rat	4 hr				2770 (LC50)	Shugaev 1969
3	Gn pig	16-40 hr				1300 (LC100)	Spencer et al. 1942
4	Mouse	2 hr				4940 (LC50)	Shugaev 1969
Systemic							
5	Human	1 d (occup)	Renal		212 (increased urinary levels of alanine aminopeptidase)		Aliberti and Severini 1987
6	Human	15-45 min	Resp Derm/oc	216	216 (nasal irritation) 376 (eye and skin irritation)		Stewart et al. 1968
7	Mouse	3 min	Resp		156 (irritation of upper respiratory tract)		Alarie 1973
Neurological							
8	Human	1 d (occup)			55 (slowed reaction time)		Gamberale et al. 1976
9	Human	1 hr			87 (inhibition of vestibular- oculomotor system)		Odkvist et al. 1982
10	Human	7 hr			99 (impaired balance)		Stewart et al. 1968

TABLE 2-1 (Continued)

Key to figure <sup>a</sup>	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
11	Human	1 d (occup)			92 (tiredness, slow reaction times, mood changes)		Cherry et al. 1980
12	Mouse	4 hr			413 (behavioral changes)		DeGaurriz et al. 1983
Developmental							
13	Rat	10 d 7hr/d		600			Murray et al. 1978
14	Rabbit	13 d 7hr/d		600			Murray et al. 1978
15	Hamster	12 d 6hr/d		750		1000 (fetal deaths or resorptions)	Kankaanpaa et al. 1980
Reproductive							
16	Mouse	5 d 6hr/d		300			Salomaa et al. 1985
INTERMEDIATE EXPOSURE							
Systemic							
17	Rat	21 d 5d/wk 4hr/d	Resp	150	1000 (nasal mucosa effects)		Ohashi et al. 1986
18	Rat	11 wk 5d/wk 6hr/d	Hepatic		300 (enzyme alterations, liver morphology)		Vainio et al. 1979
			Renal	300			
19	Rat	13 wk 5d/wk 7hr/d	Renal	133			Viau et al. 1987

TABLE 2-1 (Continued)

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
20	Gn pig	26 wk 5d/wk 7-8hr/d	Derm/oc			1300 (nasal irritation, severe lung irritation after a few exposures)	Spencer et al. 1942
21	Pig	3 wk 5d/wk 6hr/d	Hemato	360			Johnston et al. 1983
Neurological							
22	Rat	3 mo (cont)		90	320 (astroglial alterations)		Rosengren and Haglid 1989
23	Rat	18 wk 5d/wk 16hr/d		1400			Kulig 1988
24	Rat	21 d 14hr/d			800 (ototoxicity)		Pryor et al. 1987
CHRONIC EXPOSURE							
Systemic							
25	Human	5.1 yr (occup)	Hepatic	120			Harkonen et al. 1984
26	Human	ND (occup)	Hemato		44 (lowered red blood cell count)		Checkoway and Williams 1982
27	Human	1-20 yr (occup)	Hepatic		100 (increased serum levels of OCT and ALAT)		Hotz et al. 1980
28	Human	6 yr (mean)	Renal	24			Viau et al. 1987

TABLE 2-1 (Continued)

Key to figure <sup>a</sup>	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
29	Human	11 yr (mean) (occup)	Renal	53			Vyskocil et al. 1989
30	Human	>1 yr (occup)	Hepatic		100 (elevated serum amino-transferase levels)		Axelsson and Gustavson 1978
31	Rat	18-21 mo 5d/wk 6hr/d	Hepatic		600 (increased liver weight)		Jersey et al. 1978
Neurological							
32	Human	5.1 yr (mean) (occup)			31 (EEG abnormalities)	55 (visuomotor accuracy and psychomotor performance decline)	Harkonen et al. 1978
33	Human	8.6 yr (mean) (occup)			25 <sup>b</sup> (decreased verbal learning skills)		Mutti et al. 1984a
34	Human	6.2 yr (mean) (occup)			130 (neuroendocrine effects)		Mutti et al. 1984b
Cancer							
35	Rat	52 wk 5d/wk 4hr/d				100 <sup>c</sup> CEL (mammary tumors)	Conti et al. 1988

TABLE 2-1 (Continued)

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
36	Rat	18-21 mo 5d/wk 6hr/d				600 <sup>c</sup> CEL (mammary adenocarcinomas - females)	Jersey et al. 1978

<sup>a</sup>The number corresponds to entries in Figure 2-1.

<sup>b</sup>Used to derive a chronic inhalation MRL of 0.06 ppm: exposure level adjusted by 5/7 and 8/24 to account for intermittent exposure, and divided by an uncertainty factor of 100 (10 for use of a LOAEL, and 10 for human variability).

<sup>c</sup>There is significant uncertainty in this CEL value for styrene; see text for discussion of study limitations.

ALAT = alanine aminotransferase; CEL = cancer effect level; cont = continuous; d = day(s); Derm/oc = dermal/ocular; EEG = electroencephalograph; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LC100 = lethal concentration, 100% kill; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; ND = no data; NOAEL = no-observed-adverse-effect level; occup = occupational (typically 5 d/wk, 8 hr/d); OCT = ornithine carbamyl transferase; Resp = respiratory; wk = week(s); yr = year(s)

**FIGURE 2-1. Levels of Significant Exposure to Styrene – Inhalation**

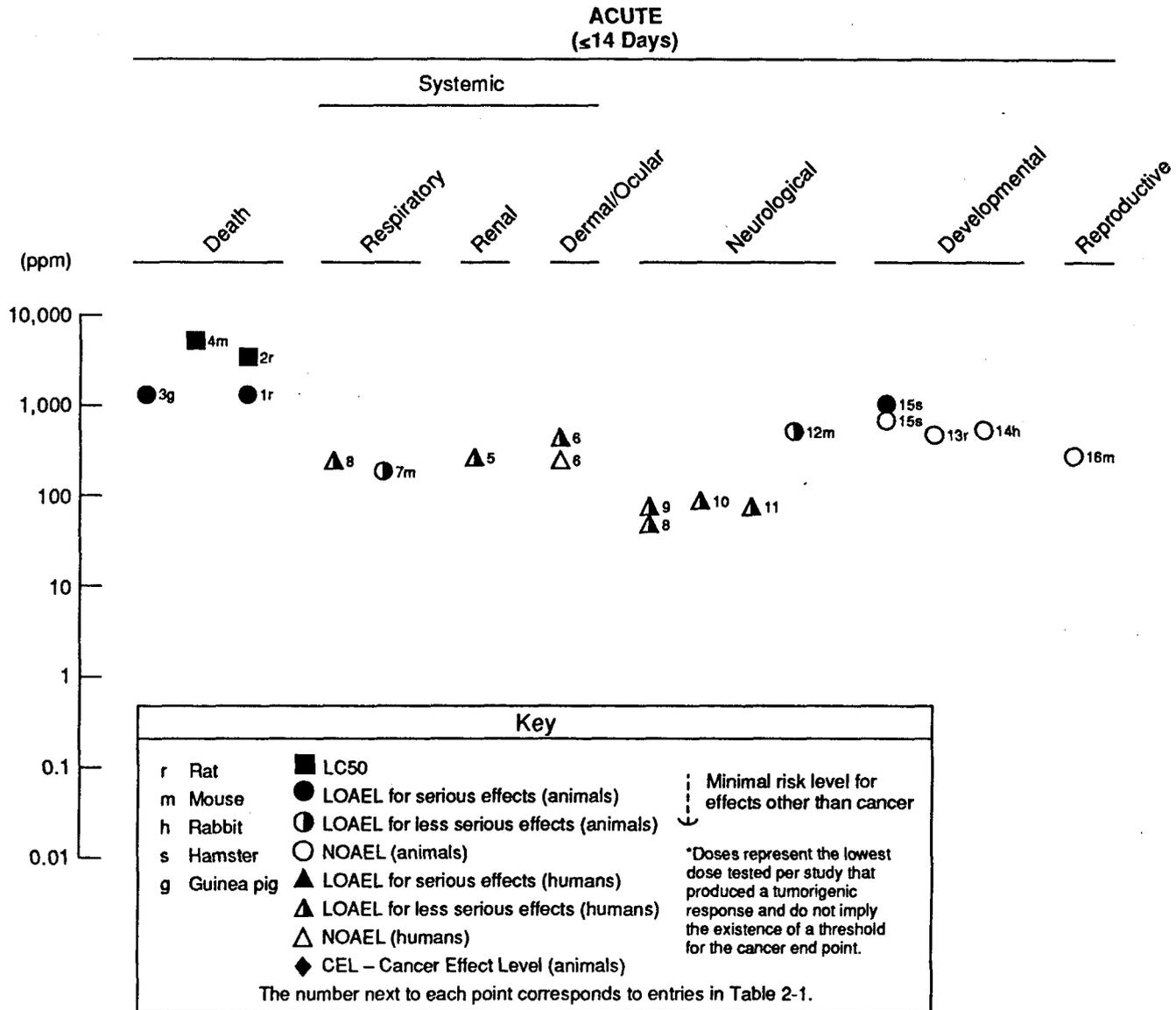
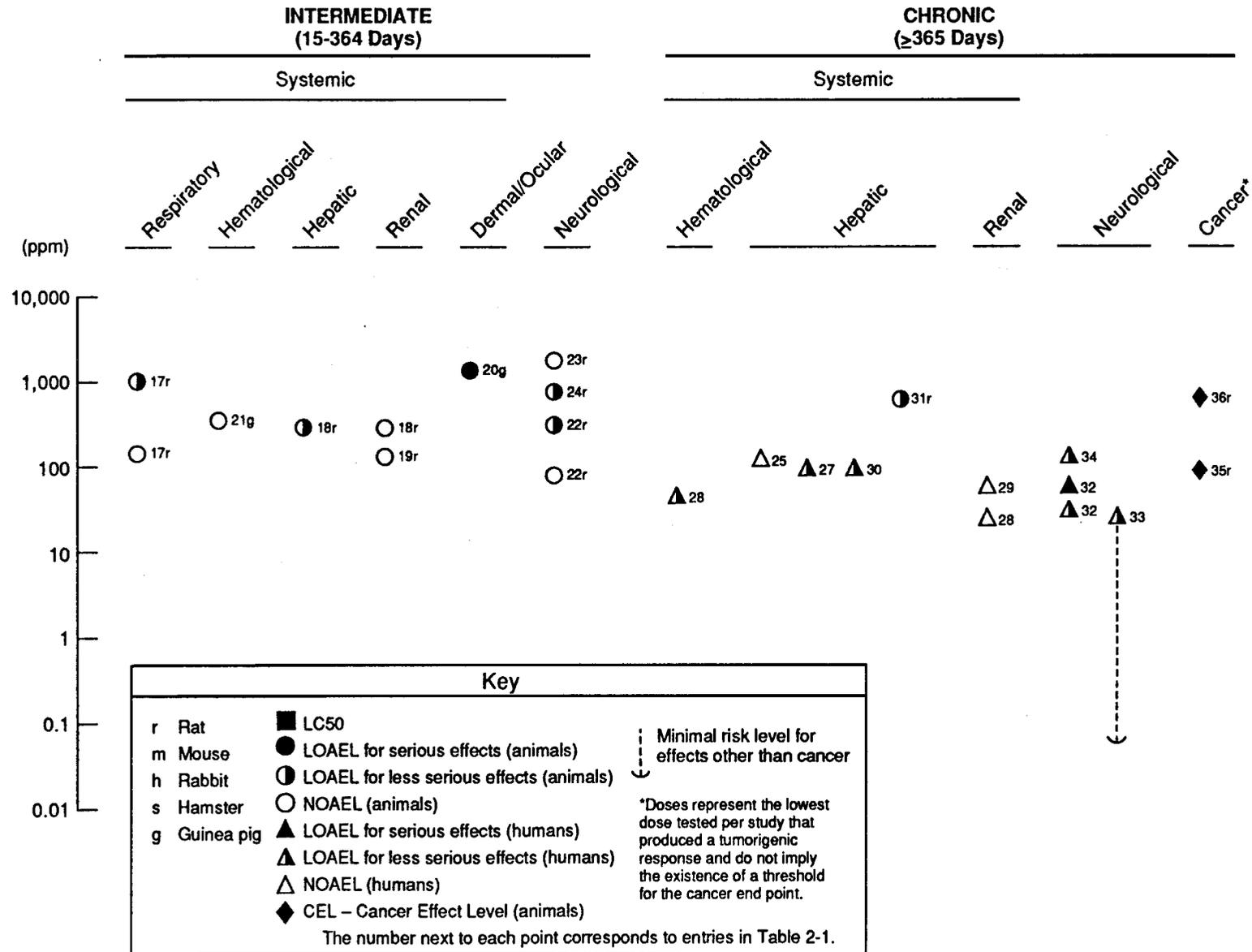


FIGURE 2-1 (Continued)



## 2. HEALTH EFFECTS

**Respiratory Effects.** Several human studies have examined the respiratory effects caused by inhalation exposure to styrene. The most commonly reported general symptom is mucous membrane irritation. Irritation of the upper respiratory tract (i.e., nose and throat) has occurred in human volunteers (Carpenter et al. 1944; Stewart et al. 1968) and workers (NIOSH 1983). Throat irritation and increased nasal secretion occurred following exposure of two male subjects to 800 ppm for 4 hours (Carpenter et al. 1944). Nasal irritation was observed in all volunteers after exposure to 376 ppm styrene for 60 minutes (Stewart et al. 1968). Obstructive lung changes were observed in 4 of 21 workers exposed to styrene for about 10 years (Chmielewski and Renke 1975; Chmielewski et al. 1977). However, exposure levels were not defined.

Similar effects have been reported in animals following exposure to styrene vapor. In rats, pathological changes in the respiratory mucosa were found following exposure to 1,000 ppm styrene for 4 hours/day, 5 days/week for 3 weeks. The upper nasal mucosa demonstrated decreased ciliary activity and abnormal morphology. Also, vacuolization and increased numbers of dense bodies of respiratory epithelial cells and sporadic rupture of the cytoplasmic membrane were observed in the rats exposed to 1,000 ppm for 21 days (Ohashi et al. 1986).

Rats and guinea pigs exposed to styrene at a level of 1,300 ppm for 7-8 hours/day, 5 days/week for 6 months showed nasal irritation, but rabbits and monkeys did not (Spencer et al. 1942). Histopathological examinations revealed no changes between test and control rats, but pronounced lung irritation was seen in guinea pigs that died after a few exposures. The irritation, which included congestion, hemorrhages, edema, exudation, and a general acute inflammatory reaction, was not seen in the guinea pigs, rabbits, and monkeys that survived the 6-month exposure period (Spencer et al. 1942). In another study, sensory irritation of the upper respiratory tract in mice was observed following exposure to a styrene aerosol of 666 mg/m<sup>3</sup> (156 ppm) (Alarie 1973). This effect was determined by measuring the decrease in respiratory rate during the exposure of the mice to the aerosol.  $\beta$ -Nitrostyrene, which was also tested in this study, exhibited much greater activity than styrene. No pathological data were available.

These well conducted human and animal studies (see Table 2-1 and Figure 2-1) demonstrate the characteristic irritant properties of styrene on the upper respiratory tract.

**Gastrointestinal Effects.** Nausea was observed in humans exposed to 376 ppm styrene after 1 hour exposure (Stewart et al. 1968). This effect is probably secondary to effect on the central nervous system, although mucociliary transport of styrene aerosol droplets from the upper respiratory tract to the gastrointestinal tract might also contribute to gastrointestinal irritation. A Russian study (Basirov 1975) reviewed by the World Health Organization (WHO 1983) investigated the effects of styrene on digestive function by testing the secretory, excretory, motor, and pepsinogen-generating functions of the stomach in 20 unexposed and 80 exposed workers. The authors

## 2. HEALTH EFFECTS

reported that some workers in the styrene-butadiene synthetic rubber manufacture exposed to 60-130 mg/m<sup>3</sup> (14-31 ppm) styrene for less than 5 to more than 10 years had decreased digestive function and decreased stomach acidity.

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

**Hematological Effects.** Several studies indicate that inhalation exposure of humans to styrene cause mild or no effects on the blood. In one study, the incidence of abnormal values for hematological parameters including erythrocyte, leukocyte, and platelet counts, and hemoglobin levels for 84 styrene workers generally exposed to less than 1 ppm styrene for 1-36 years was investigated. However, these workers were also exposed to intermittent high levels of styrene as well as to other chemicals. The percentages of the exposed group with abnormally low hemoglobin and erythrocyte values or abnormally high leukocyte values were less than those percentages in the 62 person control group. There were no abnormal thrombocyte values reported in either the exposed or control groups (Thiess and Friedheim 1978). Findings from a group of 93 workers engaged in the manufacture of styrene polymers and exposed to generally less than 1 ppm styrene for 1-38 years were also presented in this study; only the incidence of abnormally low erythrocyte counts (in the group exposed to styrene) was found to be statistically significant ( $p \leq 0.05$ ). However, because exposures could not be determined accurately and because there were concomitant exposures to other chemicals, the results of these studies are difficult to interpret.

Lowered erythrocyte counts, hemoglobin, platelets, and neutrophils and slightly higher mean corpuscular red cell volumes and neutrophil band counts were observed in workers in a styrene-butadiene rubber manufacturing plant (Checkoway and Williams 1982). The highest mean styrene level was 13.67 ppm. However, interpretation of this study is limited because multiple-chemical exposures were involved and exposure and clinical signs were measured at the same time and only once. An earlier study of styrene workers showed no definite pattern of hematological changes (Lorimer et al. 1978). In these studies, exposure levels were uncertain and multiple chemicals were involved.

In an animal inhalation study, no adverse hematological effects were noted in Jersey pigs exposed to 72 or 360 ppm styrene for 3 weeks (Johnston et al. 1983). In rats exposed to 49 ppm styrene, erythrocyte-aminolevulinate dehydratase (ALA-D) was depressed markedly. The decrease in enzyme activity was accompanied by a decrease in the enzyme content in bone marrow cells (Fujita et al. 1987). The author's suggestion that the changes may have been a result of styrene oxide reducing the enzyme protein is based on in vitro data.

The well-conducted Thiess and Friedheim (1978) study as well as the more limited studies indicate that few adverse hematological effects occurred in styrene-exposed workers. However, the full meaning of the findings is not clear because of poor characterization of the exposure level and concurrent

## 2. HEALTH EFFECTS

exposures to other chemicals. The animal data do not permit a characterization of hematological effects in animals after inhalation exposure to styrene. However, oral animal data support the suggestive evidence in humans that styrene may affect hematological parameters (Section 2.2.2.2).

**Hepatic Effects.** Human studies on the hepatic effects of styrene inhalation frequently used serum levels of enzymes as indicators of liver dysfunction. In general, human studies have resulted in negative or equivocal results (Harkonen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978). The effects of styrene, at exposure levels generally less than 1 ppm, were evaluated in 84 styrene workers exposed for 1-36 years (Thiess and Friedheim 1978). In this study, serum glutamate-oxalacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT) and gammaglutamyl transferase (GGT) were measured in exposed workers and a reference population. Within the styrene-exposed group the incidence of high SGOT or SGPT values was less than the reference group. The number in the exposed group having abnormally high GGT values was twice as high as the control group. However, only a small number of exposed workers and controls were included in this study and the results were not statistically significant. In another study, workers exposed to styrene in the range of 100-300 ppm as an 8-hour time-weighted average in small manufacturing operations showed elevated levels of liver amino transferase (Axelson and Gustavson 1978). However, the cause of the increased levels and effects on liver function are uncertain. In another exposed population of 93 workers exposed to less than 1 ppm styrene for 1-38 years, hepatic enzyme levels (SGOT, SGPT, and GGT) were measured (Thiess and Friedheim 1978). There were no statistically significant differences in the hepatic enzyme levels of the exposed and reference population.

Liver enzyme levels were also measured in 57 workers exposed to styrene in the polyester industry for 1-20 years (Hotz et al. 1980). The styrene exposure concentrations were from 1 to 100 ppm. The hepatic enzymes, ornithine carbamyl transferase (OCT), aspartate amino transferase (ASAT), alanine amino transferase (ALAT), and GGT were measured and showed increased activity compared to control values. The OCT and ALAT levels correlated better than the GGT and ASAT levels with the degree of styrene exposure. These study results suggest hepatic injury at 100 ppm and less. In another study, the effect of styrene exposure in 34 styrene-exposed and 34 control female workers was evaluated (Harkonen et al. 1984). These workers were exposed to approximately 50-120 ppm styrene for a mean duration of 5.1 years in the breathing zone with the highest levels temporarily exceeding 200 ppm. Liver function was assessed by measurement of ASAT, ALAT, and GGT. Bile acid concentrations were also measured. The styrene-exposed group did not have higher activity levels of either liver enzymes or bile acids when compared to the control group values. A few abnormal values in both the exposed and control groups were associated with the use of drugs or alcohol and the study results indicated no hepatic effects associated with exposure to styrene. In

## 2. HEALTH EFFECTS

a different study, workers exposed to approximately 5-20 ppm styrene for up to 20 years or more were found to have high GGT values even when the use of alcohol was taken into consideration (Lorimer et al. 1978). However, no other hepatic parameters were affected.

In animal studies, rats were exposed to 300 ppm styrene intermittently for 11 weeks (Vainio et al. 1979). Free glutathione in rat liver significantly decreased (approximately 59%) after an exposure period of 2 weeks. The glutathione depression continued throughout the intermittent 11-week exposure. The cytochrome P-450 content of hepatic microsomes was doubled during the first 2 weeks of exposure to 300 ppm. The epoxide hydratase and UDP glucuronosyltransferase activity in rat liver increased upon exposure to 300 ppm over 11 weeks of intermittent exposure. Degenerative morphologic alterations were also observed in the parenchymal cells of the liver 2 weeks after exposure to 300 ppm (Vainio et al. 1979). In another study by the same author, a 4-day exposure at even lower styrene levels (less than 200 ppm) resulted in decreased free glutathione in rat liver. In this case the decrease was reversible as evidenced by a slight elevation of hepatic glutathione concentrations in styrene exposed animals 18 hours after exposure.

In a 24 month study of rats exposed to 600 or 1,000 ppm styrene, increased absolute and relative liver weights were observed in females at both exposure levels at 6 months (Jersey et al. 1978). At 12 months and terminal necropsy, these effects were inconsistent and not dose-related. Histopathological findings were similar for exposed and control females at the 6 and 12 month intervals. For males, there was evidence of a nutritional state associated with decreased body weight gain. At termination, alveolar histiocytosis was observed in the lungs of females exposed to 1,000 ppm only. Excessive mortality and chronic mucosa pneumonia prevented an appropriate evaluation of the male rat histopathology.

Although the well-conducted studies on workers generally gave negative results, the animal studies involving higher exposures suggest that styrene inhalation may affect liver function.

**Renal Effects.** Human studies generally confirm the importance of urinary enzymes as indicators of kidney damage due to exposure to styrene (Aliberti and Severini 1987; Viau et al. 1987; Vyskocil et al. 1989) and other chemicals. The urine of 15 subjects exposed to styrene (900 mg/m<sup>3</sup> or 212 ppm) for an 8-hour workshift and 20 unexposed control subjects was evaluated for urinary enzyme effects (Aliberti and Severini 1987). The subjects exposed to styrene demonstrated higher levels of alanine-aminopeptidase (AAP) at the end of the workshift compared to unexposed controls (p<0.001). The N-acetylglucosaminidase (NAG) was increased much less than AAP but the increase over the control group was statistically significant (p<0.01). These results are considered to represent an early biochemical indication of adverse renal effects. Viau et al. (1987) measured urinary excretion of  $\beta$ -microglobulin, retinol-binding protein and albumin in 65 workers exposed to styrene (24 ppm) for a mean duration of 6 years. No significant difference was observed in the urinary excretion of proteins when compared to controls. No significant

## 2. HEALTH EFFECTS

difference was found by Vyskocil et al. (1989) in the urinary excretion of albumin  $\beta$ -microglobulin, retinol-binding protein, total protein, glucose, lysozyme, lactate dehydrogenase, and  $\beta$ -N-acetyl-D-glucosaminidase in workers exposed to an average of 53 ppm styrene when compared to a control group. The minor kidney effects noted in these well-conducted human studies indicate that styrene may exert a minor effect on some kidney enzyme functions.

Minor changes in renal enzyme activities and no effects on morphology (Vainio et al. 1979; Viau et al. 1987) have also been observed in animals after exposure to styrene. Intermittent 11-week exposure to styrene by inhalation (300 ppm) induced the activities of the drug hydroxylating enzymes ethoxycoumarin O-deethylase, and cytochrome P-450. Activities of the conjugating enzymes, epoxide hydratase, and UDP glucuronosyltransferase were also induced in the exposed rats (Vainio et al. 1979). Since there were no degenerative morphologic alterations observed in the kidney, this is not a clear adverse effect. In another study, no functional or morphological renal changes could be detected in rats exposed to 133 ppm styrene (5 days/week) for 13 weeks (Viau et al. 1987).

**Dermal/Ocular Effects.** Eye irritation in humans has been reported at high styrene concentrations (Carpenter et al. 1944; Stewart et al. 1968). Immediate eye irritation was reported in two human subjects exposed to 800 ppm styrene for 4 hours (Carpenter et al. 1944). Eye irritation was also noted by Stewart et al. (1968) in two of five volunteers exposed to 376 ppm styrene for 1 hour. Also, 345 styrene-exposed workers (98% male) were evaluated for ocular toxicity due to exposure to styrene (5-200 ppm) for 7-20 years. No evidence of optic neuritis, central retinal vein occlusion, or retrobulbar neuritis was found. Conjunctival irritation was a complaint of 22% of the 345 workers exposed to styrene levels above 50 ppm (Kohn 1978). Eye and nasal irritation was observed in rats and guinea pigs exposed to 1,300 or 2,000 ppm styrene, 7-8 hours/day, from 21 to 30 weeks (Wolf et al. 1956). 5 days/week for durations ranging Rabbits and monkeys were exposed for up to 360 days with no effects.

**Other Effects.** Exposure to styrene vapors has been found to increase the levels of several pituitary hormones (prolactin, growth hormone) in female workers (Mutti et al. 1984b). This effect is probably mediated through the nervous system, and so is discussed in Section 2.2.1.4.

### 2.2.1.3 Immunological Effects

No dose-related differences in the concentrations of serum alpha, beta and gamma globulins were found in workers exposed to different concentrations of styrene (Chmielewski et al. 1977). However, exposure levels and durations were not specified. In patch-testing studies of cross-reactors to styrene, styrene epoxide was more sensitizing than styrene itself (Sjoberg et al. 1984). The authors interpreted this as evidence that styrene requires metabolism by skin aryl hydrocarbon hydroxylase to styrene epoxide for its sensitizing activity.

## 2. HEALTH EFFECTS

No other studies were located regarding immunological effects in humans or animals after inhalation exposure to styrene.

### 2.2.1.4 Neurological Effects

Several epidemiological and clinical studies have shown that styrene exposure causes alterations of central nervous system functions in humans. Men exposed to levels of 52-117 ppm (mean = 92 ppm) in a boat-building factory were more subject to mood changes, were more likely to report feeling tired, and had slower reaction times than unexposed workers (Cherry et al. 1980). A similar decrease in reaction time was observed in four groups of workers exposed to styrene at levels of 17-101 ppm (mean = 55 ppm) (Gamberale et al. 1976). Workers exposed to styrene in several industries at mean concentrations of 5-125 ppm had mild sensory neuropathy characterized by decreased sensory conduction amplitude and increased duration, but there were too few people to define no-adverse-effect levels (Rosen et al. 1978). An increased occurrence of fast activity in central and precentral areas of the brain was also noted in styrene workers. These effects were clearly visible in workers exposed to an average of 47 ppm or more. In a study by Stewart et al. (1968), no toxicity was noted following 1- or 2-hour exposure to 51 ppm (3 subjects) or 117 ppm (1 subject) styrene, respectively. In the same study, 6 subjects were exposed to 99 ppm styrene vapor for 7 hours. Three of these subjects reported that they were having difficulty performing the modified Romberg test which measures balance and coordination. Also, 1-hour exposure to 376 ppm styrene vapor resulted in abnormal neurological findings and complaints of nausea and inebriation. In another study, immediate muscular weakness, listlessness, drowsiness and impaired balance was observed in two human subjects exposed to 800 ppm styrene (Carpenter et al. 1944). Odkvist et al. (1982) investigated the inhibition of the vestibular-oculomotor system in ten human subjects experimentally exposed to 87-139 ppm styrene for 1 hour. Visual suppression was disturbed and the authors concluded that styrene acts, along with other organic solvents, to block cerebellar inhibition of the vestibula-oculomotor system.

Chronic exposure of workers to styrene results in increased incidence of abnormal electroencephalograms (EEGs) (Harkonen et al. 1978). In this study, exposure levels were estimated from an empirical relationship that was established between workplace air concentrations and urinary levels of mandelic acid (MA) in exposed workers. This relationship is expressed as:

$$\ln(\text{styrene air concentration, ppm}) = -3.4915 + 1.0568 \cdot \ln(\text{urinary MA concentration, mg/L})$$

The authors had previously observed a strong correlation ( $r^2 = 0.86$ ,  $p < 0.001$ ) between the time weighted average styrene concentrations in air and urinary mandelic acid concentrations. Thus, exposure estimates derived from urinary metabolite levels are considered to be sufficiently reliable to establish meaningful dose-response relationships. Exposure to an 8 hour time-weighted average of 31 ppm or above resulted in a 30% incidence of altered EEGs, compared to 10% in workers exposed to less than 31 ppm. The abnormalities

## 2. HEALTH EFFECTS

included local slow wave activity (14/23), diffuse theta activity (8/23), and bilateral discharges (2/23). Exposure to 55 ppm or higher resulted in decreased visuomotor accuracy and impaired psychomotor performance. As part of the same study, 9 out of 40 workers who displayed subjective symptoms of styrene exposure were found to have abnormal nerve conduction velocities. However, no clear relationship between the altered conduction velocity and styrene exposure could be established. Mutti et al. (1984a) reported verbal learning skills were significantly impaired in workers exposed to mean daily concentrations of styrene greater than 25 ppm (this value is also estimated from levels of urinary metabolites). This exposure level (25 ppm) is the lowest concentration known to have caused significant neurological effects in humans, and so has been selected to calculate a chronic inhalation MRL of 0.06 ppm, as described in the footnote to Table 2-1. Logical memory and visuo-constructive abilities were also significantly affected in workers exposed to greater than 50 ppm styrene.

Inhalation exposure to styrene may also cause peripheral neuropathy. A man exposed to an undetermined concentration of styrene vapor for 5 years (4-10 hours/day, 7 days/week) developed burning sensations in the feet and moderate slowing of nerve conduction velocity in the lower limbs (Behari et al. 1986). Histologic examination revealed demyelination of sural nerve fibers. However, this individual also had a history of prescription drug use and may have been exposed to chemicals other than styrene. Therefore, this report does not contain adequate information to establish an unequivocal cause-effect relationship.

The effects of styrene on the neuroendocrine activity of the tuberoinfundibular dopaminergic system (TIDA) in humans was indirectly investigated with measurements of adenohipophysial hormones, including serum prolactin (PRL), human growth hormone (HGH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in 30 female workers exposed to approximately 130 ppm styrene and 30 age-matched controls (Mutti et al. 1984b). The exposed subjects' serum levels of PRL were more than double the reference values and correlated with exposure to styrene. The serum levels of HGH in exposed women were also higher than the reference group. The investigators concluded that the styrene-induced neuroendocrine effects were mostly due to acute exposure and were not influenced by the duration of exposure after control for age and concentration of styrene.

The effect of occupational exposure to styrene on high-frequency hearing loss was evaluated in workers exposed to 35-165 ppm styrene. The studies did not demonstrate an increased age-dependent decrease in hearing high frequencies when compared to controls (Muijser et al. 1988). However, a comparison within the exposed group indicated a statistically significant difference in hearing thresholds for high frequencies in the workers exposed to the highest concentration of styrene (up to 700 mg/m<sup>3</sup>).

Limited neurobehavioral and neurotoxic effects of styrene have been investigated in animal studies. In rabbits, exposure to 750 or 1,500 ppm of styrene resulted in dose-dependent decreases in striatal and tubero-

## 2. HEALTH EFFECTS

infundibular dopamine and homovanillic acid levels. Noradrenalin levels were not significantly changed (Mutti et al. 1984c). Mice exposed to 413-851 ppm styrene for 4 hours exhibited decreased immobility in a confined area swimming test (DeCeurris et al. 1983). In another study, groups of rats were exposed to 350, 700, and 1,400 ppm of styrene for 18 weeks (Kulig 1988). Compared to controls, styrene-treated rats exhibited an initial reduction in activity and grip strength, but this effect tended to diminish during the study period. This suggests that some level of tolerance might develop during continuous exposure. Coordinated movement and nerve conduction time were not affected. Initially there were some styrene-related neurobehavioral effects. However, at the end of the exposure period the performance of styrene-treated rats was not significantly different from the control group and there were no deficits in performance during the post-exposure period. In another animal study, Rosengren and Haglid (1989) demonstrated that constant styrene exposure of rats to 320 ppm (24 hours/day) for 3 months induced increases in glial fibrillary acidic proteins 4 months after the exposure period. Using this glial cell marker, this study suggests that styrene may induce abnormalities in the central nervous system of rats. Pryor et al. (1987) reported that 800 ppm styrene caused an elevation in behavioral auditory response thresholds (12kHz) in rats exposed for a 3 week period (14 hours/day). No differences were found between exposure groups in the acquisition of multisensory conditioned avoidance response tasks.

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

### 2.2.1.5 Developmental Effects

Limited information concerning developmental effects of styrene in humans is available from studies of delivery outcome of women employed in the plastics industry (processing styrene or polyurethane plastics). Case-control studies performed in Sweden and Norway did not detect an increase in the odds ratio for developmental effects (stillbirth, infant death, malformations, low birth weight) in women who worked in the plastic industry (Ahlborg et al. 1987). However, actual levels of styrene exposure were not known for either group of workers. In another study, the birth weights of infants whose mothers worked during pregnancy in the reinforced plastics industry were analyzed by Lemasters et al. (1989). Women who worked in areas with elevated levels of styrene (estimated from industrial hygiene data to average about 82 ppm) had offspring with adjusted birthweights that were 4% less than the offspring of unexposed women. However, this decrease was not statistically significant ( $p=0.08$ ). These studies suggest that developmental effects in exposed workers are not of major concern, but the data are not adequate to exclude this effect. Moreover, interpretation of the results is complicated due to exposure of the workers to other chemicals in the workplace such as toluene, xylene, acetone, methylene chloride, and methyl ketone (Lemasters et al. 1989), as well as thermal degradation products of styrene polymers (Ahlborg et al. 1987). Workers may also be exposed to aerosols containing aldehydes, ketones, alcohols, esters, acids, and anhydrides.

## 2. HEALTH EFFECTS

Evaluations of developmental effects of styrene in rats, rabbits, mice, and hamsters have been reported (Kankaanpaa et al. 1980; Murray et al. 1978). Rats were exposed to 0 or 300 ppm styrene on days 6 to 15 of gestation and additional rats were subsequently exposed to 0 or 600 ppm styrene (Murray et al. 1978). The average fetal crown-rump length was significantly reduced in the 300 ppm group, but not in the 600 ppm group. The authors concluded this effect was not treatment-related. The number of live fetuses or resorptions/litter was not affected by exposure to styrene. A few skeletal variants such as lumbar spurs and delayed ossification of sternebrae occurred in the styrene-exposed litters at a higher incidence than the control litters; however, the occurrence of this effect was similar to historical controls. Additionally, it was reported that there were no fetotoxic or teratogenic effects in rabbits exposed to 300 or 600 ppm styrene on days 6-18 of gestation (Murray et al. 1978). Although there was a significant increase in the incidence of unossified sternebrae in the 600 ppm group, it did not exceed that found in historical control data. Embryotoxicity was observed following exposure of pregnant mice to 250 ppm styrene on days 6-16 of gestation (Kankaanpaa et al. 1980). The incidence of dead or resorbed fetuses was higher in the exposed group but was not statistically significant ( $p < 0.10$ ). Some minor skeletal malformations (rib fusions, extra ribs) were observed in the mice. In the same study, hamsters were exposed to 300, 500, 750, and 1,000 ppm of styrene on days 6-18 of gestation. Fetotoxicity (dead or resorbed fetuses) was observed only at 1,000 ppm and teratogenicity was not reported at any of the exposure levels. The incidence of dead or resorbed fetuses was 26% in the control group versus 60% in the exposed group. No skeletal malformations were noted in the hamsters.

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

### 2.2.1.6 Reproductive Effects

Information on the reproductive effects of styrene in humans is available from epidemiological studies of the reproductive outcomes of females employed in the various industrial operations in which styrene is used. However, exposures to styrene were not adequately quantified in any of the studies cited. In one study, spontaneous abortions among 9,000 Finnish chemical workers from 1973 to 1976 were analyzed (Hemminki et al. 1980). The risk of spontaneous abortion (expressed as number of abortions per 100 pregnancies) was significantly higher in women employed in styrene production compared to all women in Finland (15.0 vs. 5.5). However, this increase was not detected in a follow-up study of the same workers (Hemminki et al. 1984). The possible embryotoxic effects of styrene on 67 female lamination workers compared to 67 age-matched controls were evaluated in a second study (Harkonen and Holmberg 1982). The number of births was significantly lower among the workers exposed to styrene. This result was explained in part by a greater number of induced abortions in the styrene-exposed group. The number of spontaneous abortions was not elevated in the exposed women. No increased risk of spontaneous abortions among workers processing polymerized plastics or

## 2. HEALTH EFFECTS

heated plastics made of vinyl chloride or styrene was reported (Lindbohm et al. 1985). The authors reported that the statistical power of the study was low due to the small study population. These studies are not conclusive since the workers were exposed to chemicals other than styrene in the workplace and the concentrations of styrene were not adequately reported.

Mice exposed to 150 or 300 ppm styrene by inhalation for 5 days (6 hours/day) did not have a statistically significant increase in the frequency of abnormal sperm heads 3-5 weeks after exposure (Salomaa et al. 1985). These findings suggest that reproductive effects, if they exist, may not be produced through a genotoxic mechanism.

### 2.2.1.7 Genotoxic Effects

Chromosomal damage in peripheral lymphocytes and other cellular effects have frequently been studied in workers exposed to styrene in the production of reinforced plastic products and styrene/polystyrene production. In general, these studies are limited by the fact that workers in these industries are often exposed to chemicals other than styrene such as methylene chloride and epoxide resins. Confounding factors such as age, sex, and smoking status must also be considered. Studies of this nature may also be limited by small sample sizes and differing cell culture methodologies.

Chromosomal aberrations have been reported in several studies of workers exposed to styrene for 1 to 15 years in reinforced plastic operations (Andersson et al. 1980; Hogstedt et al. 1979; Meretoja et al. 1977, 1978). For example, in an evaluation of lymphocytes from 16 men exposed to styrene (1-140 ppm) and 5 controls, styrene-exposed men showed 11% - 26% aberrant cells versus 3% or less in the control subjects (Meretoja et al. 1977). The aberrations were almost totally chromosome breaks. The frequency of micronuclei and cells connected with nuclear bridges were also increased in exposed workers. In another study, 10 styrene-exposed workers (1-140 ppm) and 5 controls were reexamined. It was reported that the frequencies of aberrant lymphocytes varied from 10% to 26% in the exposed group and from 1% to 4% in the referents (Meretoja et al. 1978). The most frequent class of aberrations was again chromosome breaks or gaps. The incidence of sister chromatid exchange (SCE) among styrene-exposed workers in this study was not significantly higher in the controls. In another study of 36 exposed workers and 37 controls, Andersson et al. (1980) reported an increase in the incidence of chromosome breaks/gaps and SCEs (21 exposed subjects (2.8-154 ppm) versus 20 control subjects for the SCE subset). Chromosome aberrations in lymphocytes from peripheral blood were more frequent in 6 workers when compared to 6 age- and sex-matched controls (Hogstedt et al. 1979). In this study workroom concentrations were a little lower (12-74 ppm) than in previously reported studies. In another study, negative results were reported for chromosomal aberrations and SCEs in reinforced plastics workers (16 exposed versus 13 controls) in workroom exposures from 33 to less than 70 ppm styrene (Watanabe et al. 1981).

## 2. HEALTH EFFECTS

Styrene exposures are generally lower (1-58 ppm) in styrene and polystyrene manufacturing facilities than in reinforced plastic operations, and studies of chromosome damage and other cellular effects in these facilities have been generally negative (Hansteen et al. 1984; Nordenson and Beckman 1984; Thiess et al. 1980). For example, Thiess et al. (1980) reported that 24 employees exposed to styrene in the laboratory (6.0 ppm) and a polyester processing plant (58.1 ppm) showed a nonstatistically significant increase in chromosomal aberration rates compared to controls. In another study, chromosomal aberrations were studied in lymphocytes of 15 workers and 13 controls employed in the manufacture of polyester reinforced windowglass fiber where workroom exposure was 24 ppm styrene. No increased frequency of chromosome breaks/gaps was observed, but the number of micronuclei was significantly increased (Nordenson and Beckman 1984). The authors concluded that the mitotic spindle membranes may be more sensitive to styrene and its metabolites than DNA. Eighteen workers exposed to less than 50 ppm styrene were found to have a significant increase in chromosome gaps (Hansteen et al. 1984). No increase in the number of chromosome breaks and SCE's was found compared to controls. In another study, increased frequency of lymphocyte micronuclei in workers exposed to a mean 13 ppm styrene was reported (Hogstedt et al. 1983). An increase in chromosomal aberrations was observed in workers exposed to a mixture of phenol, styrene, and formaldehyde (levels not specified) (Mierauskiene and Lekevicius 1985). In an evaluation of cytogenetic monitoring of industrial populations potentially exposed to genotoxic chemicals including styrene in the Netherlands, DeJong et al. (1988) concluded that the results of chromosome analyses are difficult to interpret due to variable and high background levels of chromosome aberration in control populations.

Male and female rats exposed to styrene vapor (600 and 1,000 ppm) for 1 year did not show an increased incidence of chromosome abnormalities in bone marrow cells collected at the end of the last exposure (Sinha et al. 1983), although detectable chromosomal abnormalities are not likely to endure for such a long period.

In summary, the mutagenicity data from studies of workers exposed to styrene suggest that styrene exposure can produce an increased incidence of chromosomal aberrations (primarily gaps and breaks). However, interpretation of these data are complicated by the possible involvement of concomitant exposures to other chemicals. The data are insufficient to show styrene exposure produces an increased incidence of sister chromatid exchanges or micronuclei formation.

Other genotoxicity studies are discussed in Section 2.4.

### 2.2.1.8 Cancer

Although there are several epidemiologic studies which suggest there may be an association between styrene exposure and an increased risk of leukemia and lymphoma, the evidence is generally inconclusive due to multiple chemical exposures and inadequate documentation of the levels and durations of exposure

## 2. HEALTH EFFECTS

to styrene. In a study of employees who worked in the development or production of styrene-based products, deaths due to malignant neoplasia were fewer than expected in the total study group (2,904 subjects) (Ott et al. 1980). An increase in lymphatic leukemia (4 observed deaths versus 0.5 expected) was observed in a group of employees exposed to polymer extrusion fumes, solvents, and colorants but was not found to be related to duration or level of exposure. A retrospective cohort mortality study was conducted for two styrene-butadiene rubber plants, designated as Plant A and Plant B (Meinhardt et al. 1982). Occupational history records were available from 1943 at Plant A and from 1950 at Plant B to the study end-date of March 31, 1976. No statistically significant excess in total or cause-specific mortality rates was observed for the overall worker population at either plant. Plant A workers had a statistically nonsignificant increase in leukemia and aleukemia. The mean concentrations of styrene, butadiene and benzene in Plant A were 0.94, 1.24, and 0.1 ppm, respectively, and in Plant B styrene and butadiene levels were 1.99 and 13.5 ppm, respectively. The presence of a known leukemogenic agent, benzene, obviously further confounded the study results with regard to styrene carcinogenicity. The authors concluded that the study findings suggested that the production and manufacture of styrene-butadiene rubber may be associated with an excess of lymphatic and hematopoietic neoplasms. In a study of 560 male employees of a styrene-polystyrene manufacturing plant who had at least 5 years of exposure, there were no significant increases in cause-specific mortality (Nicholson et al. 1978). The reported leukemia incidence suggested the need for further study. In another study, a statistically significant excess of lymphoma deaths in an exposed population (662 subjects) was reported, and 2 of the 3 deaths occurred in men less than 40 years of age who had been exposed for at least a year (Hodgson and Jones 1985). However, the lack of association with actual exposure levels or specific durations and the small number of observed deaths requires cautious interpretation. In a very large epidemiological study of nearly 16,000 workers in the styrene plastic industry, the death rate from leukemia was twice as high in areas of high exposure as in areas of low exposure (Wong 1990). However, there were too few cases for this to be statistically significant. Several other studies in humans have not detected any evidence of leukemia, lymphoma, or other cancers (Coggon et al. 1987; Okun et al. 1985; Matanoski and Schwartz 1987). The International Agency for Research on Cancer (IARC) has concluded that the evidence for carcinogenicity in humans from epidemiological studies is inadequate and classifies styrene in Group 2B, possibly carcinogenic to humans (IARC 1987). EPA agreed that results of epidemiological studies were confounded by multiple chemical exposures and considered the epidemiological evidence inadequate to determine potential human carcinogenicity of styrene (EPA 1988b).

Three chronic animal inhalation studies (Conti et al. 1988; Jersey et al. 1978; Maltoni et al. 1982) have been conducted to evaluate the carcinogenicity of styrene. These studies have produced variable results. Groups of 85 male and 85 female rats were exposed to 600 or 1,200 ppm styrene (99.5% purity) for 6 hours/day, 5 days/week for 18-20 months (Jersey et al. 1978). The concentration in the high-dose group was decreased to 1,000 ppm due to decreased weight gains in male rats. The incidence of mammary

## 2. HEALTH EFFECTS

adenocarcinomas in the 600 ppm female group was significantly higher than in controls. However, there was no significant response evident at 1,000 ppm, and the control rats had an unusually low mammary adenocarcinoma incidence when compared with historical controls. In the same study, the incidence of lymphosarcomas and leukemia in females was identical for both exposed groups at 5.27% and 1.04%, respectively. These values were not statistically higher than the respective values of concurrent control animals, but were significant when compared to historical control data. However, there was an absence of dose response. A high incidence of chronic murine pneumonia in these rats makes a complete evaluation of the data difficult and the results uncertain.

In a second study, designed to determine if styrene would induce brain tumors, groups of 40 male and 40 female rats were exposed to 0, 25, 50, 100, 200, and 300 ppm styrene for 52 weeks (Maltoni et al. 1982). There was no increased incidence of brain tumors in any of the exposed groups of rats. In a third study (performed by the same group as the second study), 30 male and 30 female rats were exposed to 25, 50, 100, 200, or 300 ppm styrene for 52 weeks (Conti et al. 1988). A higher incidence of total malignant tumors in the group exposed to 100 ppm styrene was observed. The increased incidence was not due to any specific type of tumor. However, the higher incidence of total malignant tumors in the 100 ppm styrene-exposed group was not dose related since the 200 and 300 ppm groups did not have significantly higher total malignant tumor incidences. A higher incidence of malignant and total (benign plus malignant) mammary tumors was observed in females of all the groups exposed to styrene. Although the authors did not report tests for statistical significance or levels of significance, the data provided in tabular form clearly indicate a dose trend of increased incidence of combined benign and malignant mammary tumors. Although statistical methods are not provided, the data reported indicate that statistical significance may be marginal at the two lower doses (25 and 50 ppm) and significant at 100 ppm and above.

### 2.2.2 Oral Exposure

No studies were located regarding health effects in humans after oral ingestion of styrene. Based on the animal data that follow, the oral toxicity of styrene in humans would be expected to be low to moderate.

#### 2.2.2.1 Death

No deaths in humans from ingesting styrene have been reported in the evaluations of case studies (EPA 1989c; Gosselin et al. 1984; NIOSH 1983).

The approximate reported oral LD<sub>50</sub> for male and female rats was 5,000 mg/kg (Wolf et al. 1956). A 100% survival rate and 100% mortality rate were reported in rats exposed to single oral doses of styrene (observation period 2 weeks) at 1,600 and 8,000 mg/kg, respectively (Spencer et al. 1942). Death in this study was mainly due to pronounced irritation of the esophagus and stomach. In another study, female mice were given a single oral dose of 1,350 mg/kg styrene on the 17th day of pregnancy (Ponomarev and Tomatis

## 2. HEALTH EFFECTS

1978). After weaning, the progeny received the same dose once per week. The treatment was suspended after 16 weeks due to high mortality among the progeny (including both males and females). Fifty percent of the males and 20% of the females had died after 20 weeks, despite the suspension of treatment at week 16. The cause of death was liver necrosis and lung congestion. A high mortality rate (number not specified) was reported in 40 female rats exposed to 250 mg/kg/day styrene for 52 weeks (Conti et al. 1988). Mortality was significantly elevated in male and female rats administered styrene by gavage at a dosage level of 2,000 mg/kg/day for 78 weeks (NC1 1979b). In this study, mortality was unaffected at dosage levels of 500 and 1,000 mg/kg/day in male and female rats. Male mice administered styrene at doses of 150 or 300 mg/kg/day for 78 weeks showed increased mortality; however, the female mice did not.

The highest reliable LOAEL values and LD<sub>50's</sub> values in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or dermal/ocular effects in humans or animals after oral exposure to styrene.

For the following systemic effects resulting from oral exposure to styrene, the highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

**Respiratory Effects.** No studies were located regarding respiratory effects in humans after oral exposure to styrene.

Severe lung congestion was observed in mice that were the offspring of dams given a single oral dose of styrene at 1,350 mg/kg on the 17th day of gestation and that continued to receive the same dose once per week after weaning (Ponomarkov and Tomatis 1978). The lung congestion was noted following continuous administration of the styrene for 16 weeks.

**Hematological Effects.** No studies were located regarding hematological effects in humans after oral exposure to styrene.

Male and female purebred beagle dogs were exposed to 0, 200, 400, or 600 mg/kg/day styrene by gavage for up to 561 days (Quast et al. 1979). Treatment with styrene was stopped on day 316 in the 600 mg/kg/day group and resumed on day 470 for 90 additional days to investigate the reversibility of any effects. There were only minimal toxicological changes. Intraerythrocytic Heinz bodies were regularly detected in a dose-related manner in males and females in the 400 and 600 mg/kg/day groups and sporadically in females in the 200 mg/kg/day group. There were occasional decreased red blood

TABLE 2-2. Levels of Significant Exposure to Styrene - Oral

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	1 d		1600		8000 (100% lethality)	Spencer et al. 1942
2	Rat	(GO)	1 d				5000 (LD50)	Wolf et al. 1956
Systemic								
3	Rat	(GO)	7 d 1x/d	Renal		900 (decreased glutathione content)		Das et al. 1983
4	Rat	(GO)	7 d 1x/d	Hepatic		900 (decreased glutathione content)		Das et al. 1981
Neurological								
5	Rat	(GO)	7 d 1x/d		270	450 (inhibition of glutathione-S-transferase, glutathione depletion)		Dixit et al. 1982
6	Rat	(GO)	14 d 1x/d		100	200 (increased serotonin levels in several brain sections)		Husain et al. 1985
Developmental								
7	Rat	(GW)	10 d 1x/d		300			Murray et al. 1978

TABLE 2-2 (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive								
8	Rat	(GW)	10 d 1x/d		300	(35% decreased weight gain on days 6-9 of gestation, reduced food consumption)		Murray et al. 1978
INTERMEDIATE EXPOSURE								
Death								
9	Mouse	(GO)	16 wk 1x/wk				1350 (50% of males and 20% of females dead 4 weeks after treatment suspended)	Ponomarkov and Tomatis 1978
Systemic								
10	Rat	(GO)	100 d 6d/wk 1x/d	Hepatic	200 <sup>b</sup>	(changes in mitochondrial and microsomal enzymes)	400 (small areas of necrosis with degenerated hepatocytes and inflammatory cells)	Srivastava et al. 1982
11	Rat		6 mo 5d/wk	Hepatic	133	400 (increased liver weight)		Wolf et al. 1956
				Renal	133	400 (increased kidney weight)		
12	Mouse	(GO)	16 wk 1d/wk	Resp			1350 (severe lung congestion)	Ponomarkov and Tomatis 1978
Neurological								
13	Rat	(GO)	90 d 1x/d		200	(increased spiroperidol binding to brain membranes)		Agrawal et al. 1982

TABLE 2-2 (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive								
14	Rat	(GO)	60 d 6d/wk 1x/d		200		400 (decreased spermatozoa, tubular degeneration)	Srivastava et al. 1989
15	Rat	(W)	90 d (cont)		35			Beliles et al. 1985
Cancer								
16	Mouse	(GO)	16 wk 1d/wk				1350 CEL (lung tumors)	Ponomarkov and Tomatis 1978
CHRONIC EXPOSURE								
Death								
17	Rat	(GO)	78 wk 5d/wk 1x/d				2000 (decreased survival in males and females)	NCI 1979b
Systemic								
18	Rat	(W)	105 wk 7d/wk	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other	21 21 21 21 21 21 21 21			Beliles 1985
19	Dog	(GO)	561 d 1x/d	Hemato	200	400 (Heinz body formation)		Quast et al. 1979

TABLE 2-2 (Continued)

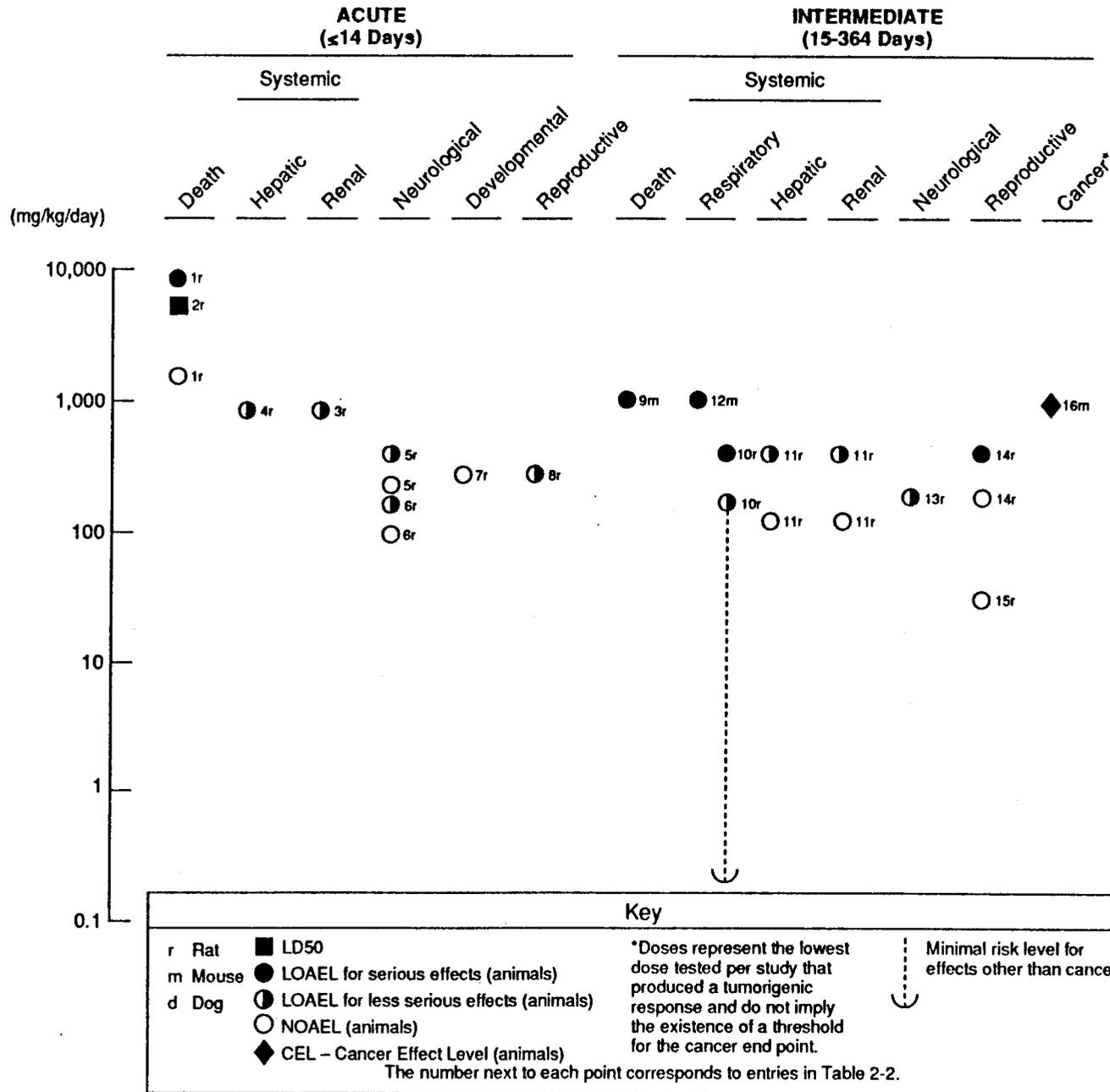
Key to figure*	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Cancer								
20	Mouse	(GO)	78 wk 5d/wk 1x/d				300 CEL (lung tumors)	NCI 1979b

\*The number corresponds to entries in Figure 2-2.

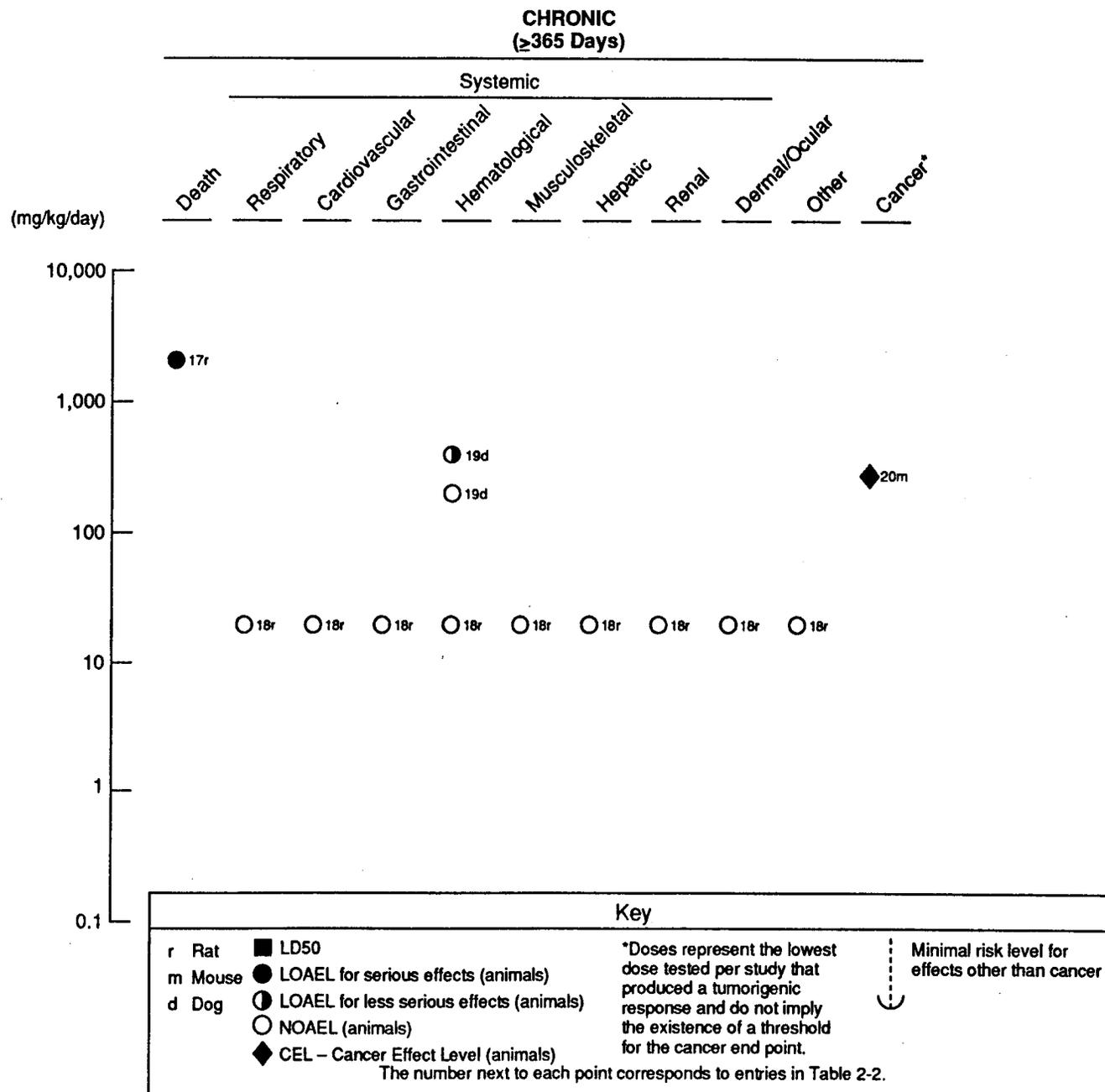
<sup>b</sup>Used to derive an intermediate oral minimal risk level (MRL) of 0.2 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 10 for human variability and 6/7 for less than continuous exposure).

Cardio = cardiovascular; CEL = cancer effect level; cont = continuous; d = day(s); Derm/oc = dermal/ocular;  
 Gastro = gastrointestinal; (GO) = gavage - oil; (GW) = gavage - water; Hemato = hematological; LD50 = lethal dose, 50% kill;  
 LOAEL = lowest-observed-adverse-effect level; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect  
 level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

**FIGURE 2-2. Levels of Significant Exposure to Styrene – Oral**



**FIGURE 2-2. (Continued)**



## 2. HEALTH EFFECTS

cell counts, hemoglobin levels and erythrocyte sedimentation rates in males and females in the 600 mg/kg/day groups. Increased hemosiderin deposits and intranuclear inclusions in liver were noted in animals dosed with 600 mg/kg/day. This was probably secondary to the effects on the red blood cells. The formation of intra-erythrocytic Heinz bodies was readily reversible upon discontinuing the administration of styrene in the 600 mg/kg/day group.

**Hepatic Effects.** No studies were located regarding hepatic effects in humans after oral exposure to styrene.

Hepatic glutathione content was reduced in rats orally administered 900 mg/kg styrene for 7 consecutive days (Das et al. 1981). In male rats that received 200 or 400 mg/kg/day styrene by gavage for 100 days, changes in mitochondrial and microsomal enzymes were observed at both doses. In addition to elevated enzyme activity, small areas of focal necrosis were noted in rats administered 400 mg/kg/day indicating a dose-response trend. In another study, growth depression and increased liver weight (general indicators of toxicity) were noted in rats orally administered 400 and 667 mg/kg/day styrene for 6 months (Wolf et al. 1956). As noted above, increased numbers of hemosiderin deposits and intranuclear crystalline inclusions were reported in the hepatocytes of dogs orally administered 600 mg/kg/day of styrene by gavage for 316 days (Quast et al. 1979). This was presumably secondary to Heinz body formation, and no other hepatic histological effects were in this study. The LOEL of 200 mg/kg/day for enzyme level changes in rats (Srivastava et al. 1982) was selected as the basis for an oral intermediate MRL of 0.2 mg/kg/day. This MRL value is supported by the study by Wolf et al. (1956) in which a LOEL of 400 mg/kg/day and a NOAEL of 133 mg/kg/day were reported. Additional support comes from other intermediate oral studies in which renal, neurological, and reproductive effects have been observed at or near the critical LOEL (Agrawal et al. 1982; Srivastava et al. 1989; Wolf et al. 1956).

**Renal Effects.** No studies were located regarding renal effects in humans after oral exposure to styrene.

A decrease in renal glutathione content and decreased glutathione-transferase activity was noted in rats orally administered 900 mg/kg styrene for 7 days (Das et al. 1983). This was similar to a reduction in the activity of these enzymes that was seen in hepatic tissue (Srivastava et al. 1982). Growth depression and increased kidney weight were reported in female rats orally administered 400 and 667 mg/kg/day of styrene for 6 months (Wolf et al. 1956). Histopathological examination of kidney tissue showed no abnormalities. Elevated levels of serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were observed at 667 mg/kg/day. Dose-dependent increases of the cytochrome 450-dependent enzymes, benzo[a]pyrene hydroxylase and aminopyrine-N-demethylase were also observed. In another study, female rats and **mice** were exposed to 1,350 mg/kg/day of styrene on the 17th day of gestation. The offspring were also administered styrene, by gavage, at the following doses: rats, 500 mg/kg/day; O<sub>20</sub> mice, 1,350 mg/kg/day; and C57B1

## 2. HEALTH EFFECTS

mice, 300 mg/kg/day. Treatment was weekly for 120 weeks. Hyperplasia of the kidney pelvis epithelium was frequently reported in the offspring of the rats but not in the mice (Ponomarkov and Tomatis 1978).

### 2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to styrene.

The World Health Organization (WHO 1983) reviewed a Russian study (Sinitskij 1969) in which styrene was fed to 36 rabbits at doses of 250 mg/kg for 58 days, 5 mg/kg for 216 days, and 0.5 mg/kg for 202 days. Impairment of the immunological defense system was indicated by a nearly total suppression of leukocyte phagocytic activity. Although no statistical analysis was provided, the data showed a dose-response relationship for both the severity of the effect and the time of onset.

### 2.2.2.4 Neurological Effects

Although it is not clear if oral administration of styrene causes neurological effects in humans, the following animal studies support, in part, a biochemical basis for neurological effects of inhaled styrene.

It has been suggested that exposure of rats to styrene alters the biotransformation capacity of the brain dependent on glutathione content (Dixit et al. 1982). Significant inhibition of aryl hydrocarbon hydroxylase and glutathione-S-transferase activity followed by glutathione depletion was observed in rats exposed to styrene at 450 and 900 mg/kg/day for 7 days (Dixit et al. 1982). Oral intubation of male rats with styrene (94 mg/kg/day) for 15 days resulted in increased serotonin and noradrenalin levels in brain tissue (Husain et al. 1980).

Behavioral effects were observed by Husain et al. (1985) in rats exposed to styrene at 100 or 200 mg/kg/day for 14 days. Styrene significantly increased the mean percent avoidance response (learning) but no definite doseresponse relationship was evident. Conditioned stimuli, consisting of the sound of a buzzer and turning on light in the test chamber were used during an induced pole climbing task. The unconditioned stimulus was electric shock. Serotonin levels in hippocampus, hypothalamus, and mid-brain were raised at the 200 mg/kg/day styrene exposure. The study results indicate that elevated serotonin levels may account for the increased avoidance response.

In another study, styrene was administered to rats at doses of 200 or 400 mg/kg/day for up to 90 days. A significant increase in specific binding of <sup>3</sup>H-spiroperidol to the striatal membranes of the brain 24 hours after the last dose was observed (Agrawal et al. 1982). The data suggested that styrene altered the sensitivity of the dopamine receptors. Other neurotoxic chemicals such as acrylamide and manganese also are known to involve the dopaminergic system (Ali et al. 1983; ATSDR 1990).

## 2. HEALTH EFFECTS

The highest NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to styrene.

No teratological effects were observed in the offspring of rats given oral doses of either 180 or 300 mg/kg/day styrene during gestation (Murray et al. 1978).

The highest NOAEL value for developmental effects is recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to styrene.

Exposure of pregnant rats to 180 or 300 mg/kg/day of styrene on days 6-15 of gestation resulted in no significant effects on maternal mortality or percent pregnancy (Murray et al. 1978). However, a 35% decrease in maternal weight gain was observed in the 300 mg/kg/day group during days 6-9 of gestation.

A three-generation reproduction study (Beliles et al. 1985) was conducted in which rats were maintained on styrene-treated drinking water for 2 years (7.7-21 mg/kg/day). The styrene-treated rats had no treatment-related changes, including mortality patterns. There was no evidence of adverse reproductive performance related to exposure to styrene. The only finding was that styrene-treated rats exhibited reduced water consumption due to poor palatability. In another study, styrene was administered by gavage to adult male rats for 60 days (Srivastava et al. 1989). At the high dose of 400 mg/kg/day, the activities of some marker enzymes for testicular function were significantly altered and there was a decrease in spermatozoa count. Histopathological examination revealed degeneration of seminiferous tubules and lumina devoid of sperm. The study results indicate that the male reproductive system may be sensitive to styrene exposure.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in rats in the acute and intermediate duration categories are recorded in Table 2-2 and plotted in Figure 2-2.

### 2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to styrene.

## 2. HEALTH EFFECTS

The capacity for orally administered styrene to induce chromosomal aberrations in animals was studied by Sbrana et al. (1983). No mouse bone marrow cell chromosomal aberrations were detected after a 0-day treatment with 500 mg/kg/day or a 70-day exposure to 200 mg/kg/day. In a 3-generation reproduction study, no cytogenetic effects were noted in the bone marrow of pups born to rats that received styrene in their drinking water at doses of 125 or 250 ppm for approximately 90 days before mating (Beliles et al. 1985).

Other genotoxicity studies are discussed in Section 2.4.

### 2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to styrene.

Investigations of the carcinogenic potential of styrene in animals after oral exposure have yielded variable results. Studies were conducted in which 29 female O<sub>20</sub> mice (1,350 mg/kg), 15 female C57Bl mice (300 mg/kg), and 21 female BDIV rats (1,350 mg/kg) received styrene, by gavage administration, on day 17 of gestation (Ponomarkov and Tomatis 1978). The offspring of the C57Bl mice and BDIV rats were treated with styrene for life. The O<sub>20</sub> mice offspring were only treated for 16 weeks due to excessive mortality from toxic effects. The weekly doses used for offspring were 1,350 mg/kg for O<sub>20</sub> mice, 300 mg/kg for C57Bl mice, and 500 mg/kg for BDIV rats. After 100 weeks, the oral administration of styrene resulted in an increased incidence of lung tumors in male and female O<sub>20</sub> mice compared to olive oil controls. An increased incidence of liver tumors was reported in styrene-treated C57Bl mice (12%) as compared to controls (3%), although this was not a statistically significant increase. There were no statistically significant increases in tumor incidences in the styrene-exposed BDIV rats. However, a few rare tumors were observed in styrene-exposed rats including stomach tumors and neurinomas of the heart and intestine. These results provide only weak evidence of the carcinogenicity of styrene in the O<sub>20</sub> and C57Bl mice.

The carcinogenic potential of styrene was evaluated in male and female Fischer 344 rats (500, 1,000, and 2,000 mg/kg/day) and B6C3F1 mice (300 and 150 mg/kg/day) (NC1 1979b). In male mice, there was a significant positive association between styrene dosage and the combined incidence of adenomas and carcinomas of the lung. However, the statistical significance of this result may have been due to an unusually low tumor incidence in the concurrent controls, since the results were not statistically significant when compared to historical controls from the same laboratory. No association was detected between styrene exposure and tumor incidence in female mice or in rats. The NC1 concluded that, while there was suggestive evidence for carcinogenicity in male mice, overall the results were not convincing for carcinogenicity in either rats or mice.

Styrene was also evaluated for its chronic toxicity and carcinogenic potential in male and female Sprague-Dawley and Wistar rats administered the chemical in the drinking water for 105 weeks (Beliles et al. 1985). The doses

## 2. HEALTH EFFECTS

were 17.5 and 35 mg/kg/day. There was some difficulty in maintaining the styrene level in the drinking water; the levels averaged 89.8% for the low level and 88.5% for the high level. Although there were incidental findings (e.g. ocular opacity) in both test and control rats, there were no gross pathological findings at the 52-week interim kill or terminal necropsy which were associated with the chronic administration of styrene. Likewise, there were no histopathological findings. The authors concluded that there was no evidence of carcinogenicity under the conditions of the study.

The potential for styrene to induce brain tumors was evaluated in Sprague-Dawley rats exposed for 52 weeks to 50 or 250 mg/kg/day styrene (Maltoni et al. 1982). The tumor incidence was not significantly different in exposed rats versus vehicle or historical controls. Similarly, in a 2-year study, no brain tumors were observed in male or female rats administered styrene at levels of 125 and 250 ppm in their drinking water (Beliles et al. 1985). In another study, the carcinogenic potential of styrene was investigated in Sprague-Dawley rats exposed to 50 or 250 mg/kg styrene for 52 weeks (Conti et al. 1988). The results of this study were also negative. However, due to a higher mortality rate, a lower incidence of total benign and malignant tumors and total mammary tumors was observed in rats at the highest (250 mg/kg/day) dose.

The International Agency for Research on Cancer (IARC) has concluded that evidence for styrene carcinogenicity in humans is inadequate, while evidence for carcinogenicity of styrene in animals is limited (IARC 1987). Using the lung tumor incidence of B6C3F1 mice (NC1 1979b) and appropriate dose conversions, the EPA (1988b) calculated a slope factor (potency factor or  $q_1^*$ ) of  $0.03 \text{ (mg/kg/day)}^{-1}$ . EPA has requested public comment on the EPA group cancer classification of styrene for regulation under the Safe Drinking Water Act (EPA 1989b). The EPA has proposed the possibility of classification in Group B2 (Probable Human Carcinogen) or Group C (Possible Human Carcinogen).

### 2.2.3 Dermal Exposure

No studies were located regarding health effects in humans after dermal exposure to styrene.

#### 2.2.3.1 Death

No studies were located regarding lethality in humans or animals after dermal exposure to styrene.

#### 2.2.3.2 Systemic Effects

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

**Dermal/Ocular Effects.** Marked irritation with denaturation of the skin was noted when styrene was applied in small amounts over a 4 week period to

## 2. HEALTH EFFECTS

the shaved abdomen of rabbits at 20,000 mg/kg (total dose) (Spencer et al. 1942). This study is summarized in Table 2-3. In another study, moderate conjunctival irritation and transient corneal injury of the eyes were observed when undiluted styrene was tested in rabbit eyes (Wolf et al. 1956). The effects were produced immediately (within 3 minutes) by a single administration of two drops (about 0.1 mL) and persisted throughout the 7-day observation period.

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

### **2.2.3.3 Immunological Effects**

### **2.2.3.4 Neurological Effects**

### **2.2.3.5 Developmental Effects**

### **2.2.3.6 Reproductive Effects**

### **2.2.3.7 Genotoxic Effects**

Genotoxicity studies are discussed in Section 2.4.

### **2.2.3.8 Cancer**

No studies were located regarding cancer affects in humans or animals after dermal exposure to styrene.

## **2.3 TOXICOKINETICS**

### **2.3.1 Absorption**

#### **2.3.1.1 Inhalation Exposure**

The uptake of styrene following inhalation exposure in humans and animals is rapid (Ramsey and Anderson 1984; Ramsey and Young 1978; Ramsey et al. 1980; Withey and Collins 1979; Withey and Karpinski 1985). Pulmonary retention of inhaled styrene in humans is approximately 2/3 of the administered concentrations (Engstrom et al. 1978a, 1978b). For example, male human subjects were exposed to styrene in inspired air during 30 minute rest and three 30-minute work periods on a bicycle ergometer. The mean uptake was approximately 63% (range was 59%-70%) of the amount of inspired styrene. Exposures of rats to styrene concentrations of from 50 to 2,000 ppm for 5 hours yielded blood uptakes which showed a continued and increasing rapid absorption, proportional to the styrene air level (Withey and Collins 1979). Plateau levels of styrene in rats' blood were reached within 6-8 hours during exposures ranging from 80 to 1,200 ppm styrene for up to 24 hours (Ramsey and Young 1978). Physiologically-based inhalation pharmacokinetic models indicate that styrene metabolism becomes saturated at inhaled levels above 200 ppm in mice, rats, and humans (Ramsey and Andersen 1984). When inhaled concentrations are below 200 ppm, the ratio of styrene concentration in the blood to inhaled air is moderated by perfusion-limited metabolism rather than blood:air partition coefficients.

TABLE 2-3. Levels of Significant Exposure to Styrene - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference
				Less serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rabbit	1 d	Derm/oc		0.1 mL (moderate conjunctival irritation, transient corneal injury)		Wolf et al. 1956
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit	4 wk	Derm/oc		20 g/kg (total) irritation with blistering, hair loss)		Spencer et al. 1942

d = day(s); Derm/oc = dermal/ocular; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

## 2. HEALTH EFFECTS

### 2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to styrene.

The absorption of styrene from the gastrointestinal tract was rapid and complete in rats deprived of food overnight and given styrene by gavage at a total dose of 3.147 mg styrene in 10 mL aqueous solution. A peak blood level of 6 µg/mL was reached in a few minutes. There was a much slower uptake of the styrene administered in vegetable oil (Withey 1976). Styrene administered in vegetable oil at a total dose of 32.61 mg produced a peak level of 12 µg/mL. This was reached at about 100 minutes (Withey 1976).

### 2.3.1.3 Dermal Exposure

Limited data indicate that absorption of styrene via the dermal route is probably low compared to absorption via other routes. When liquid styrene was applied to the forearms of male subjects, the absorption rate was estimated to be 9-15 mg/cm<sup>2</sup>/hour (Dutkiewicz and Tyras 1968). By contrast, the rate of absorption through human skin was very low (1±0.5 µg/cm<sup>2</sup>/min) in subjects who dipped one hand into liquid styrene (Berode et al. 1985). It is believed that the higher absorption rate reported by Dutkiewicz and Tyras (1968) also included the disappearance rate of the solvent from the surface of the skin (Guillemin and Berode 1988). Riihimaki and Pfaffli (1978) demonstrated that in humans, dermal exposure to moderate concentrations of styrene vapor (300 and 600 ppm) resulted in percutaneous penetration corresponding to approximately 0.1%-2% of the amount estimated to be absorbed from the respiratory tract.

Although absorption of styrene applied to the abdomen of rabbits was reported, there was no information on absorption rates (Spencer et al. 1942).

## 2.3.2 Distribution

### 2.3.2.1 Inhalation Exposure

Inhalation studies in both humans and animals resulted in the widespread distribution of styrene with the highest concentration in adipose tissue.

Three humans were exposed to 8-20 ppm styrene which resulted in a mean daily uptake of 193-558 mg styrene (Engstrom et al. 1978b). The concentration of styrene in adipose tissue was 2.8-8.1 mg/kg at the beginning of the week and 4.7-11.6 mg/kg at the end of the week. The authors estimated the half-life of styrene in the subcutaneous fat of man to be about 72 hours. Subsequent studies by this author confirmed this estimate and reported the half-life of styrene in adipose tissue to be 24-96 hours (Engstrom et al. 1978a).

## 2. HEALTH EFFECTS

Fiberglass factory workers exposed to greater than 215 mg/m<sup>3</sup> of styrene for 8-hour work shifts had blood styrene levels which ranged from 120-684 µg /L at the end of the shift (Apostoli et al. 1983). The concentrations of urinary MA and phenylglyoxilic acid (PGA) were 133-2,100 and 107-685 mg/L, respectively. These levels were also determined at the end of the work-shift. Distribution of styrene was also studied in adult men exposed to about 300 mg/m<sup>3</sup> of styrene for 2 hours during light physical exercise (Wigaeus et al. 1983). Blood styrene reached a level of approximately 20 µmol/l after 75 minutes. The concentrations of styrene in adipose tissue was about 50 µmol/kg after 30-90 minutes of exposure.

Rats were exposed for 5 hours to styrene at concentrations ranging from 50 to 2,000 ppm (Withey and Collins 1979). Tissue concentrations of styrene in the heart, liver, lung, kidney, spleen, brain, and perirenal fat demonstrated different patterns of distribution as the dose increased. The styrene concentration in perirenal fat was 10 times greater than in other organs. The largest amounts of styrene were found in the subcutaneous fat of male rats exposed to about 45 ppm of radioactively labeled styrene in the inspired air for 1-8 hours (Carlsson 1981). The concentration increased steadily during the first 4 hours of exposure. Styrene concentrations in brain tissue and muscles were about 70% of the arterial blood value. Other investigators (Ramsey and Anderson 1984; Ramsey and Young 1978; Savolainen and Pfaffli 1978; Withey 1976) demonstrated that higher levels of styrene in adipose tissue increase with higher exposures to styrene. Styrene was found to distribute to the fetuses of pregnant rats after inhalation exposure, but at concentrations much lower than those measured in maternal organs and tissues (Withey and Karpinski 1985).

### 2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to styrene.

An oral dose of 20 mg/kg of <sup>14</sup>C styrene was administered to male and female rats (Plotnick and Weigel 1979). Tissue levels peaked at 4 hours or earlier after dosing. Less than 10% of the administered dose was found in the stomach, small intestine, and large intestine 8 hours after dosing. The kidney had the highest concentration of radioactivity at all time intervals, with decreasing amounts in the liver and pancreas. Fat tissue showed increased levels after 2 hours. All tissue levels were below 1 µg /g at 24 hours and at 48 and 72 hours were below the limit of detection. Excretion data from the Plotnick and Weigel (1979) study are presented in Section 2.3.4.2.

### 2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to styrene.

## 2. HEALTH EFFECTS

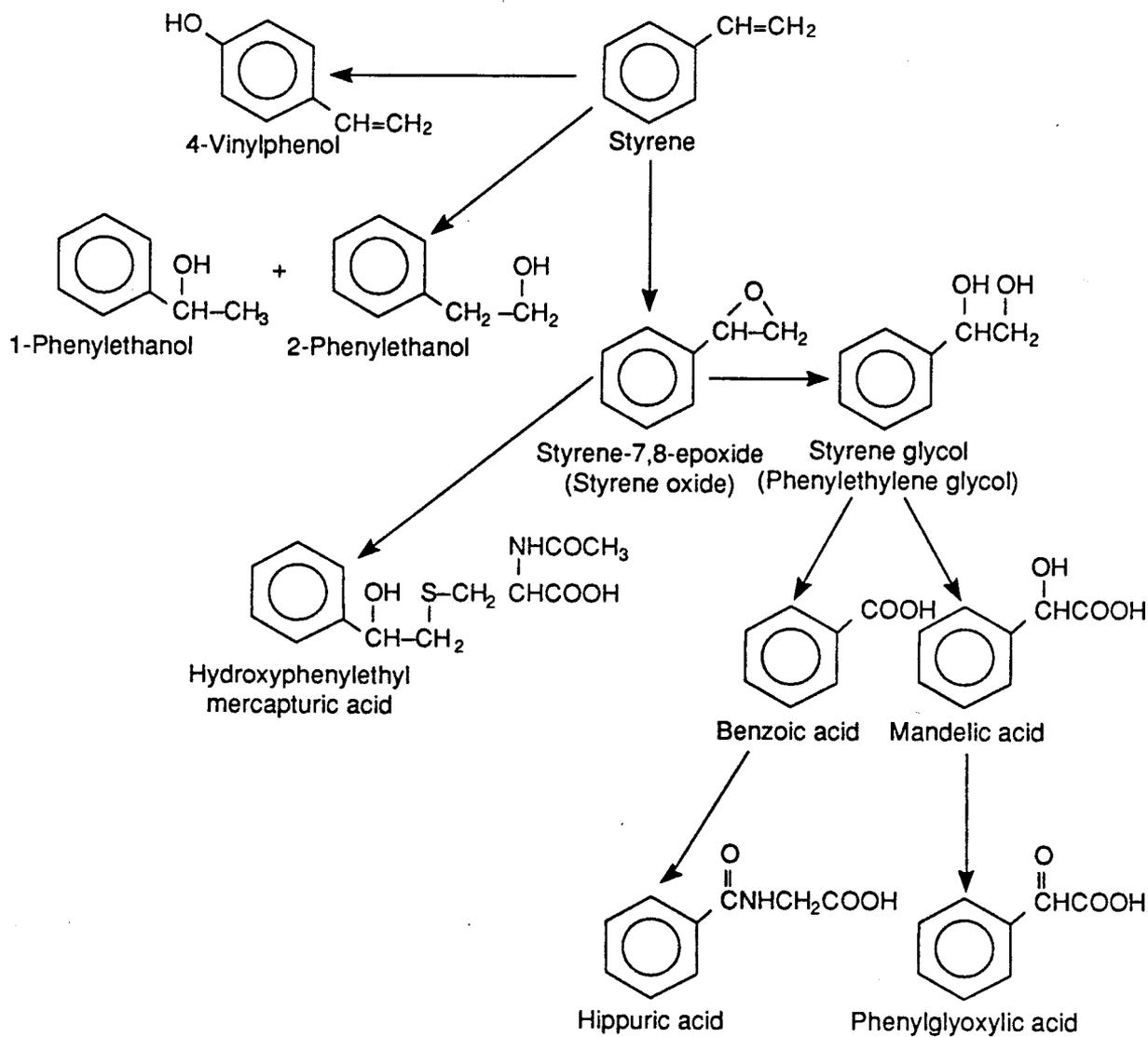
One animal study involved immersion of rats' tails in pure liquid styrene for 1 hour (Shugaev 1969). This procedure resulted in styrene levels in the liver and brain that were estimated to be between 50% and 70% of the concentrations found in the same organs after 4-hour inhalation exposure to a vapor concentration of 11.8 g/m<sup>3</sup>.

### 2.3.3 Metabolism

There have been numerous studies, conducted primarily via inhalation, that address the metabolism of styrene in humans and animals (Drummond et al. 1989; Engstrom et al. 1976; Korn et al. 1984; Korn et al. 1987; Leibman 1975; Lof et al. 1983; Withey and Collins 1979; Young et al. 1979). The proposed pathways of styrene metabolism are shown in Figure 2-3. Styrene is metabolized by the microsomal NADPH-cytochrome P-450 dependent mono-oxygenase to styrene oxide. The styrene oxide is then hydrated to phenylethylene glycol (styrene glycol). This transformation is catalyzed by microsomal epoxide hydratase. The styrene glycol is then metabolized directly to MA or to benzoic acid and then hippuric acid. Mandelic acid is also metabolized to PGA. The MA, hippuric acid and PGA are excreted in the urine. In another pathway, styrene oxide is metabolized by cystolic glutathione-S-transferase to mercapturic acids appearing in the urine as hydroxyphenylethyl mercapturic acid. A minor metabolic pathway of styrene in rats involves the formation of 1- and 2-phenylethanol and ring hydroxylation to form vinyl phenol as urinary metabolites. The presence of 4-vinylphenol has been reported in the urine of workers exposed to styrene, but this may have been due to the contamination of the styrene to which the subjects were exposed (Pfaffli et al. 1981). The urinary metabolites that predominate in humans are MA and PGA. In rats, the predominant urinary metabolites are MA, PGA, hippuric acid and glucuronide. Metabolic conversion to styrene-7,8-epoxide (styrene oxide) by the microsomal mixed function oxidase and epoxide hydratase from the liver and spleen of several rodent species has been demonstrated (Belvedere and Tursi 1981; Cantoni et al. 1978; Leibman 1975; Lof et al. 1984; Vainio et al. 1979). However, styrene oxide has only been found at low concentration, close to detection levels (0.02  $\mu$ mol/L), in the blood of workers exposed to styrene (Lof et al. 1986a). Mendrala et al. (1991) investigated the species differences in the in vitro hepatic metabolism of styrene. The results indicated that mice had the greatest capacity to produce styrene oxide, (highest styrene epoxidase activity), followed by rats and then humans. In addition, humans may have the highest capacity to metabolize styrene oxide to styrene glycol, since the human form of styrene oxide hydratase had the highest affinity (lowest Km) for styrene oxide. Assuming that styrene oxide is the metabolite responsible for styrene-induced toxicity (see, below), the results of this study indicate that care must be taken in extrapolation of data from animal studies to humans for risk assessment.

The formation of styrene oxide may be a key step in the carcinogenicity of styrene. Several studies indicate that styrene oxide is genotoxic (DeMeester et al. 1981; Vainio et al. 1976), and three studies in animals indicate that ingestion of styrene oxide leads to hyperplasia and neoplasia of

## 2. HEALTH EFFECTS

**FIGURE 2-3. Metabolic Pathways of Styrene\***

\*Adapted from Bond 1989; EPA 1988b; Leibman 1975

## 2. HEALTH EFFECTS

the stomach (Conti et al. 1988; Lijinsky 1986; Ponomarkov et al. 1984). The fact that tumors occurred in the stomach and were not detected in other tissues suggests that styrene oxide acts mainly at the point of contact. Thus, tissues most active in metabolizing styrene to styrene oxide might be most susceptible to the carcinogenic potential of styrene. Direct dermal application of styrene oxide did not cause a statistically significant increase in skin tumors in mice (Van Duuren et al. 1983).

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

Several studies have demonstrated that styrene is almost totally excreted as urinary metabolites in humans, and at higher doses, the elimination profile indicates saturation of metabolic excretion or processes (Ramsey and Young 1978; Ramsey et al. 1980). Most of the inhaled styrene is excreted in urine as MA and PGA. In a study of the excretion of styrene and its metabolites resulting from a 100-ppm/8-hour inhalation exposure, 2.6% of the total uptake was excreted as unchanged styrene in exhaled air (Guillemin and Berode 1988). The metabolites MA, PGA, and hippuric acid were excreted in the urine at 56.9%, 33% and 7.5% of the absorbed dose, respectively. In human volunteers exposed to 80 ppm styrene, it is cleared from the blood in a bi-phasic manner, indicating a two-compartment pharmacokinetic model. The half-lives for the rapid and slow clearance phases are 0.58 and 13.0 hours, respectively. The half-life of styrene in subcutaneous adipose tissue of humans is 2-4 days (Engstrom et al. 1978a). The quantities of the major metabolites of styrene in urine compared with the quantity of styrene eliminated unchanged in expired air indicated that approximately 97% is cleared by the metabolic route (Ramsey et al. 1980).

Another human inhalation study determined that between 59%-66% of inhaled styrene (50-200 ppm) was retained after a 4-8 hour exposure (Guillemin and Bauer 1979). Urinary elimination of MA was biphasic with a half-life for the first phase of 4 hours and for the second phase, 25 hours. These findings were comparable to those reported by Engstrom et al. (1976). The half-life of urinary elimination of PGA was determined to be 11 hours. This was regarded by the authors as being the first phase of elimination since MA is a precursor of PGA.

Styrene is almost totally excreted as urinary metabolites in animals. The blood elimination curve for rats is biphasic exponential at 80 and 200 ppm styrene over 6 hours. For exposures greater than 600 ppm exposure levels for (6 hours duration), a nonlinear blood elimination curve following Michaelis-Menten kinetics was observed. In going from 80 to 1,200 ppm (a 15-fold increase) the area under the blood concentration curves increases by 112-fold (Ramsey and Young 1978; Young et al. 1979). Rats exposed to 50-2,000 ppm styrene by inhalation for 5 hours exhibited a dose dependent biphasic pattern of elimination (Withey and Collins 1979).

## 2. HEALTH EFFECTS

### 2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to styrene.

Excretion of styrene was studied in the same rats for which there was good distribution data (Plotnick and Weigel 1979). Styrene was rapidly excreted in the urine with 90% of the dose detected in the urine within 24 hours of administration, Less than 2% of the dose was found in the feces. Detectable tissue levels were not found 48 and 72 hours after administration.

### 2.3.4.3 Dermal Exposure

In a study of the absorption of liquid styrene applied to the forearms of male volunteers, about 13% of the absorbed dose was excreted as MA (Dutkiewicz and Tyras 1968).

No studies were located regarding excretion in animals after dermal exposure to styrene.

## 2.4 RELEVANCE TO PUBLIC HEALTH

Illness or injury from exposure to styrene is most commonly reported among workers using styrene in the production of polystyrene plastics, protective coatings, polyester resins, and other products. Exposure of the general public to high levels of styrene in air from the home, in the urban environment, or around hazardous waste sites is unlikely, based on occurrence data. The most commonly reported adverse health effects from exposure to styrene include subjective symptoms of central nervous system depression and irritation of the eyes and upper respiratory tract. Oral or dermal exposure to styrene in significant amounts has not been commonly reported in the workplace or the general environment.

Studies in workers exposed to styrene in workplace air suggest that neurological effects are probably the most sensitive indicator of styrene toxicity. Available data do not provide a clear picture of the NOAEL for neurological effects following acute- or intermediate-duration inhalation exposure, but two chronic studies in workers identify LOAELs of 25 ppm (Mutti et al. 1984a) and 31 ppm (Harkonen et al. 1978). Based on the lower LOAEL (25 ppm), a chronic inhalation MRL of 0.06 ppm has been derived using factors of 8/24 and 5/7 to account for exposure 8 hours/day, 5 days/week, and an uncertainty factor of 100 (10 to account for human variability, and 10 to account for use of a LOAEL). Oral studies in animals suggest that hepatic effects may be the most sensitive indicator of toxicity (Srivastava et al. 1982). Based on a LOAEL of 200 mg/kg/day, an intermediate oral MRL of 0.2 mg/kg/day was derived. The LOAEL was multiplied by 6/7 to account for exposure occurring 6 days/week, and was then divided by an uncertainty factor of 1,000 (100 to account for intraspecies and interspecies extrapolation, and 10 to account for use of a LOAEL). Available data do not permit for the derivation of acute or chronic oral MRLs. Dermal MRLs were not derived for

## 2. HEALTH EFFECTS

styrene due to lack of dose-response data and lack of an appropriate methodology for the development of dermal MRLs.

**Death.** No deaths of humans have been reported after inhalation, oral or dermal exposure to styrene (EPA 1989c; NIOSH 1983). Although no deaths were reported in humans exposed to styrene by inhalation at concentrations in workplace air that exceeded 1,000 ppm (NIOSH 1983) or in laboratory studies at 800 ppm (Carpenter et al. 1944), these levels are severely irritating to the eyes, nose, and throat. Animal studies confirmed the relatively low to moderate acute toxicity following inhalation (Jaeger et al. 1974; Shugaev 1969; Spencer et al. 1942), oral (Ponomarkov and Tomatis 1978; Spencer et al. 1942; Wolf et al. 1956), and dermal (Spencer et al. 1942) exposures. Levels of styrene at hazardous waste sites (1-6 mg/m<sup>3</sup>) are orders of magnitude below the workplace levels, and oral exposure to significant levels from food or water is unlikely. However, the potential effects on human longevity of longterm inhalation or dermal exposure of humans to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

### **Systemic Effects.**

**Respiratory Effects.** Occupational and laboratory studies of humans have demonstrated that the most commonly reported immediate symptom after exposure to styrene is irritation of the mucous membranes of the nose and throat. The symptoms appeared when workers were exposed to styrene below 300 ppm for short-time periods (NIOSH 1983). Similarly, human volunteers exposed to 216 ppm for 20 minutes or 376 ppm for 1 hour developed the characteristic nasal irritation (Stewart et al. 1968). The effect has been confirmed in animal studies in which the styrene exposures were high (1,000 ppm) over a period of 3 weeks (Ohashi et al. 1986). Pathological changes of the respiratory mucosa of the rats were also observed. No respiratory effects have been seen in humans after oral exposure to styrene. Mice that were administered styrene one time per week at a dosage of 1,350 mg/kg/week for 6 weeks developed severe lung congestion. This single observation is difficult to correlate with other aspects of styrene toxicity. There are no reports of respiratory effects associated with dermal exposure of humans or animals to styrene. It appears that the respiratory system and the central nervous system are important target organs of styrene. However, the potential effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Hematological Effects.** No significant hematological effects have been reported in humans exposed to styrene. However, effects on erythrocytes were reported in dogs exposed to high doses of styrene (Quast et al. 1979). Increased numbers of Heinz bodies in the erythrocytes, decreased packed cell values and sporadic decreases in hemoglobin and erythrocyte counts were seen in dogs that received oral doses of 400 or 600 mg/kg/day by gavage for 560 days. No such effects were seen in dogs administered 200 mg/kg/day. The EPA has used the NOAEL of 200 mg/kg/day identified in this study to derive a chronic oral RfD of 0.2 mg/kg/day (IRIS 1991). However, the NOAEL for this

## 2. HEALTH EFFECTS

effect (200 mg/kg/day) is quite close to a chronic LOAEL for increased mortality (Conti et al. 1988), and is also close to doses that caused biochemical changes in the brain in several acute oral exposure studies in animals (Agrawal et al. 1982; Husain et al. 1985; Srivastava et al. 1982). Therefore, the true chronic oral NOAEL is judged to be sufficiently uncertain and no chronic oral MRL is derived. No studies were located that relate dermal exposure of humans or animals and hematological effects. However, based on experimental data that demonstrated eye, nose, and throat irritation are principal effects of styrene, it is unlikely that sufficient concentrations would be tolerated on the skin for a long enough time to accumulate and cause hematological effects. However, the potential effects on the blood and blood-forming organs of the body from long-term exposure of humans to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Hepatic Effects.** Evaluation of the potential adverse effects of styrene on the liver has resulted in mixed results in human and animal studies. The studies either involved occupational exposures of workers or inhalation and oral studies in animals. There are no studies relating dermal exposure and hepatic effects in humans or animals. Measurements to identify elevated serum enzyme levels in styrene-exposed workers have been inconclusive in determining if styrene causes a decrement in liver function (Harkonen et al. 1984; Hotz et al. 1980; Thiess and Friedheim 1978). Rodent inhalation studies have demonstrated that exposure to 300 ppm styrene for 11 weeks results in depletion of glutathione levels and an increase in the cytochrome P-450 content of liver cells (Vainio et al. 1979). A reduction in glutathione content was also seen in rats orally administered 900 mg/kg/day styrene for 7 days (Das et al. 1981). Similarly, increases in liver weights were noted in rats orally administered 400 and 667 mg/kg/day for 6 months (Wolf et al. 1956). Although the results of both human and animal studies are difficult to interpret, and their findings may be nonspecific, the enzyme and organ weight changes reported in these studies suggest that the liver must be regarded as an end point for the inhalation and oral routes of exposure. No changes in microsomal and mitochondrial liver enzymes were observed in rats receiving 200 or 400 mg/kg/day styrene by oral gavage (Srivastava et al. 1982). In addition, areas of focal necrosis were noted in animals administered the high dose, indicating a dose-response trend. Based on the LOAEL of 200 mg/kg/day (Srivastava et al. 1982) an intermediate oral MRL of 0.2 mg/kg/day has been derived. This MRL value is supported by the study by Wolfe et al. (1956) in which a LOAEL of 400 mg/kg/day and a NOAEL of 133 mg/kg/day were identified for hepatic effects. In addition, inhalation studies serve to indicate the liver as a target of styrene toxicity (Axelson and Gustavson 1978; Hotz et al. 1980; Jersey et al. 1978; Vaino et al. 1979). Other studies in the intermediate oral data base have reported renal, neurological, and reproductive effects at doses at or near the critical LOAEL (Agrawal et al. 1982; Srivastava et al. 1989; Wolf et al. 1956). The potential hepatic effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment, have not been evaluated.

## 2. HEALTH EFFECTS

**Renal Effects.** The potential for styrene to cause kidney toxicity has been evaluated in both humans and animals following inhalation exposures. There are no studies relating oral or dermal exposure and renal effects in humans or animals. Human studies generally confirm the importance of urinary enzymes as indicators of kidney damage due to occupational exposure to styrene (Aliberti and Severini 1987; Viau et al. 1987; Vyskocil et al. 1989). However, findings indicate only minor effects of styrene on some kidney enzyme functions. Similar evidence for styrene causing minor effects on the kidney is provided by animal studies involving both inhalation (Vainio et al. 1979; Viau et al. 1987) and oral (Das et al. 1983) exposures. The induction reported in the activity of these enzymes is similar to that seen in hepatic tissue. This may mean that the kidney is a potential end point for evaluation of the inhalation and oral routes of exposure. As with the liver, histopathological findings are lacking. The potential renal effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Immunological Effects.** Systemic immunological studies of styrene have not been conducted in humans or animals by the inhalation, oral, or dermal routes of exposure. However, there is limited information that suggests immunotoxicological concerns. For example, styrene has produced sensitizing reactions in humans. It has also been shown that styrene is apparently metabolized in the skin by aryl hydrocarbon hydroxylase to the more sensitizing epoxide (Sjoborg et al. 1984). Effects of styrene on lymphocyte chromosomes are discussed under "Genotoxic Effects" (below). Because of the association of dermal exposure and immunological reactions, the lack of data on styrene or its metabolites makes it difficult to reach conclusions about potential immunotoxicological concerns. Also, potential immunological effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Neurological Effects.** Epidemiological and clinical studies on workers have demonstrated that inhalation exposure to styrene may cause alterations of central nervous system function. The symptoms are typical of central nervous system depression, and appear to be the most sensitive end point for styrene exposure via the inhalation route (Kulig 1988; Pryor et al. 1987). High levels (800 ppm) produced immediate muscular weakness, listlessness, drowsiness, and impaired balance within minutes of exposure (Carpenter et al. 1944). Exposures to levels in the range of 50-200 ppm have resulted in a number of signs and symptoms, including impairment of balance and coordination, altered reaction times, sensory neuropathy, impaired manual dexterity, headaches, nausea, mood swings, malaise, and decrement in concentration (Cherry et al. 1980; Lindstrom et al. 1976; Mutti et al. 1984a; Rosen et al. 1978; Stewart et al. 1968). Exposure levels above 50 ppm were frequently encountered in the workplace in the past, but current regulations restrict workplace concentrations to less than 50 ppm (see Chapter 7). However, the study of Harkonen et al. (1978) indicates that some neurological effects, as evidenced by altered EEGs, occur at exposure levels as low as 31 ppm, and the study of Mutti et al. (1984a) indicates effects may occur at a

## 2. HEALTH EFFECTS

level of 25 ppm. Based on a LOAEL of 25 ppm from the Mutti et al. study, a chronic inhalation MEL of 0.06 ppm has been derived.

Less information is available on neurological effects following oral exposure to styrene. No data were located for humans, but studies in animals reveal that repeated oral exposure can lead to altered enzyme levels in brain (Dixit et al. 1982), increased brain levels of several neurotransmitters (serotonin, norepinephrine) (Husain et al. 1980), increased binding of spiroperidal to brain membranes (Agrawal et al. 1982), and increased avoidance response learning (Husain et al. 1985). Some of these responses are similar to those seen following inhalation exposure. For example, the increased spiroperidal binding noted in the oral study of Agrawal et al. (1982) might be due to the decreased dopamine levels noted in the inhalation study by Mutti et al. (1984). However, other effects do not always agree between oral and inhalation studies. For example, the increased levels of norepinephrine in brain reported by Husain et al. (1980) following oral exposure were not observed in rabbits following inhalation exposure (Mutti et al. 1984c). Similarly, the increased conditional response reported by Husain et al. (1985) following oral exposure was not observed in a study of rats exposed by inhalation (Pryor et al. 1987). These apparent differences in effect between routes might be the result of toxicokinetic differences between exposure routes, or might simply be the result of differing experimental designs (different species, doses, durations, end points).

The potential neurological effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated. No data are available concerning the neurological effects following dermal exposure to styrene in either humans or animals.

**Developmental Effects.** Evaluation of the potential developmental effects in occupationally exposed styrene workers suggests that styrene is not teratogenic in humans (Ahlborg et al. 1987). However, a single study (Lemasters et al. 1989) reported that women who work in high styrene exposure settings, such as laminators in fiberglass boat manufacturing companies, had offspring with a 4% lower birthweight than unexposed women. However, this effect was not statistically significant. The actual levels of styrene exposure were not adequately determined for the workers in either the Ahlborg or Lemasters studies. Further, interpretation of the data is complicated by the fact that the women were exposed to other chemicals in the workplace including thermal degradation products of styrene polymers. There are no studies of developmental effects in humans after oral or dermal exposure. Animal studies have produced mixed results. No fetotoxicity or teratogenicity was observed in rats or rabbits exposed via inhalation to either 300 or 600 ppm styrene (Murray et al. 1978). However, an increase in dead or resorbed fetuses was observed in mice exposed to 250 ppm and hamsters exposed to 1,000 ppm (Kankaanpaa et al. 1980). No teratogenic effects were observed in the mice and hamsters. Limited oral studies in rats and rabbits revealed no fetotoxicity or teratogenicity (Murray et al. 1978). There are no reports

## 2. HEALTH EFFECTS

of developmental effects after dermal exposure of animals to styrene. Based on the human and animal data and the low concentrations of styrene in air (1-6  $\mu\text{g}/\text{m}^3$ ) that have been reported at hazardous wastes sites, developmental effects should not be expected. However, potential developmental effects associated with long-term human exposure to the low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Reproductive Effects.** The results of some studies of occupationally exposed female workers in the plastics industry in which styrene is used have suggested an increased risk of spontaneous abortion (Hemminki et al. 1980). Other studies suggest no such increased risk (Lindbohm et al. 1985). Interpretation of these studies is difficult because small study populations were used and there were multiple chemical exposures in the workplace environment. There are no studies of reproductive effects in humans after oral or dermal exposure. Animal studies, either by the inhalation (Salomaa et al. 1985) or the oral route (Beliles et al. 1985; Murray et al. 1978), indicate that styrene is not a reproductive toxicant. However, male rats administered styrene by gavage for 60 days had altered testicular function at the high dose of 400 mg/kg/day (Srivastava et al. 1989). There are no reports of reproductive effects after dermal exposure of animals to styrene. The potential reproductive effects associated with long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Genotoxic Effects.** Styrene has been tested for genotoxic potential in a variety of systems, and the results have been mixed. Bacterial assays for gene mutation in the absence of activation have been negative, while studies with activation were positive in two out of six cases (see Table 2-4). The lack of evidence for styrene genotoxicity in bacteria may be due in part to volatilization of styrene from the test systems, or possibly to metabolism of styrene to nongenotoxic forms (Dunkel et al. 1985; Yoshikawa et al. 1980). Styrene has induced genotoxic effects in animals following intraperitoneal injection. Male mice were injected with single doses of styrene at levels of 250, 500, 1,000 or 1,500 mg/kg b.w. Significant increases in micronuclei of polychromatic erythrocytes were observed only at the 250 and 1,000 mg/kg levels, and nonsignificant increases were noted at the other two doses. In another study, styrene administered intraperitoneally to male mice at single doses of 177-1,051 mg/kg b.w. induced increases in single-strand breaks in DNA. This genotoxic effect observed in the kidney, liver, lung, testes, and brain 1 hour after administration and in all organs except the liver after 24 hours (Wallis and Orsen 1983).

Styrene production of chromosomal aberrations (breaks and gaps) in peripheral lymphocytes of workers in the styrene industry has been reported (Andersson et al. 1980; Hogstedt et al. 1979; Meretoja et al. 1977, 1978) (see Table 2-5). However, positive findings are limited by the fact that workers are often exposed to other chemicals besides styrene, and that aberrations also depend upon parameters such as age and smoking. On the other hand, negative studies (e.g., Thiess et al. 1980; Watanabe et al. 1981) may also be

TABLE 2-4. Genotoxicity of Styrene In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<u>Salmonella typhimurium</u> (2 strains, plate incorporation method)	Gene mutation	+	-	Vainio et al. 1976
<u>S. typhimurium</u> (3 strains, plate incorporation method)	Gene mutation	-	-	Vainio et al. 1976
<u>S. typhimurium</u> (3 strains, vapor exposure - desiccator test)	Gene mutation	+	-	DeMeester et al. 1981
<u>S. typhimurium</u> (4 strains, vapor exposure - desiccator test)	Gene mutation	-	-	DeMeester et al. 1981
<u>S. typhimurium</u> (5 strains, preincubation method)	Gene mutation	-	-	Dunkel et al. 1985
<u>Escherichia coli</u> (1 strain, preincubation method)	Gene mutation	-	-	Dunkel et al. 1985
Mammalian cells:				
Human lymphocytes	Sister chromatid exchange	No data	+	Norppa et al. 1983
Human lymphocytes	Chromosomal aberrations	No data	+	Jantunen et al. 1986

+ = positive result; - = negative result

TABLE 2-5. Genotoxicity of Styrene In Vivo

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human lymphocytes	Chromosomal aberrations	+	Meretoja et al. 1977
Human lymphocytes	Chromosomal aberrations	+	Meretoja et al. 1978
Human lymphocytes	Chromosomal aberrations	+	Hogstedt et al. 1979
Human lymphocytes	Chromosomal aberrations	-	Thiess et al. 1980
Mouse bone marrow, liver cells, and alveolar macrophages	Sister chromatid exchange	+	Conner et al. 1980
Human lymphocytes	Chromosomal aberrations	-	Andersson et al. 1980
	Sister chromatid exchange	+	
Human lymphocytes	Chromosomal aberrations	-	Watanabe et al. 1981
	Sister chromatid exchange	-	
Mouse bone marrow, polychromatic erythrocytes	Micronuclei	±	Norppa 1981
Mouse kidney, liver, lung, testes, and brain	DNA	+	Walles and Orsen 1983
Human lymphocytes	Unscheduled DNA synthesis	+	Pero et al. 1982
Mouse bone marrow	Chromosomal aberrations	-	Sbrana et al. 1983
Rat bone marrow	Chromosomal aberrations	-	Sinha et al. 1983
Human lymphocytes	Chromosomal aberrations	-	Nordenson and Beckman 1984
	Micronuclei	+	
Human lymphocytes	Chromosomal aberrations	-	Hansteen et al. 1984
	Sister chromatid exchange	-	
Human lymphocytes	Micronuclei	+	Hogstedt et al. 1983
Human lymphocytes	Chromosomal aberrations	-	Maki-Paakkanen 1987
	Sister chromatid exchange	-	
	Micronuclei	-	
Human lymphocytes	Chromosomal aberrations	-	Jablonicka et al. 1988

+ = positive result; - = negative result; DNA = deoxyribonucleic acid

## 2. HEALTH EFFECTS

due to the wide variability in aberration levels. Thus, evidence for styrene-induced chromosomal aberrations in humans is suggestive, but not conclusive. One inhalation study has been conducted in order to evaluate chromosome changes, and this was negative (Sinha et al. 1983). The results were also negative in two studies in which styrene was orally administered to mice (Sbrana et al. 1983) and rats (Beliles et al. 1985). Levels of styrene in air at hazardous waste sites ( $1-6 \mu\text{g} / \text{m}^3$ ) are not likely to cause genotoxicity regardless of the route or duration of exposure. However, potential genotoxic effects of long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not been evaluated.

**Cancer.** There are several epidemiologic studies of styrene workers that suggest an association between occupational exposure and an increased incidence of leukemia (Meinhardt et al. 1982; Nicholson et al. 1978; Ott et al. 1980) and lymphoma (Hodgson and Jones 1985). However, the reported studies are inconclusive due to exposure to multiple chemicals (including benzene) and the small size of the cohorts. Other studies have reported negative results (Coggon et al. 1987; Matanoski and Schwartz 1987; Okun et al. 1985). There are no reports of cancer resulting from styrene exposure by the oral or dermal routes in humans. It is, therefore, unknown if styrene causes cancer in humans.

Although animal evidence is limited, the results suggest that styrene is weakly carcinogenic in some strains of rats and mice. Overall, human and animal studies suggest that styrene may be a weak human carcinogen. This conclusion is supported by the presence of small amounts of the metabolite styrene oxide (a carcinogen and mutagen) in the blood of styrene industry workers (Lof et al. 1986a).

Three chronic inhalation studies have been conducted in which rats were exposed to styrene vapor (Conti et al. 1988; Jersey et al. 1978; Maltoni et al. 1982). In one study, there was an increased incidence of mammary adenocarcinomas in female rats at the low dose (600 ppm), but a significant response was not evident at the higher dose (1,200 ppm reduced to 1,000 ppm due to growth retardation) (Jersey et al. 1978). In another rat study, designed to detect an elevated incidence of brain tumors, the results were negative (Maltoni et al. 1982). The third inhalation study in rats reported a higher incidence of total (benign and malignant) mammary tumors and malignant mammary tumors in females (Conti et al. 1988).

Other studies have investigated the effects of styrene in animals after long-term oral exposure. In one study, styrene was administered to BD IV rats (500 mg/kg/day) and mice (1,350 mg/kg/day for O<sub>20</sub> strain and 300 mg/kg/day for C57Bl strain) for 100 days. There was an increased incidence of lung tumors in the O<sub>20</sub> strain of mice (Ponomarkov and Tomatis 1978). In another study (NC1 1979b), rats and mice were given styrene for a lifetime. In male mice, there was a significant increase in the combined incidences of adenomas and carcinomas of the lung. However, this was significant only when compared to concurrent controls but not compared to historical controls from the same laboratory. Another study (Maltoni et al. 1982) did not detect an increased

## 2. HEALTH EFFECTS

incidence of brain tumors in rats. A more recent study to evaluate the carcinogenicity of styrene via the oral route in rats was negative (Conti et al. 1988).

There are no reports of cancer effects associated with dermal exposure of animals to styrene.

Based on the information obtained from human and animal studies, it is not known if styrene causes cancer in humans, and the EPA has not yet assigned styrene to a cancer weight of evidence category (IRIS 1991). The IARC has assigned styrene to Group 2B, possibly carcinogenic to humans (IARC 1988). However, cancer effects associated with long-term human exposure to low levels of styrene at waste sites, in industrial neighborhoods, or in the environment have not 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 styrene 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 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

## 2. HEALTH EFFECTS

(e.g., DNA adducts). Biomarkers of effects caused by styrene are discussed in Section 2.5.2.

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

### 2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Styrene

The elimination of styrene via expired air may be used to identify exposure to styrene (Guillemin and Berode 1988; Stewart et al. 1968). Only a small percentage of unchanged styrene is expired after cessation of exposure. There are no adequate studies correlating post-exposure exhaled styrene with previous exposure levels. Assessment of occupational exposure involving measurement of unchanged styrene in urine has been reported (Dolara et al. 1984). In this study of workers, the styrene air concentrations were 16-61 mg/m<sup>3</sup> and the urinary concentrations of styrene were 0-7-4.1 µg/L. Urinary mutagenic activity was also evaluated in this study and was not a good indication of exposure to styrene. Only a small fraction of unchanged styrene is recovered in the urine. However, measurement of styrene in urine is a reliable indicator of styrene exposure if the exposure is recent (Dolara et al. 1984; Guillemin and Berode 1988; Pezzagno et al. 1985).

Analysis of unchanged styrene in blood may be used as a qualitative indicator of styrene exposure (Antoine et al. 1986). In one study, styrene was detected in the blood of humans exposed to 80 ppm (Ramsey et al. 1980). The maximum blood concentration at the end of exposure was 0.92±0.26 µg/mL. The half-life values for rapid and slow clearance curves were 0.58 and 13 hours, respectively. In another study, the concentration of styrene in blood (0.2-3.7 mg/L) increased with the level and duration of styrene exposure (Baselt 1988a).

The presence of styrene in adipose tissue is also an indicator of exposure. The concentration of styrene in the adipose tissue of two workers exposed to 32-85 mg/m<sup>3</sup> of styrene during a work week suggested a half-life of 5.2 days for one worker and 2.8 days for the other worker. The elimination time was estimated to be 5 weeks (Engstrom et al. 1978b).

Levels of occupational exposure to styrene may also be estimated by measurement of styrene metabolites such as MA and PGA in urine (Bartolucci et al. 1986; Elia et al. 1980; Engstrom et al. 1976; Sedivec et al. 1984; Sollenberg et al. 1988). It should be noted that large intra-individual differences in MA and PGA urinary concentrations have been reported. Some studies found a good correlation between the time-weighted styrene exposure and urinary MA concentrations (Engstrom et al. 1976; Harkonen et al. 1979), while other studies found a better correlation with the sum of urinary MA and

## 2. HEALTH EFFECTS

PGA at the end of the work period (Elia et al. 1980; Sollenberg et al. 1988). Total MA and PGA measured the morning after exposure may be a more reliable biological indicator of styrene exposure in factories where there is high variability in the environmental styrene concentration (Bartolucci et al. 1986).

Reference levels of styrene likely to be observed in workers exposed to the TWA concentrations by inhalation have been reported. These are called biological exposure indices (ACGIH 1988-1989). Values recommended are: MA in urine, 1 g/L; PGA in urine, 250 µg/L, styrene in mixed-exhaled air (before shift) 40 ppb; styrene in mixed-exhaled air (during shift), 18 ppm; styrene in blood (before shift), 0.02 mg/L; and styrene in blood (end of shift), 1 mg/L.

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Styrene

The most common symptom of styrene exposure is depression of the central nervous system. Other organic solvent vapors cause similar effects. However, neurological symptoms can be used with caution to estimate styrene exposure and adverse effects. Central nervous system depression induced by styrene has been correlated with a urinary MA concentration in excess of 800 mg/L. A measured decrement in psychomotor performance has been associated with urinary MA concentrations of greater than 1,200 mg/L (Harkonen et al. 1978).

Logic, memory, and visuo-constructive abilities were significantly affected in 50 workers with MA and PGA levels corresponding to greater than 50 ppm of styrene in air (Mutti et al. 1984a). Reaction time to a sequence of light stimuli in two female workers resulted in marked impairment in workers with the highest MA excretion. The correlation coefficient for reaction time versus urinary MA (measured as mmol/mmol creatinine) was 0.86 (Mackay and Kelman 1986).

Cytogenetic monitoring of peripheral lymphocytes as a biomarker of effect has been proposed (DeJong et al. 1988; Pero et al. 1982). Future biomarkers may include hemoglobin adducts. Using unscheduled DNA synthesis (UDS) as an indicator of DNA damage, the lymphocytes of 38 individuals occupationally exposed to styrene were evaluated. The induced UDS was significantly increased for the group exposed to 1-40 ppm styrene (Pero et al. 1982). Measurement of chromosome aberration in peripheral blood lymphocyte has been used for many years to monitor the biologic effects of genotoxic chemicals. However, due to high background levels of chromosomal aberration and exposures to other genotoxic workplace chemicals, the sensitivity of this biomarker for the effects of styrene is probably not adequate (DeJong et al. 1988). The role of hepatic glutathione in the toxicity of styrene has been proposed as inhibiting the covalent binding of styrene. This has been confirmed in animal studies by decreased glutathione in styrene-exposed animals (Parkki 1978). However, its use as a biomarker of effect in humans remains to be demonstrated since data on the adverse effects of styrene on the human liver are insufficient.

## 2. HEALTH EFFECTS

Levels of styrene oxide may also be a useful biomarker of effect, since this metabolic intermediate may be responsible for many of styrene's toxic effects. However, no data were located regarding a correlation between styrene oxide and any adverse health effect.

### 2.6 INTERACTIONS WITH OTHER CHEMICALS

Styrene metabolism is known to be inhibited by the presence of other chemicals such as toluene, trichloromethylene, and ethyl benzene. The biotransformation of styrene in rats to PGA, MA, and hippuric acid was suppressed by coadministration of toluene (Ikeda et al. 1972). This may be due to competitive inhibition of oxidative mechanisms. Similar results were reported by Ikeda and Hirayama (1978) in rats when styrene metabolism was inhibited by the administration of trichloroethylene. Urinary metabolites of styrene may be markedly reduced when humans or animals are concurrently exposed to organic solvents that inhibit styrene metabolism.

### 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Styrene is a hazardous substance found in the workplace with much lower levels found in the environment. Therefore, the populations at risk are workers in industries making polystyrene plastics, coating, polyester resins, and other products'. Persons with pre-existing respiratory or neurological problems would be at risk for the irritant action and central nervous system depressant effects of styrene, respectively. Individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) may be at increased risk since Heinz bodies, which are readily formed in the blood of G6PD-deficient humans (Wintrobe et al. 1970), have been found in the red blood cells of dogs orally exposed to styrene. Women from families pre-disposed to mammary gland tumors may also be at increased risk since this type of tumor was observed in some animal studies. Some studies suggest that the incidence of adverse reproductive outcome (low birth weight, spontaneous abortions) may be elevated in styrene-exposed female workers (see Section 2.2.1.6), therefore, pregnant women may be susceptible. Individuals with liver dysfunction might also be somewhat more susceptible, since this liver is affected by styrene.

### 2.8 MITIGATION OF EFFECTS

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

Human exposure to styrene may occur by inhalation, ingestion, or by dermal contact. General recommendations for reducing absorption of styrene following exposure include removing the exposed individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, they are flushed with water. There are some disagreements

## 2. HEALTH EFFECTS

regarding appropriate procedures for mitigation of absorption of styrene following oral exposure. Since aspiration of styrene into the lung can cause pulmonary edema and hemorrhage, some authors advise against the use of emetics, but recommend administration of water for dilution of gastric lavage (Bronstein and Currance 1988; Haddad and Winchester 1990). Others suggest administration of syrup of ipecac to induce vomiting, but consider the usefulness of activated charcoal to bind the styrene and cathartics to speed fecal excretion as questionable (Ellenhorn and Barceloux 1988). Following acute inhalation exposure, administration of oxygen and use of mechanical ventilation to support respiration have been suggested (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Administration of aminophylline and inhaled bronchodilators may be required to treat bronchospasm (Ellenhorn and Barceloux 1988). Furthermore, cardiac monitoring has been suggested. Supportive treatment may be needed for neurological effects of styrene exposure (Haddad and Winchester 1990).

Styrene is metabolized by the body, and most styrene that is absorbed is excreted in the urine as metabolites of the parent compound. Styrene is cleared rapidly from the human body. Its half-life is several hours in the blood and about 2-4 days in subcutaneous adipose tissue (see Section 2.3). No method is commonly used to enhance the elimination of the absorbed dose of styrene.

In humans, central nervous system depression and upper respiratory tract irritation were reported following acute exposure to higher styrene concentrations (see Section 2.2). Studies in animals indicate that chronic styrene exposure causes liver and kidney effects and may induce cancer. Styrene oxide was found to be the active mutagenic metabolite of styrene in several studies (de Raat 1978; Donner et al. 1979; Norppa et al. 1979, 1980a, 1980b, 1981, 1984, 1988; Pohlova et al. 1985; Vainio et al. 1976). Based on these studies, it can be concluded that styrene is a typical indirect mutagen that needs metabolic activation to be able to bind covalently to macromolecules (e.g., nucleic acids). In one of the possible metabolic pathways, styrene oxide is further metabolized to hydroxyphenylethyl mercapturic acid. The reaction utilizes glutathione (Bond 1989). It has been demonstrated that mutagenic activity of styrene oxide was decreased in the presence of glutathione in *S. typhimurium* TA 100 (Yoshikawa et al. 1980). This experiment, therefore, suggests that glutathione may reduce the mutagenic effects of styrene oxide.

The formation of styrene oxide may also contribute to other effects following styrene exposure. It is well established that glutathione decreases the cytotoxicity of many reactive chemicals by acting as a scavenger of toxic metabolites. It was found that exposure of rodents to high levels of styrene caused depletion of glutathione content in the liver cells of these animals (Das et al. 1978; Vainio et al. 1979). It was suggested that glutathione decreases the hepatotoxicity by preventing styrene oxide reaction with other endogenous macromolecules. Similarly, depletion of glutathione was found in all regions of rat brain following exposure to styrene oxide (Dixit et al. 1982; Trenga et al. 1990). The authors speculated that the depletion of brain glutathione may lead to an increased concentration of free styrene oxide with

## 2. HEALTH EFFECTS

increased binding to cellular nucleophiles. This process would contribute to oxidative injury to neuronal and glial cells and may be a part of styrene-induced neurotoxicity. It should be noted, however, that styrene itself, being a lipophilic compound, may disrupt the nerve membrane function in a manner similar to anesthetic agents.

Although results from in vitro studies in bacteria and in vivo animal studies demonstrate that exogenous glutathione precursors may decrease the effects of styrene toxicity, it is not known whether this treatment would be beneficial in humans. For low level exposure cases it is unlikely that endogenous glutathione levels would be decreased to a significant extent. Therefore, it is unlikely that exogenous glutathione precursors such as N-acetylcysteine may be effective in mitigating the toxic effects of styrene. Exogenous doses of reducing agents may be useful following acute high dose exposure to styrene. In this case, a significant depletion of glutathione may occur as a result of the presence of high levels of styrene oxide. However, there is no clinical data available to date which supports the use of this treatment.

### 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 styrene 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 styrene.

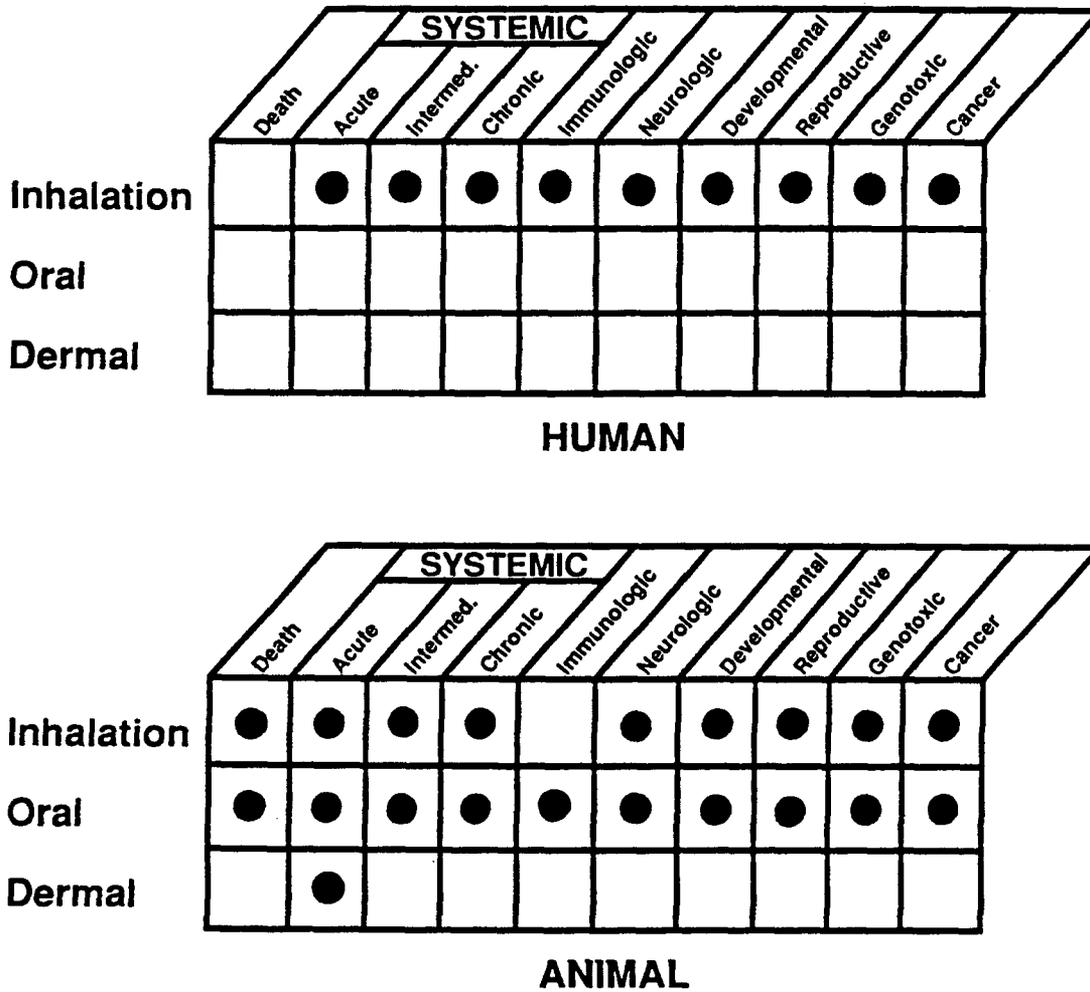
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 2.9.1 Existing Information on Health Effects of Styrene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to styrene are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of styrene. 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. HEALTH EFFECTS

**FIGURE 2-4. Existing Information on Health Effects of Styrene**



● Existing Studies

## 2. HEALTH EFFECTS

There is information on most categories of human toxicity via the inhalation route from occupational studies. However, data are not available on humans exposed to styrene by the oral or dermal routes. Data from animal studies are more extensive, with studies available for most areas of toxicity resulting from exposure via the oral and inhalation routes; however, there are no data on immunologic effects via inhalation. Little is known about the effects of dermal exposure to styrene in animals.

### 2.9.2 Data Needs

**Acute-Duration Exposure.** The possibility for brief human exposure to high concentrations of styrene exists in occupational settings, and might also exist near major spills. Exposure of the general public to episodic high concentrations of styrene at hazardous waste sites, in the home, or in the general environment is unlikely. The respiratory tract and central nervous system are the likely target organ systems for inhaled styrene (Alarie 1973; Carpenter et al. 1944; DeCeaurriz et al. 1983; Kankaanpaa et al. 1980; Murray et al. 1978; Spencer et al. 1942; Stewart et al. 1968). The data are not considered sufficient to establish an inhalation acute-duration MRL. Episodic high-level exposures to styrene from contaminated food or water are unlikely. There are no data on humans orally exposed to styrene, and the animal data are not considered sufficient to derive an oral acute-duration MRL. Thus, additional single-dose oral and inhalation studies are needed to better define toxicity thresholds. However, the potential carcinogenicity of styrene prevents the design of controlled laboratory exposures in humans. Dermal exposure to styrene at significant levels is unlikely except in the case of workplace spills and dermal absorption is probably low based on limited human studies. However, the almost complete lack of dermal toxicity data in animals and humans creates a degree of uncertainty on this issue. Therefore, single dose dermal studies would be useful in determining target organs and thresholds for dermal exposure. In designing these types of studies, precautions should be taken to avoid concomitant inhalation exposure.

**Intermediate-Duration Exposure.** Intermediate-duration exposure studies in animals and humans confirm that the upper respiratory tract and central nervous system are the target organ systems for inhaled styrene (Kulig 1988; Ohashi et al. 1986; Pryor et al. 1987; Rosengren and Haglid 1989; Spencer et al. 1942). However, additional studies are needed, as the data are not considered sufficient to derive an intermediate-duration inhalation MRL. Oral exposure studies of intermediate-duration are limited. Animal studies indicate that renal and neurological end points need further evaluation (Johnston et al. 1983; Vainio et al. 1979; Viau et al. 1987). The data are considered sufficient to derive an oral intermediate-duration RfD of 0.2 mg/kg/day based on liver enzyme changes in rats (Srivastava et al. 1982). However, additional data would be valuable since the critical study does not define a NOAEL. Basic information on the adverse effects of intermediateduration dermal exposure to styrene in animals is also needed due to the sparsity of available data.

## 2. HEALTH EFFECTS

**Chronic-Duration Exposure and Cancer.** Chronic studies are available that investigated the adverse health effects of styrene on workers in the plastics industry (Harkonen et al. 1978, 1984; Hotz et al. 1980; Lemasters et al. 1989; Lorimer et al. 1978; Mutti et al. 1984a,b; Thiess and Friedheim 1978). Although the lung and liver are both affected by chronic exposure, neurological effects such as decreased short term memory or impaired visuomotor performance seem to be the most sensitive indicators of toxicity (Harkonen et al. 1984; Mutti et al. 1984a). Based on a LOAEL of 25 ppm identified by Mutti et al., a chronic inhalation MRL of 0.06 ppm has been derived. Further research to define the dose-response curve more fully and to identify a chronic inhalation NOAEL for neurological effects would be valuable and would help reduce uncertainty in the MRL. Data on chronic oral exposure to styrene is only available through animal studies (Beliles et al. 1985; Conti et al. 1988; NC1 1979b; Quast et al. 1979). In these studies, the most sensitive indicator of toxicity appears to be Heinz body formation in red blood cells (Quast et al. 1979), and the EPA has calculated a chronic oral RFD based on this study (IRIS 1991). However, as discussed above (Section 2.4), there is some doubt regarding the chronic oral NOAEL, and whether hematological effects are really more sensitive than neurological effects. Moreover, decreased survival has been noted in rats at exposure levels only slightly higher than the no-effect level for hematological effects (Conti et al. 1988). Therefore, no chronic oral MRL has been derived. Further studies on the effects of oral exposure, with special emphasis on neurological or neurobehavioral effects, would be valuable. Although chronic dermal exposure by the general public is not likely, there may be some potential for dermal contact with soil at hazardous waste sites. Therefore, data on longterm effects of dermal contact with styrene would be useful.

Taken together, the animal and human data indicate that styrene may possibly be a weak human carcinogen. Although data from epidemiological studies are limited due to concurrent chemical exposures and small cohorts, the data are suggestive of some carcinogenic potential in humans (Coggon et al. 1987; Hodgeson and Jones 1985; Matanoski and Schwartz 1987; Meinhardt et al. 1982; Nicholson et al. 1978; Okun et al. 1985; Ott et al. 1980; Wong 1990). Studies in rats and mice have indicated that styrene may be a weak animal carcinogen via the oral and inhalation routes. Clarification of the data is needed in several areas. Interpretation of existing animal bioassays is complicated by the marginal statistical significance of elevated tumor incidences and by the lack of adequate dose response data. Almost all of the available epidemiological studies involve concurrent exposures to other chemicals. Additional studies that account for these issues would be valuable. Finally, the role of the metabolism of styrene to styrene oxide in humans and animals needs to be clarified. This might best be accomplished by studies of industrially exposed (worker) populations.

**Genotoxicity.** On-going studies by Perera (Columbia University) and Rappaport (University of California) will address links between styrene exposure and cytogenic response. The results of genotoxicity tests for styrene both *in vivo* and *in vitro* are frequently conflicting, and the genotoxic potential of styrene is not clear (Andersson et al. 1980; Beliles

## 2. HEALTH EFFECTS

et al. 1985; Hogstedt et al. 1979; Meretoja et al. 1977, 1978; Watanabe et al. 1981). The reasons for the mixed or conflicting genotoxicity results may be differences in the metabolism or detoxification of styrene in the various test systems employed. The role of the metabolite styrene oxide in genotoxicity assays on styrene should be fully evaluated, preferably in mammalian in vivo systems. Toxicokinetic studies evaluating the presence, level, and activity of styrene oxide in humans will influence the interpretation of genotoxicity studies on styrene and their relevance to public health.

**Reproductive Toxicity.** Additional studies are needed to determine the potential effects of styrene exposure on spontaneous abortion rates in female workers in the styrene industry. The exposures in existing studies were not quantified and therefore, interpretation of results is difficult (Harkonen and Holmberg 1982; Hemminki et al. 1980; Lindbohm et al. 1985). A single threegeneration study showed no styrene-related reproductive effects; however, one reproductive study in animals indicated altered testicular function (Beliles et al. 1985; Salomaa et al. 1985). Additional reproductive data on occupationally-exposed males would be useful in evaluating the existing animal data that indicates altered testicular function.

**Developmental Toxicity.** Data on the developmental effects of inhalation exposure to styrene are available in humans and animals. Developmental effects were not generally observed in animal studies, but some fetal- and embryo-toxicity was observed (Kankaanpaa et al. 1980). This information, in combination with observations of reduced birth weight in the offspring of female workers in the styrene industry (Lemasters et al. 1989), indicates that additional repeated dose animal studies and epidemiological studies would be useful. Little information is available on the potential developmental effects of oral exposure to styrene. The single negative study in rats (Murray et al. 1978) should be supplemented by confirmatory studies in other species.

**Immunotoxicity.** Immunotoxicity data in humans are limited to one study in which styrene exposure had no effect on serum alpha, beta and gamma globulin concentrations in workers (Chmielewski et al. 1977). In another study, it was found that styrene epoxide was more sensitizing to humans than styrene itself (Sjoberg et al. 1984). Limited data in animals indicate that oral exposure to styrene has some immunotoxic potential (Sinitskij 1969). It would be useful to investigate the potential for styrene-induced immunotoxicity in future studies.

**Neurotoxicity.** Central nervous system depressant effects in humans from inhalation exposure to styrene are well known (Carpenter et al. 1944; Harkonen et al. 1978; Mutti et al. 1984a,b; Stewart et al. 1968). Although the threshold for neurologic effects is not well defined, the studies of Harkonen et al. (1979) and Mutti et al. (1984a) provide sufficient dose-response data to permit derivation of a chronic inhalation MRL. Since this is based on a LOAEL, further studies which define the chronic NOAEL, as well as acute- and intermediate-duration NOAELs, would be valuable especially at levels of styrene causing problems with coordination and psychological function. These

## 2. HEALTH EFFECTS

and other neurological effects may play a role in the rate of workplace accidents and the level of performance. Additional studies in mammalian animal models are needed to determine if styrene causes chronic damage to the central and/or peripheral nervous systems and to determine the associated mechanism of toxicity. Also, information is needed to determine if neurotoxicity can result from exposure to styrene via the oral route.

**Epidemiological and Human Dosimetry Studies.** Since acute effects such as upper respiratory tract irritation and eye irritation have been frequently noted in occupational health studies and in laboratory experiments, additional epidemiological studies of workers are needed to determine the chronic respiratory effects of styrene. Since liver function evaluation of workers exposed to styrene has resulted in equivocal results (Harkonen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978), additional studies are necessary and should include complete profiles of serum hepatic enzymes of exposed workers. Further epidemiological information is needed to determine if exposure to styrene causes reproductive effects, developmental effects, or cancer.

**Biomarkers of Exposure and Effect.** Available studies indicate that there are good quantitative relationships between styrene metabolites (MA and PGA) in the urine and styrene exposure levels in humans (Harkonen et al. 1978; Mutti et al. 1984a). Efforts to establish styrene oxide as a biomarker would also be valuable, since this metabolite may underlie many of styrene's toxic effects. However, methods which focus on these metabolites are mainly useful for determining exposure within 1 day of exposure. Efforts to identify biomarkers of prior exposures would also be valuable.

There are currently no biomarkers specific for the effects of styrene that are not also typical of other central nervous system depressants. Further research is needed to evaluate potential biomarkers of effect in the areas of chromosome aberrations, psychomotor decrement, hepatic glutathione depletion, and adipose tissue retention of styrene. These potential biomarkers should be evaluated in terms of long-term or chronic exposure periods, and their specificity for exposure to styrene.

**Absorption, Distribution, Metabolism, and Excretion.** Styrene oxide (styrene epoxide) has been identified as an intermediate metabolite of styrene (Drummond et al. 1989; Engstrom et al. 1976; Korn et al. 1984, 1987; Leibman 1975; Lof et al. 1983; Withey and Collins 1979; Young et al. 1979). However, styrene oxide has only been found in minute amounts in human studies (Lof et al. 1986a). The presence of styrene oxide, a mutagen and carcinogen, may account for some conflicting results and/or interspecies variation in mutagenicity tests and cancer bioassays. The role, if any, of styrene oxide in the overall toxicity of styrene needs to be evaluated by additional metabolism studies to confirm its presence, level, and duration in human tissues. The toxicokinetics of styrene exposure via inhalation are reasonably well defined. However, oral and dermal exposure data are needed to better characterize absorption rates and the elimination ratios of the metabolites (MA and PGA).

## 2. HEALTH EFFECTS

**Comparative Toxicokinetics.** Interspecies variations in styrene metabolism have been established by noting, for example, different ratios of MA and PGA in different species (Ramsey et al. 1980; Ramsey and Young 1978; Young et al. 1979). Mendrala et al. (1991) reported species differences in the *in vitro* metabolism of styrene and styrene oxide which indicated that mice and rats had a higher capacity to produce styrene oxide from than humans. Efforts should continue to identify which animal model best approximates human metabolism of styrene. Although urinary metabolites of styrene in man are known, the occurrence and significance of styrene oxide needs to be evaluated.

**Mitigation of Effects.** Recommended methods for the mitigation of acute effects of styrene intoxication include mechanical ventilatory support, administration of oxygen, and drug therapy for bronchospasm, if exposure is by inhalation (Bronstein and Curran 1988; Ellenhorn and Barceloux 1988). Thorough washing or flushing with water is recommended for dermal/ocular exposure. There is disagreement concerning the use of emetics to prevent absorption of styrene following ingestion due to potential of aspiration into the lung (Bronstein and Curran 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Supportive treatment is indicated for neurological effects of styrene exposure (Haddad and Winchester 1990). No information was located concerning mitigation of effects of lower-level or longer-term exposure to styrene. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating styrene-exposed populations in the vicinity of hazardous waste sites. This includes further studies on the mechanism(s) of styrene toxicity, so that methods may be developed to interfere with or block styrene's toxic actions in the body.

### 2.9.3 On-going Studies

A number of research projects are in progress investigating styrene. These projects are summarized in Table 2-6.

## 2. HEALTH EFFECTS

TABLE 2-6. On-going Studies on the Health Effects of Styrene

Investigator	Affiliation	Research description	Sponsoring agency
S. M. Rappaport	University of California	Occupational health study	NIOSH
W. J. Nicholson	Mt. Sinai School of Medicine	Epidemiological study	NIEHS
F. P. Perera	Columbia University	Biological markers	NCI
A. M. Jeffrey	Columbia University	Biologically effective doses in humans and mice	NCI
J. Roycroft	NTP	Two-year inhalation bioassays in rats and mice	NCI
M. Kogevinas	IARC	Epidemiological study on 20,000 styrene workers	IARC
R. Nolan	Dow	Metabolism/Kinetics	SIRC
J. Mattson	Dow	Ototoxicity studies	SIRC
J. Filser	GSF Toxicology Institute, Munich	Metabolism/Kinetics	ECETOC
W. Lutz	Institute of Toxicology, Zurich	DNA-binding	ECETOC

DNA = Deoxyribonucleic acid; ECETOC = European Chemical Industry Ecology and Toxicology Center; IARC = International Agency for Research on Cancer; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Sciences; NIOSH = National Institute for Occupational Health and Safety; NTP = National Toxicology Program; SIRC = Styrene Information and Research Center



### 3. CHEMICAL AND PHYSICAL INFORMATION

#### 3.1 CHEMICAL IDENTITY

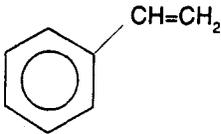
Table 3-1 lists common synonyms, trade names and other pertinent identification information for styrene.

#### 3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of styrene.

## 3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Styrene

Characteristic	Information	Reference
Chemical name	Styrene	Verschuieren 1983
Synonyms	Vinylbenzene; ethenylbenzene; cinnamene; phenylethylene	Verschuieren 1983
Trade names	No data	
Chemical formula	C <sub>8</sub> H <sub>8</sub>	Windholz 1983
Chemical structure		
Identification numbers:		
CAS registry	100-42-5	Sax and Lewis 1987
NIOSH RTECS	WL3675000	HSDB 1989
EPA hazardous waste	No data	
OHM/TADS	7216911	HSDB 1989
DOT/UN/NA/IMCO shipping	UN 2055	NLM 1989
	IMCO 3.3	HSDB 1989
HSDB	171	HSDB 1989
NCI	C02200	NLM 1989

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

## 3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Styrene

Property	Information	Reference
Molecular weight	104.16	Weast 1985
Color	Colorless to yellowish	Windholz 1983
Physical state	Liquid	Sax and Lewis 1987
Melting point	-30.6°C	Weast 1985
Boiling point	145.2°C	Weast 1985
Density at 20°C	0.906	Weast 1985
Odor	Sweet, sharp	Verschuieren 1983
Odor threshold:		
Water	0.73 mg/L	HSDB 1989
	0.011 mg/L	Amoore and Hautala 1983
Air	1.36 mg/m <sup>3</sup>	Amoore and Hautala 1983
Solubility:		
Water at 20°C	300 mg/L	Verschuieren 1983
Organic solvents	Soluble in alcohol, ether, acetone, carbon disulfide	Windholz 1983
Partition coefficients:		
Log octanol/water	2.95	EPA 1984a
Log K <sub>oc</sub>	No data	
Vapor pressure at 20°C	5 mmHg	Verschuieren 1983
Henry's law constant: at 25°C	2.61 x 10 <sup>-3</sup> atm-m <sup>3</sup> /mol (calculated)	EPA 1983
Autoignition temperature	914°F (490°C)	Sax and Lewis 1987
Flashpoint	87°F (31°C) (closed cup)	Windholz 1983
Flammability limits	No data	
Conversion factors	1 mg/m <sup>3</sup> = 0.23 ppm 1 ppm = 4.33 mg/m <sup>3</sup>	Verschuieren 1983 Verschuieren 1983
Explosive limits	1.1-6.1%	Sax and Lewis 1987



#### 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

##### 4.1 PRODUCTION

In the United States, styrene is produced principally by the catalytic dehydrogenation of ethylbenzene. Hence, ethylbenzene is a common contaminant. It is also produced by oxidation of ethylbenzene to its peroxide which is then reacted with propylene to produce propylene oxide and alpha-methylphenyl carbinol. The carbinol is then further dehydrated to produce styrene (Dickson et al. 1983; HSDB 1989; IARC 1979).

Styrene has been manufactured in the United States since 1938. Its production has increased 1.8% in the decade between 1978 and 1988 with a 4.8% increase in production during the 5-year period between 1983 and 1988. Production of styrene for 1987 was over 8 billion pounds, and 1989 production is predicted to be almost 9 billion pounds (Dickson et al. 1983; Heylin 1989; SRI 1988a, 1989; USITC 1987, 1988).

Information regarding the locations of the numerous styrene production facilities and the amounts of styrene which may be present on-site is presented in Table 4-1.

##### 4.2 IMPORT/EXPORT

Imports of styrene have generally been less than 1% of United States domestic production volumes with imports reported to be 26.4 million pounds for 1976, 28.6 million pounds for 1981, and 21 million pounds for 1982. Data regarding current styrene imports were not located. Styrene exports were over 1 billion pounds in 1981 and over 1 billion pounds in 1982, which represents a steady increase in styrene exports since the early years of styrene production (Dickson et al. 1983; IARC 1979).

##### 4.3 USE

Styrene is used predominantly in the production of polystyrene plastics and resins (62%). Some of these resins are used for construction purposes such as in insulation or in the fabrication of fiberglass boats. Styrene is also used as an intermediate in the synthesis of materials used for ion exchange resins and to produce copolymers such as styrene-acrylonitrile (SAN), acrylonitrile-butadiene-styrene (ABS), and styrene-butadiene rubber (SBR).

Consumer products made from styrene-containing compounds include packaging, electrical, and thermal insulation materials, pipes, automotive components, drinking tumblers, other food-use utensils, and carpet backing. The Food and Drug Administration (FDA) permits styrene to be used as a direct additive for synthetic flavoring and an indirect additive in polyester resins, ion-exchange membranes, and in rubber articles (5% by weight maximum) intended for use with foods (HSDB 1989; IARC 1979; NIOSH 1983).

## 4. PRODUCTION, IMPORT, USE AND DISPOSAL

TABLE 4-1. Facilities That Manufacture or Process Styrene<sup>a</sup>

State <sup>b</sup>	No. of facilities	Range of maximum amounts on site in thousands of pounds <sup>c</sup>	Activities and uses <sup>d</sup>
AL	10	1-9,999	1, 4, 7, 8, 9, 11, 13
AR	14	0.1-9,999	2, 3, 7, 8, 9
AZ	8 (1) <sup>e</sup>	1-99	3, 7, 8, 9
CA	81 (6) <sup>e</sup>	0.1-49,999	2, 3, 7, 8, 9, 10, 11, 13
CO	5	1-9,999	3, 6, 7, 8, 9
CT	5	0.1-49,999	3, 7, 10, 12
DE	3	10-999	7, 8, 9
FL	44	1-9,999	1, 2, 3, 7, 8, 9, 11, 12, 13
GA	24	0.1-9,999	3, 4, 7, 8, 9
IA	16	0.1-9,999	2, 3, 4, 7, 8, 9, 12, 13
ID	2	10-99	9
IL	49 (4) <sup>e</sup>	0.1-99,999	2, 3, 5, 7, 8, 9, 10, 11, 12
IN	50 (4) <sup>e</sup>	0-49,999	2, 3, 4, 5, 7, 8, 9, 11, 12, 13
KS	13	0.1-999	2, 7, 8, 9, 12, 13
KY	21 (1) <sup>e</sup>	1-49,999	1, 5, 6, 7, 8, 9
LA	16 (1) <sup>e</sup>	0.1-99,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11
MA	13 (2) <sup>e</sup>	1-9,999	7, 8, 9, 10
MD	14 (1) <sup>e</sup>	1-99	3, 4, 5, 7, 8, 9
ME	5	1-99	7, 8, 9
MI	32 (1) <sup>e</sup>	0.1-49,999	2, 5, 7, 8, 9, 10, 11, 12, 13
MN	10 (1) <sup>e</sup>	10-999	1, 3, 6, 7, 8, 9, 12
MO	17 (1) <sup>e</sup>	0.1-999	2, 3, 7, 8, 9, 11, 13
MS	10 (1) <sup>e</sup>	1-9,999	2, 3, 7, 8, 9, 11
MT	2	1-9,999	3, 6, 7, 8, 11
NC	39	0.1-49,999	2, 3, 5, 7, 8, 9, 10, 11, 12, 13
ND	1 (1) <sup>e</sup>	No Data	7
NE	5	0-99	3, 8, 9, 12
NH	5	10-999	3, 5, 7, 8, 9
NJ	32 (3) <sup>e</sup>	1-49,999	2, 3, 6, 7, 8, 9, 10, 13
NM	1	1-9	8
NV	3	10-99	9, 12

## 4. PRODUCTION, IMPORT, USE AND DISPOSAL

TABLE 4-1 (Continued)

State <sup>b</sup>	No. of facilities	Range of maximum amounts on site in thousands of pounds <sup>c</sup>	Activities and uses <sup>d</sup>
NY	13 (2) <sup>e</sup>	1-999	1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	70 (6) <sup>e</sup>	0-49,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13
OK	6 (1) <sup>e</sup>	10-49,999	3, 6, 7, 8, 9, 11
OR	11	1-999	7, 8, 9
PA	47 (2) <sup>e</sup>	0-49,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	3	1-99	3, 7, 8, 9
RI	5	10-999	2, 4, 7, 8, 9, 13
SC	25 (5) <sup>e</sup>	1-999	2, 3, 7, 8, 9, 11, 12, 13
SD	2	1-99	7, 9
TN	36 (3) <sup>e</sup>	0-9,999	2, 3, 5, 6, 7, 8, 9, 12, 13
TX	78 (4) <sup>e</sup>	0-499,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	2	1-9	4, 8, 9
VA	17 (2) <sup>e</sup>	1-49,999	2, 3, 7, 8, 9, 10, 12
WA	26 (1) <sup>e</sup>	0.1-9,999	1, 3, 6, 7, 8, 9, 11, 12
WI	23	0.1-499,999	2, 7, 8, 9, 13
WV	9 (3) <sup>e</sup>	10-9,999	3, 7, 8, 9, 10, 12
WY	1	1-9	7

<sup>a</sup>TRI 1989

<sup>b</sup>Post office state abbreviations

<sup>c</sup>Data in TRI are maximum amounts on site at each facility.

<sup>d</sup>Activities/Uses:

- |                               |                                  |
|-------------------------------|----------------------------------|
| 1. produce                    | 8. as a formulation component    |
| 2. import                     | 9. as an article component       |
| 3. for on-site use/processing | 10. for repackaging only         |
| 4. for sale/distribution      | 11. as a chemical processing aid |
| 5. as a byproduct             | 12. as a manufacturing aid       |
| 6. as an impurity             | 13. ancillary or other use       |
| 7. as a reactant              |                                  |

<sup>e</sup>Number of facilities reporting "no data" regarding maximum amount of the substance on site.

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

**4.4 DISPOSAL**

Typical means of styrene disposal include absorption on vermiculite or similar material, followed by disposal in an EPA-permitted landfill. Incineration is also a useful disposal method, but this must be carefully controlled since pure styrene is highly flammable. No data were located regarding the quantities of styrene disposed by these means (HSDB 1989).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.1 OVERVIEW

Styrene is a widely used industrial chemical with reported atmospheric emissions of more than 30 million pounds annually in the United States. Styrene photodegrades in the atmosphere, usually with a half-life of less than 12 hours, depending on the levels of hydroxyl radical and ozone. Styrene is moderately mobile in soil and volatilizes from water to the atmosphere. Styrene may also undergo biodegradation in soil and water. Bioconcentration does not appear to be significant.

The principal route of styrene exposure for the general population is probably by inhalation of contaminated indoor air. Mean indoor air levels of styrene have been reported in the range of 1-9  $\mu\text{g}/\text{m}^3$ , attributable to emissions from building materials, consumer products, and tobacco smoke. Occupational exposure to styrene by inhalation is the most likely means of significant exposure. The highest potential exposure is probably in the reinforced plastics industry and polystyrene factories. Exposure may also be high in areas near major spills. Exposure to styrene from hazardous waste sites is potentially important but the magnitude of the problem is unknown.

Styrene has been identified in 52 of the 1,177 NPL hazardous waste sites in the United States (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

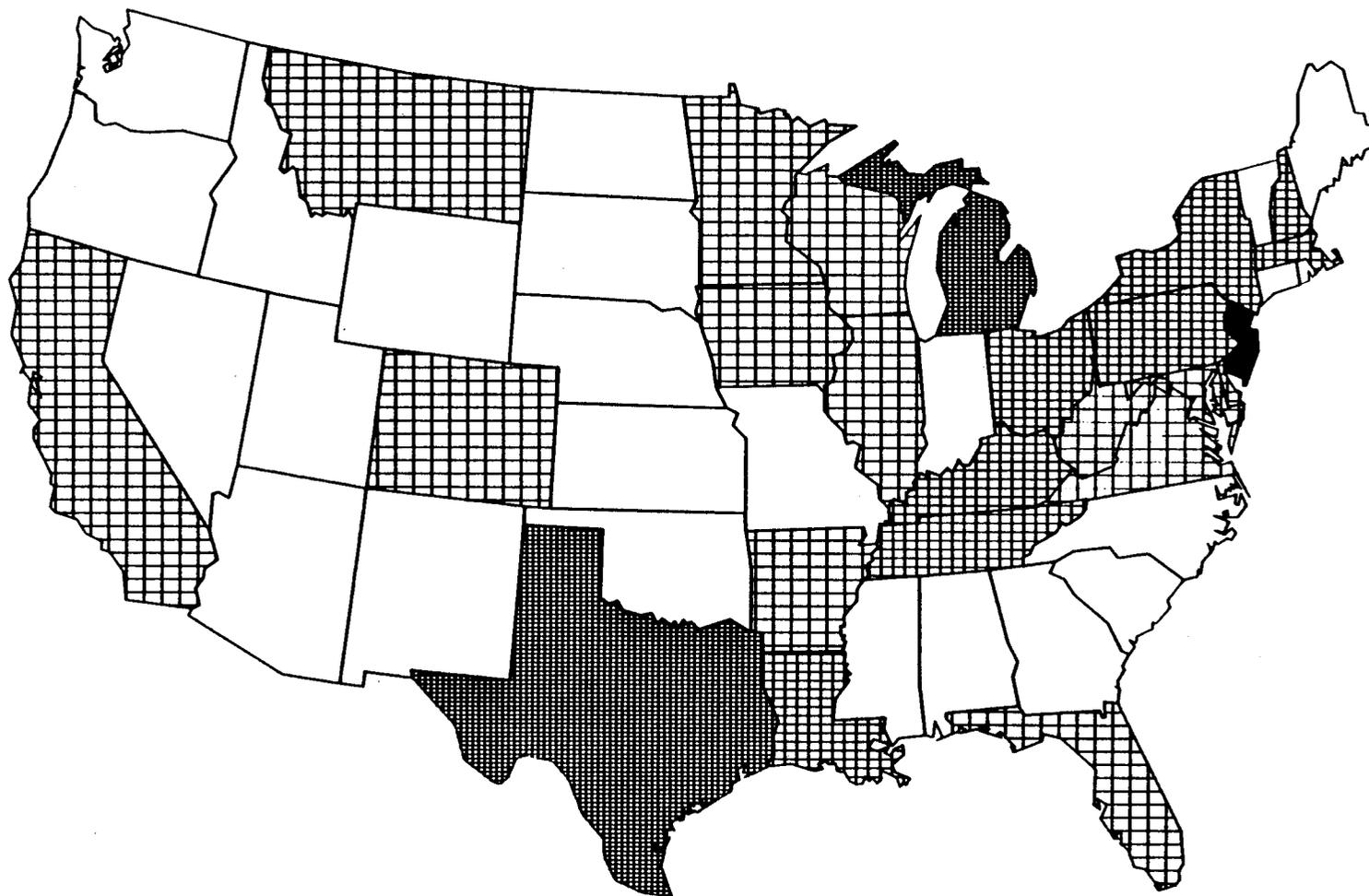
### 5.2 RELEASES TO THE ENVIRONMENT

Manufacturers, processors, and users of styrene are required to report the quantities of styrene released to environmental media annually (EPA 1988a). The data currently available, compiled in the Toxic Chemical Release Inventory (TRI 1989), are for releases in 1987 and are summarized in Table 5-1. Data relevant to specific media are discussed below.

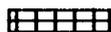
#### 5.2.1 Air

Styrene may be emitted to the atmosphere from industrial production and usage processes, motor vehicle operation, combustion processes, building materials, and consumer products. Estimated industrial styrene emissions reported to EPA for the 1987 Toxics Release Inventory (TRI) totaled over 30 million pounds, 18 million pounds from point sources and more than 12 million pounds as fugitive emissions (EPA 1989c). Styrene ranked 20th among air emissions chemicals in the United States in 1987. Since EPA regulations which require reporting of toxic chemical emissions apply only to selected facilities producing and/or using substantial quantities of the chemical (EPA 1988a), the total air emissions of styrene are probably greater than those reported. Typical sources of industrial styrene emissions are those facilities producing styrene, polystyrene, other plastics, synthetic rubber, and resins (Abrams et al. 1975; EPA 1987d; Graedel 1978; IARC 1979; NIOSH 1983). Facilities reporting styrene emissions for the TRI are listed in Table 5-1.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH STYRENE CONTAMINATION \*



FREQUENCY

 1 SITE  
 2 TO 3 SITES  
 6 SITES

 2 TO 3 SITES  
 9 SITES

\* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Styrene<sup>a</sup>

State <sup>d</sup>	No. of facilities	Range of reported amounts released in thousands of pounds <sup>b</sup>						
		Air	Underground injection	Water	Land	Total Environment <sup>e</sup>	POTW <sup>c</sup> transfer	Off-site waste transfer
AL	10	0.1-77	0-0	0-0.3	0-0	0.1-77	0-0	0-4.6
AR	14	0-641.2	0-0	0-0.8	0-0.3	0-641.2	0-2	0-25.3
AZ	8	3.8-273	0-0	0-0	0-0	3.8-273	0-0	0-0.8
CA	81	0-240	0-0	0-0.1	0-0.8	0-240	0-28.2	0-86.1
CO	5	0-4.3	0-0	0-0.5	0-7.8	0-12.1	0-0	0-7.8
CT	5	0-11.8	0-0	0-0.3	0-0	0-11.8	0-0.3	0-291.4
DE	3	8-51.3	0-0	0-0	0-0	8-51.3	0-0.1	0-22.6
FL	44	0-1,000	0-0	0-0	0-20	0-1,000	0-0.1	0-107.3
GA	24	0-248	0-0	0-0.1	0-45	0-248	0-0.3	0-526
IA	16	0-643	0-0	0-0.1	0-0.3	0-643	0-16	0-8.4
ID	2	20-26	0-0	0-0	0-0	20-26	0-0	0-0.8
IL	49	0-856	0-0	0-0.3	0-6.6	0-856	0-0.3	0-899.6
IN	50	0-525	0-0	0-0	0-3.9	0-525	0-0	0-216.7
KS	13	0-39.9	0-0	0-0	0-0.8	0.3-39.9	0-0.1	0-6.6
KY	21	0.1-184.7	0-0	0-0.1	0-18	0.1-184.7	0-15.9	0-70.2
LA	16	0.1-199	0-0	0-1.1	0-0	0-199	0-0	0-26.5
MA	13	0-120	0-0	0-0.3	0-0	0-120	0-0.3	0-404.9
MD	14	0-57.6	0-0	0-0.3	0-0.3	0-57.6	0-0.3	0-0.8
ME	5	0.5-41	0-0	0-0	0-0	0.5-41	0-0.3	0-0
MI	32	0-337	0-0	0-0.3	0-0.3	0-337	0-3.8	0-257
MN	10	0.2-355.2	0-0	0-0.1	0-0	0.2-355.2	0-0	0-7.2
MO	17	0-40	0-0	0-0	0-0.3	0-40	0-0	0-1,258
MS	10	0.3-121.9	0-0	0-0.3	0-0	0.3-121.9	0-0	0-13.7
MT	2	2.4-2.6	0-0	0-0.3	0-0	2.4-2.8	0-0	0-0.3
NC	39	0-222.8	0-0	0-0	0-0	0-222.8	0-1.2	0-22
ND	1	8.2-8.2	0-0	0-0	0-0	8.2-8.2	0-0	0-0
NE	5	0-36	0-0	0-0	0-11.7	0-36	0-0	0-11.7
NH	5	0.5-22.5	0-0	0-0	0-0	0.5-22.5	0-0.3	0-3.2
NJ	32	0.1-85	0-0	0-0.2	0-0	0-85	0-0.3	0-87
NM	1	5.2-5.2	No Data	0-0	0-0	5.2-5.2	0-0	0-0
NV	3	1.4-24.6	0-0	0-0	0-0	1.4-24.6	0-0	0-0.8
NY	13	0-46.3	0-0	0-0.7	0-27.8	0-46.3	0-0.3	0-73.6
OH	70	0-299	0-0	0-9.6	0-25	0-299.3	0-42.7	0-680
OK	6	4.8-164.1	0-0	0-0.3	0-0.3	5.3-164.1	0-0.3	0-20
OR	11	0.5-188	0-0	0-0	0-0	0.5-188	0-0	0-9.6
PA	47	0-230	0-0	0-2	0-5	0-230	0-39.2	0-117.5
PR	3	0.1-0.3	0-0	0-0	0-0	0.1-0.3	0-0.1	0-0.1
RI	5	9.1-87.5	0-0	0-0	0-0	9.1-87.5	0-0	0-6.8
SC	25	0-258.6	0-0	0-1.5	0-0.3	0-258.8	0-3.1	0-176.4
SD	2	14.4-37.1	0-0	0-0	0-0	14.4-37.1	0-0	0-0

TABLE 5-1 (Continued)

State <sup>d</sup>	No. of facilities	Range of reported amounts released in thousands of pounds <sup>b</sup>						Off-site waste transfer
		Air	Underground injection	Water	Land	Total Environment <sup>c</sup>	POTW <sup>e</sup> transfer	
TN	36	0.5-222.4	0-0	0-0.1	0-0.1	0.5-222.4	0-68.5	0-39.5
TX	78	0-1,188	0-0.3	0-18	0-18.8	0-1,188	0-5.9	0-18,099
UT	2	0.3-0.9	0-0	0-0	0-0	0.3-0.9	0-0	0-0
VA	17	0.1-305.8	0-0	0-0.3	0-0.8	0.1-305.8	0-0.3	0-5.2
WA	26	0.7-213.6	0-0	0-0	0-0	0.7-213.6	0-0	0-13.1
WI	23	0-200.8	0-0	0-0.3	0-0.3	0-200.8	0-0.3	0-44.7
WV	9	0.1-760	0-0	0-1.1	0-100	1.2-760	0-190	0-158.8
WY	1	0.5-0.5	No Data	0-0	0-0	0.5-0.5	0-0	0-0

<sup>a</sup>TRI 1989

<sup>b</sup>Data in TRI are maximum amounts released by each facility. Quantities reported here have been rounded to the nearest hundred pounds, except those quantities > 1 million pounds which have been rounded to the nearest thousand pounds.

<sup>c</sup>Publicly owned treatment works

<sup>d</sup>Post office state abbreviation

<sup>e</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility.

## 5. POTENTIAL FOR HUMAN EXPOSURE

Styrene has been identified as a component of motor vehicle emissions from both gasoline- and diesel-powered engines (Hampton et al. 1982, 1983). Styrene emission rates ranging from 6.2 to 7.0 mg/km distance for gasoline powered vehicles and 1.4-2.1 mg/km for diesel trucks have been reported (Hampton et al. 1983).

Styrene may also be emitted into the air by various combustion processes. Styrene has been identified in the stack emissions from waste incineration (Junk and Ford 1980) and Kleindienst et al. (1986) reported the presence of styrene in wood smoke emissions, but no quantitative data were reported.

Emissions of styrene from various building materials and consumer products may contribute significantly to indoor air pollution. A styrene emission rate from glued carpet of 98 ng/min/m<sup>2</sup> was calculated by Wallace et al. (1987b) and Girman et al. (1986) identified styrene as a major emittant from adhesives used in the constructing and finishing of buildings. Polystyrene products such as packaging materials, toys, housewares, and appliances that may contain small amounts of the monomer also contribute to air levels. Styrene was also detected in sidestream smoke emitted from cigarettes but concentrations were not reported (IARC 1979).

### 5.2.2 Water

The principal sources of styrene releases to water are industrial effluents. Styrene has been detected in effluents from chemical, textile, latex, and coal gasification plants (Pellizzari et al. 1979; Shackelford and Keith 1976). Styrene was also identified in one of 63 industrial effluents at a concentration of <10 µg/L (Perry et al. 1979). Styrene occurred at concentrations up to 83 µg /L in coal gasification effluents (Pellizzari et al. 1979) and King and Sherbin (1986) reported styrene concentrations up to 970 µg /L in chemical plant effluents. The daily styrene loading from a single chemical plant into the St. Clair River (just south of Lake Huron on the Michigan/Ontario border) was estimated at 133 kg (King and Sherbin 1986). Styrene was detected (but not quantified) in the leachate from an industrial landfill in a study of 58 municipal and industrial landfill leachates (Brown and Donnelly 1988).

Styrene has been detected in both surface and groundwater at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate styrene occurred at about 2% of the sites sampled at geometric mean concentrations in positive samples of 9.3 µg/L and 5.3 µg/L in surface water and groundwater, respectively (CLPSD 1986). Note that the CLPSD includes data from both NPL and non-NPL sites.

### 5.2.3 Soil

Soil and sediments may become contaminated with styrene by chemical spills, landfill disposal of styrene-containing wastes or discharge of styrene-contaminated water. Styrene was detected in soil samples at 3.5% of

## 5. POTENTIAL FOR HUMAN EXPOSURE

455 hazardous waste sites at a geometric mean concentration in positive samples of 0.530 mg/kg (CLPSD 1986).

### 5.3 ENVIRONMENTAL FATE

#### 5.3.1 Transport and Partitioning

In the atmosphere, styrene exists as a vapor. Styrene is an oily liquid that is slightly volatile; its vapor pressure has been determined to be approximately 5 mmHg at 20°C (Verschueren 1983). A small fraction of the styrene released to the atmosphere may dissolve into condensed water vapor such as clouds and raindrops. A Henry's law constant (H) is a measure of the tendency of a chemical to partition between its gas phase and water. A value for H has not been experimentally measured for styrene, but it may be estimated by dividing the vapor pressure of styrene by its solubility in water at the same temperature (Mabey et al. 1982). In this case, the value of H is approximately  $2.61 \times 10^{-3}$  atm-m<sup>3</sup>/mole at 25°C. Analogous air-water partition coefficients were measured for styrene at 37°C, yielding a value of approximately  $5.4 \times 10^{-1}$  atm-m<sup>3</sup>/mole (Sato and Nakajima 1979). The magnitude of the values suggest that only a small fraction of vapor-phase styrene would dissolve into water. Physical processes such as precipitation and dry deposition would not be significant mechanisms for removing styrene from the atmosphere because of its high photochemical reactivity (EPA 1984b).

The magnitude of the estimated Henry's law constant ( $2.61 \times 10^{-3}$  atm-m<sup>3</sup>/mole, assuming a water solubility of 300 mg/L at 25°C) suggests that a large fraction of the chemical dissolved in water will volatilize into the atmosphere, depending on temperature gradients, relative humidity, air currents, and the extent of mixing of the solution. The rate of styrene volatilization from water has not been experimentally measured, but its half-life in moving water that is 1 meter in depth may be on the order of 6 hours, based on the empirical relationship reported by Dilling (1977) for the volatilization of chlorinated hydrocarbons from water. The half-life of styrene in the Rhine River was estimated from field measurements at about 14 hours, but it was not certain whether styrene volatilized, biodegraded, and/or photodegraded (Zoeteman et al. 1980). Volatilization from ponds and lakes would be slower; half-life estimates range from 3 to 13 days (EPA 1984b).

Styrene is only sparingly soluble in water, but its exact solubility is uncertain. Values reported for the solubility of styrene range from 160 mg/L at 23°C to 310 mg/L at 20°C (Banerjee et al. 1980; Valvani et al. 1981; Verschueren 1983).

Styrene in water may also partition to soils and sediments. The extent of adsorption of sparingly water-soluble compounds is often correlated with the organic carbon content of the adsorbent (Hassett et al. 1983). When adsorption is expressed as a function of organic-carbon content, an organic carbon/water partition coefficient ( $K_{oc}$ ) is generated, and may be used to rank the relative mobility of the chemical in soil. A  $K_{oc}$  value for styrene has

## 5. POTENTIAL FOR HUMAN EXPOSURE

not been experimentally measured, but may be estimated from its solubility in water, using the empirical regression of Hassett et al. (1983). Assuming that the solubility of styrene is 300 mg/L, a calculated  $K_{oc}$  value for styrene is 260. The magnitude of this estimated  $K_{oc}$  suggests that styrene is "moderately mobile" in soil (Roy and Griffin 1985). In surface soils, where the amount of organic carbon will be highest, the movement of styrene will be retarded by adsorption. In deeper subsurface environments where the amount of organic carbon may be low, adsorption may not be as significant. Based on field measurements, the rate of movement of styrene in an aquifer was about 80 times slower than that of the groundwater, (Roberts et al. 1980) which is attributed to adsorption. No information was located to corroborate the estimated  $K_{oc}$  value, and apparently there are no studies in which the adsorption-desorption characteristics of styrene by soils and sediments have been measured.

The octanol/water partition coefficient ( $K_{ow}$ ), which reflects the partitioning of a chemical between octanol and water, is believed to be a good indication of the tendency for a chemical to accumulate in the fatty structures in plants and animal tissues (Kenaga and Goring 1980). The  $K_{ow}$  of styrene has been measured to be 1,445 (Banerjee et al. 1980) and 891 (Valvani et al. 1981), suggesting that styrene will partition to fat tissues. This is shown to be the case by the work of Engstrom et al. (1978a) and by Stanley (1986).

Even though styrene does tend to partition into fat, it does not tend to bioaccumulate to high levels, mainly because of its metabolism and excretion. A bioconcentration factor (BCF) relates the concentration of a chemical in an organism to the concentration of the chemical in the medium in which it is exposed. Based on the empirical regression of Kenaga (1980), the BCF for styrene is about 25. An experimentally-measured BCF for goldfish was 13.5 (Ogata et al. 1984). These low BCFs suggest that bioconcentration is not a significant fate of styrene released into the environment (EPA 1984b). No other measured BCFs were located to corroborate these reported values.

### 5.3.2 Transformation and Degradation

#### 5.3.2.1 Air

The major fate of atmospheric styrene is determined by the rate of photooxidation. Styrene may be transformed by direct photolysis, but the half-life of this process may be on the order of 50 years (EPA 1984b). Kopczynski et al. (1972) found that styrene was not degraded by photolysis after 6 hours of exposure.

Styrene is more quickly photooxidized by ozone and hydroxyl radicals. The rate constant for the reaction of styrene with ozone at ambient temperatures (about 25°C) has been measured and is approximately 0.17 to  $2.16 \times 10^{-19}$  cm<sup>3</sup>/molecule-sec (Atkinson et al. 1982; Hendry and Kenley 1979). Assuming that the mean concentration of ozone in the troposphere is 1012 molecules/cm<sup>3</sup> (Cupitt 1980), then the half-life of styrene would be approximately 13 hours. The rate constant for the reaction of styrene with

## 5. POTENTIAL FOR HUMAN EXPOSURE

hydroxyl radicals has been measured as  $5.3 \times 10^{-11}$  cm<sup>3</sup>/molecule-sec (Bignozzi et al. 1981). Assuming that the concentration of tropospheric hydroxyl radicals varies from  $3 \times 10^5$  to  $1 \times 10^7$  molecules/cm<sup>3</sup> (MacLeod et al. 1984), it follows that the atmospheric half-life of styrene would be between 0.5 and 17 hours. Consequently, because of the combined effect of ozone- and hydroxyl radical-initiated decay, it appears likely that styrene is labile in the troposphere. Transformation products include various oxygen-containing and saturated hydrocarbons (Sloane and Brudzynski 1979).

### 5.3.2.2 Water

Little is known about abiotic transformations of styrene in water. The reaction of styrene with peroxy radicals appears to be too slow to be significant (EPA 1984b), and no relevant information regarding photochemical reactions in water was located. There is no information that styrene will hydrolyze in water, nor would its chemical structure suggest such potential.

Styrene biodegrades in various aquatic systems. Styrene was only slightly biodegraded in the presence of one type of sewage (Pahren and Bloodgood 1961), but Bridie et al. (1979) found that 42% of the styrene initially present degraded in 5 days when unadapted sewage was used as the source of microorganisms. Very low concentrations of styrene (less than 10 µg/L) were almost completely degraded in 20 minutes in an aerobic biofilm reactor after acclimation, but the chemical was persistent in a methanogenic biofilm column (Bouwer and McCarty 1984). It was found that the rate of styrene biodegradation in groundwater was slow (Wilson et al. 1983). The half-life of styrene in groundwater was estimated to be between 6 weeks and 7.5 months. Although these studies have demonstrated the potential for styrene to biodegrade in water, no information was located about styrene degradation in ambient surface waters.

### 5.3.2.3 Soil

Styrene may also biodegrade in soils. Microorganisms were isolated from soil that were capable of using styrene as a sole-carbon source (Sielicki et al. 1978). Biodegradation products included phenylethanol and phenylacetic acid. Cultures of propane-utilizing bacteria isolated from soil and lake samples were able to degrade styrene (Hou et al. 1983). No information was located on the biodegradation of styrene in field soils.

## 5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

### 5.4.1 Air

Styrene is a common contaminant of ambient urban air. Concentrations of styrene greater than rural air concentrations have been identified in urban and industrial source areas, near hazardous waste sites, in motor vehicle tunnels, in indoor air, and in workplace environments. A summary of monitoring data for these locations is presented in Table 5-2. The data suggest that indoor air concentrations of styrene may be considerably higher

## 5. POTENTIAL FOR HUMAN EXPOSURE

than outdoor concentrations. Cigarette smoke has been implicated as a significant source of styrene in indoor air (Wallace 1987; Wallace et al. 1986a).

### 5.4.2 Water

Styrene is not frequently found in United States water supplies. Styrene was not detected in any of the more than 1,000 samples of drinking water analyzed during three federal surveys (EPA 1988b), but has been reported occasionally in drinking water supplies in several states (Abrams et al. 1975; Coleman et al. 1984; Kleopfer and Fairless 1972; Kool et al. 1982; Sanjivamurthy 1978; Shackelford and Keith 1976) well water (Kelley 1985; Krill and Sonzogni 1986), river water (Shackelford and Keith 1976; Sheldon and Hites 1978) and Lake Erie (Konasewich et al. 1978). Quantitative data were not available in these reports. Styrene concentrations in raw and treated waters ranged from 0.1 to  $\geq 1.0$   $\mu\text{g}/\text{L}$  in an evaluation of organic compounds in Canadian water supplies at nine municipalities along the Great Lakes (Otson 1987).

### 5.4.3 Soil

Limited data were located regarding estimation of styrene in soils or sediments (see Section 5.2.3).

### 5.4.4 Other Environmental Media

Styrene has been detected among the natural volatile components of roasted filberts, dried legumes, fried chicken, nectarines, and Beaufort cheese (Dumont and Adda 1978; Kinlin et al. 1972; Lovegren et al. 1979; Takeoko et al. 1988; Tang et al. 1983). Styrene may also enter foods by migration from polystyrene food containers and packaging materials (EPA 1988b). Concentrations of styrene measured in yogurt packaged in polystyrene containers ranged from 5.5 to 150  $\mu\text{g}/\text{L}$  (Withey 1976). Mean levels of styrene in foods packaged in plastic in the United Kingdom ranged from  $<1$  to 180  $\mu\text{g}/\text{kg}$  (Gilbert and Startin 1983). Similar concentrations of styrene were detected in other dairy products packaged in polystyrene containers (IARC 1979). The rate of styrene migration into food is mainly a function of the diffusion coefficient of the monomer in the polymer and of the lipophilicity of the food (Till et al. 1987). For example, 4%-6% of the free monomer in polystyrene packaging migrated into corn oil or sunflower oil within 10 days, while only 0.3%-0.6% migrated into milk, beef or water. Similarly, migration of styrene from foam cups into liquids such as water, tea or coffee was about 8  $\text{ng}/\text{cm}^2$ , while migration into 8% ethanol (as might be encountered in wine or other alcoholic drinks) was 36  $\text{ng}/\text{cm}^2$  (Varner and Breder 1981). However, Withey and Collins (1978) found no clear relationship between the styrene monomer content of packaging material (which varied widely) and the amount leached into food after comparable residence times. Styrene was detected, but not quantified, in samples of mother's milk from four urban areas (Pellizzari et al. 1982).

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2. Styrene Concentrations in Representative Air Samples in the United States

Location	Concentration ( $\mu\text{g}/\text{m}^3$ )		Reference
	Maximum	Mean	
Rural/ suburban	No data	0.28-0.34 <sup>a</sup>	Shah and Heyerdahl 1988; Graedel 1978
Urban	0.63-21	0.29-3.8	Grosjean and Fung 1984; Harkov et al. 1985; Hunt et al. 1986; Shah and Heyerdahl 1988; Wallace et al. 1986b; Wallace 1987
Industrial source areas	25	1.3 <sup>a</sup> -2.1	Brodinzky and Singh 1983; Pellizzari et al. 1978; Shah and Heyerdahl 1988
Hazardous waste sites	65	1.1-6.4	Harkov et al. 1985; La Regina and Bozzelli 1986
Tunnel	6.6	1.1-6.6 <sup>b</sup>	Hampton et al. 1983
Indoors	6,500	0.8-8.9	Shah and Heyerdahl 1988; Wallace et al. 1986a; Wallace 1987
Workplace	4.5x10 <sup>6</sup>	<1-1.5x10 <sup>6</sup>	Bartolucci et al. 1986; Cocheo et al. 1983; NIOSH 1983

<sup>a</sup>Median value<sup>b</sup>Range of values, no mean given

## 5. POTENTIAL FOR HUMAN EXPOSURE

Styrene has been identified as a component of cigarette smoke (EPA 1984b) and has been detected in concentrations of 18  $\mu\text{g}$  /cigarette in the smoke of cigarettes made in the United States (IARC 1979). Indoor air concentrations of styrene may be significantly higher in homes of smokers than nonsmokers (Wallace 1987).

### 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to styrene may occur by inhalation, ingestion, or dermal absorption. The most likely mode of exposure of the general population to styrene is by inhalation of indoor air (EPA 1988b). Based on the EPA (1989e) estimate that the average person spends 20.4 hours/day indoors (inhaling about 17  $\text{m}^3$  of air during that time based on an air inhalation rate of 20  $\text{m}^3/\text{day}$ ) and the range of mean indoor air concentrations presented in Table 5-2, typical indoor exposure levels to styrene may range from 14 to 151  $\mu\text{g}$  /day. Additional exposures may occur from inhalation of outdoor air and ingestion of food which was stored in polystyrene containers. Outdoor air concentrations are likely to be lower in rural than urban areas and are likely to be small compared to indoor air concentrations. Exposure from municipal drinking water is probably insignificant. However, groundwater at hazardous waste sites where styrene has been detected may provide significant exposure to styrene if used as local water supply.

Worst-case exposure estimates for styrene of 0-0.5  $\mu\text{g}$  /day from drinking water, 30  $\mu\text{g}$  /day from food, and 65,000  $\mu\text{g}$  /day from air were calculated by EPA (1988b). These estimates are based on the highest levels estimated or monitored and, therefore, reflect the highest potential exposure rather than typical exposure for the general population.

Exposure of the general population to styrene is confirmed by human monitoring data. Styrene has been identified in adipose tissue at concentrations of 8-350 ng/g (Stanley 1986), in blood at a mean concentration of 0.4  $\mu\text{g}$  /L (Antoine et al. 1986) and in exhaled breath at mean concentrations of 0.7-1.6  $\mu\text{g}$  / $\text{m}^3$  (Wallace 1987).

A large number of workers are potentially exposed to styrene. NIOSH estimates that approximately 300,000 workers at 22,000 facilities may be exposed to styrene (NOES 1989), about 30,000 of these on a full-time basis (NIOSH 1983). The highest potential exposure occurs in the reinforced plastics industry, where workers may be exposed to high air concentrations and also have dermal exposure to liquid styrene or resins (Lemasters et al. 1985; NIOSH 1983). Hemminki and Vainio (1984) estimated that heavily exposed workers in this industry in Finland might be exposed to up to 3 g of styrene per day. Significant occupational exposures may also occur in other industrial settings, including styrene polymerization, rubber manufacturing, and styrene-polyester resin facilities (Engstrom et al. 1978b; NIOSH 1983; Rappaport and Fraser 1977).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

People working in various styrene industries are likely to have the highest exposures to styrene. Lower levels may be encountered near industrial facilities or hazardous waste sites emitting styrene to outdoor air. High indoor styrene concentrations in the home may be due to emissions from building materials, consumer products, and tobacco smoke. Smokers and those eating a high proportion of foods packaged in polystyrene may also have above average exposure to styrene.

### 5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of styrene is available. Where adequate information is not available, ATSDR, in conjunction with the 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 styrene.

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. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 5.7.1 Data Needs

**Physical and Chemical Properties.** The solubility of an organic compound in water is indicative of how that chemical will partition between water, soil, and organisms (Banerjee et al. 1980; Hassett et al. 1983; Valvani et al. 1981). Clarification of the exact solubility of styrene in water would be helpful because currently a range of values is reported. The Henry's law constant and  $K_{oc}$  value for styrene need to be verified experimentally to provide more accurate predictions of air-water and soil-water partitioning.

**Production, Import/Export, Use, and Disposal.** Substantial quantities of styrene are currently produced and used in the United States (Heylin 1989; HSDB 1989; SRI 1989; USITC 1988). Production and import quantities, producers, and uses are well documented. There has been an increase in production volume over the past decade and further increases are projected. However, data on current styrene imports were not available. Quantities of styrene disposed of by various disposal methods are not known. Styrene releases into water are regulated by EPA, but styrene is not listed as a hazardous waste constituent and, therefore, land disposal restrictions do not apply to this compound. Additional information on disposal methods used for styrene and styrene-containing products and the quantities disposed of by each

## 5. POTENTIAL FOR HUMAN EXPOSURE

method would help to better characterize the potential for human exposure to this compound from disposal at waste sites or other locations.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions. It is likely that styrene will continue to be a high volume production chemical.

**Environmental Fate.** Styrene will partition among the environmental media, with a tendency to volatilize from water to air and to adsorb to soils (EPA 1984b; Roberts et al. 1980; Sato and Nakajima 1978). However, data on styrene volatilization from water and confirmation of the estimated  $K_{oc}$  value by adsorption/desorption data would be useful to estimate more accurately the tendency of styrene to partition to air and soil. Confirmation of the  $K_{oc}$  would also provide a more reliable basis for estimating the mobility of styrene in the various types of soil.

Although the reaction mechanisms of styrene transformations in the atmosphere are fairly well understood (Atkinson et al. 1982; Bignozzi et al. 1981; Hendry and Kenley 1979; Sloane and Brudzynski 1979), more information regarding the environmental fates of the transformation products would allow a more accurate prediction of the atmospheric fate of this compound. Data on biodegradation of styrene would be useful in predicting the fate and persistence of the compound in water and soil.

**Bioavailability from Environmental Media.** Styrene is known to be absorbed following inhalation, oral and dermal contact (Dutkiewicz and Tyras 1968; Engstrom et al. 1978a, 1978b; Ramsey and Anderson 1984; Ramsey and Young 1978; Withey 1976; Withey and Collins 1979). Absorption rates via inhalation are known (Withey and Collins 1978). Additional data are needed to evaluate absorption rates following oral and dermal exposure. It is believed that absorption of styrene from the gut is generally rapid and therefore contact with styrene contaminated food, soil, or water will probably also result in significant absorption. However, this may depend on the medium in which it is contained. However, actual absorption rates associated with ingestion are unknown and should be investigated.

**Food Chain Bioaccumulation.** Bioconcentration of styrene in aquatic organisms is not likely to be significant, based on both a measured BCF for a single species and an estimated BCF (EPA 1984b; Kenaga 1980; Ogata et al. 1984). No data on biomagnification of styrene in the food chain were located. Since significant bioaccumulation is unlikely, this lack of data may not be a major limitation. However, additional information on bioconcentration in several species would confirm this prediction.

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Exposure Levels in Environmental Media.** Monitoring data for styrene in air are extensive and recent data are available (Shah and Heyerdahl 1988; Wallace 1987). However, monitoring data in other environmental media using current, sensitive analytical methods are sparse. Additional data on styrene levels in water and soil, especially in the vicinity of hazardous waste sites would be useful in assessing the potential for human exposure. Quantification of styrene in cigarette smoke would also help in assessing exposure from smoking and passive smoke inhalation. Estimates of human intake from air, water, and soil have been made (EPA 1988b) and will undoubtedly be revised as additional data become available.

**Exposure Levels in Humans.** Styrene has been detected in human blood, breath, milk, and adipose tissue of the general population (Antoine et al. 1986; Pellizzari et al. 1982; Stanley 1986; Wallace.1987) and metabolites of styrene have been detected in urine of workers exposed to styrene (Elia et al. 1980; Sollenberg et al. 1988). Additional data on blood levels of styrene will be generated by the on-going study described in Section 5.7.2. However, data generated by biological monitoring of populations in the vicinity of waste sites with the most sensitive methods (Section 6.1) would be useful in assessing the magnitude of human exposures from this source.

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

### 5.7.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for styrene and other volatile organic compounds (NCHS 1988; Needham 1989). These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

No other on-going studies on the fate, transport, or exposure potential of styrene were located.

## 6. ANALYTICAL METHODS

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

As a volatile material, styrene is readily determined by gas chromatographic (GC) analysis. As a hydrocarbon, styrene is detected very sensitively by flame ionization detection (FID); its aromatic nature enables some selectivity by photoionization detection (PID); and it can be specifically identified by mass spectrometry. Styrene is usually collected from the gas phase or from vapor evolved from the sample matrix on a column of solid sorbent, such as Tenax®. Cryogenic (low temperature) collection and sorption in organic liquids are also possible.

Capillary gas chromatography, also known broadly as high-resolution gas chromatography (HRGC), has greatly facilitated the analysis of compounds such as styrene that can be measured by gas chromatography and has resulted in vast improvements in resolution and sensitivity. It has made the choice of a stationary phase less important than is the case with the use of packed columns. The instrumental capability to separate volatile analytes by HRGC is, for the most part, no longer the limiting factor in their analysis.

The specific analytical methods used to quantify styrene in biological and environmental media samples are summarized below. Table 6-1 lists the applicable analytical methods used for determining styrene in the biological fluids and tissues, and Table 6-2 lists the methods used for determining styrene in environmental samples.

### 6.1 BIOLOGICAL MATERIALS

Methods have been described for the determination of styrene in expired air (Kneip and Crable 1988a; Stewart et al. 1968), blood (Antoine et al. 1986; Bartolucci et al. 1986; Guillemin and Berode 1988; Withey and Collins 1977), urine (Dolara et al. 1984; Ghittori et al. 1987; Pezzagno et al. 1985), adipose tissue (Engstrom et al. 1978a), and other tissues (heart, lungs, liver, spleen, kidney, brain) (Withey and Collins 1977). These methods generally require styrene release from the sample matrix and collection on a

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Styrene analyte					
Adipose tissue	Evaporation into nitrogen collection as vapor	GC	No data	No data	Engstrom et al. 1978a
Breath <sup>a</sup>	Collection in Saran bag	GC/FID	0.05 ppm	No data	Stewart et al. 1968
Breath	Sorption onto silicagel, desorption into headspace	GC	0.1 ppm	No data	Kneip and Crable 1988a
Blood	Purge at 40-50°C with helium, collection on Tenax-GC/silica	GC/MS	No data	CV<5%	Antoine et al. 1986
Blood	Headspace analysis	GC/FID	No data	No data	Bartolucci et al. 1986
Blood	Collection in vacutainer with EDTA as anticoagulant, headspace analysis	GC	No data	No data	Guillemin and Berode 1988
Blood	Headspace analysis	GC	0.02 µg/mL	No data	Withey and Collins 1977
Heart, lungs, liver, spleen, kidney, brain	Hemogenate prepared for headspace analysis	GC	0.01 µg/g	No data	Withey and Collins 1977
Urine	Headspace from sample maintained at 37°C for 2 hr	GC/MS	No data	No data	Ghitori et al. 1987
Urine	Sorption on XAD-2, elution with n-hexane	HPLC/UV	<0.7 µg/L	72±10%	Dolara et al. 1984
Urine	Headspace analysis	GC/MS	No data	No data	Pezzagno et al. 1985
Styrene metabolite analyte					
Urine for MA	Extraction with ethyl acetate, derivatization to isopropyl ester	GC/FID	No data	No data	Korn et al. 1984
Urine for MA	Extraction with diethyl ether, silylation	GC	No data	No data	Engstrom et al. 1976
Urine for MA and PGA metabolites	Extraction and derivatization	GC/FID	0.05 ppm	94%MA 98% PGA	Bartolucci et al. 1986

TABLE 6-1 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine for MA metabolite	Acidification, extraction, derivatization	HRGC/FID	10 mg/L	No data	Kneip and Crable 1988b
Urine for PGA metabolite	Reduction, acidification, extraction, derivatization	HRGC/FID	10 mg/L	No data	Kneip and Crable 1988c
Urine for MA and PGA metabolites	Extraction with ethyl acetate, derivatization to methyl esters with diazomethane	GC	No data	No data	Sedivec et al. 1984
Urine for MA and PGA metabolites	Extraction with ethyl acetate, evaporation, derivatization	GC/FID	No data	97%-99% relative recovery	Baselt 1988a
Urine for MA, PGA, and hippuric acid metabolites	Direct injection	HPLC/UV	<1 µg/mL <sup>b</sup>	<3% deviation from true value at 5 µg/mL	Regnaud et al. 1987
Urine for MA and PGA (stereoselective)	Extraction and derivatization	HRGC/FID	No data	No data	Korn et al. 1987
Blood for styrene oxide	Extraction with n-hexanone, concentration by evaporation	GC/FID	1 ng/mL	72±8%	Kessler et al. 1990
Blood for styrene oxide	Extraction with benzene	GC/MS	10 ng/g	92±21%	Langvardt and Nolan 1991

<sup>a</sup>Unless otherwise designated, analyses are for styrene.

<sup>b</sup>Detection limits were 0.63 µg/mL for mandelic acid, 0.78 µg/mL for phenylglyoxylic acid, and 0.52 µg/mL for hippuric acid.

CV = coefficient of variation; EDTA = ethylene diaminetetracetic acid; FID = flame ionization detector; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; hr = hour(s); MA = mandelic acid; MS = mass spectrometry; PGA = phenylglyoxylic acid; UV = ultraviolet

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Homogenization, headspace sampling	GC/MS	<1 µg/kg	No data	Gilbert and Startin 1983
Air	Retention by activated carbon	GC <sup>a</sup>	No data	No data	ASTM 1989a
Air	Retention by activated carbon, elution with carbon disulfide	GC <sup>b</sup>	No data	No data	ASTM 1989b
Air	Retention by activated carbon, elution with carbon disulfide	HRGC/FID	0.01 mg/sample	No data	NIOSH 1984
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax <sup>®</sup>	GC/PID	0.01 µg/L	96%-104%	EPA 1989f
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax <sup>®</sup>	GC/PID	0.008 µg/L	No data	EPA 1989g
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax <sup>®</sup>	HRGC/MS	0.20 µg/L	120% (at 1 µg/L)	EPA 1989h
Water	Purge by helium, collection on activated charcoal/silica gel/Tenax <sup>®</sup>	HRGC/MS	0.04 µg/L	102%	EPA 1989i
Soil, low level	Purge by helium, collection on solid, thermal desorption	GC/MS	4 µg/kg	No data	EPA 1986c
Solid waste, nonwater miscible	Purge by helium, collection on solid, thermal desorption	GC/MS	500 µg/kg <sup>c</sup>	No data	EPA 1986c
Solid waste	Purge by helium, collection on solid, thermal desorption	GC/MS	500 µg/kg <sup>c</sup>	No data	EPA 1986b

<sup>a</sup>Absorption characteristics for sampling atmospheric vapor with activated carbon for subsequent analysis by GC.

<sup>b</sup>Generic method for the determination of organics.

<sup>c</sup>Estimated from detection limits in water.

FID = flame ionization detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; PID = photoionization detection; UV = ultraviolet

## 6. ANALYTICAL METHODS

column of solid sorbent or collection as headspace gas. Cryogenic collection should also be possible. Of the available methods for detecting styrene, flame ionization detection (FID) is the most sensitive and mass spectrometry (MS) is the most specific.

The major metabolites of styrene in humans are MA and PGA. Detection of these metabolites in urine is the most commonly performed procedure as an indicator of exposure to styrene. Procedures have been described for their measurement in urine (Baselt 1988a; Dolara et al. 1984; Engstrom et al. 1976; Xneip and Crable 1988b; Kneip and Crable 1988c; Korn et al. 1984; Pezzagno et al. 1985; Sedivec et al. 1984; Sollenberg et al. 1988). Generally these styrene metabolites are converted to volatile derivatives and measured gas chromatographically or determined directly by high performance liquid chromatography. Two other styrene metabolites that may result from exposure to styrene are 4-vinylphenol (Pfaffli et al. 1981) and styrene glycol-(phenyl ethylene glycol) (Guillemin and Berode 1988), but methods for the detection of these metabolites in biological materials have not been worked out in detail. Sensitive methods are also available for measuring styrene oxide in blood (Kessler et al. 1990; Langvardt and Nolan 1991), although these techniques are probably more useful in research on styrene toxicity than in detecting or quantifying styrene exposure.

Methods for detection of styrene and its metabolites in biological materials are summarized in Table 6-1.

### 6.2 ENVIRONMENTAL SAMPLES

Styrene determined in environmental samples is usually collected on solid sorbents (from air) or on solid sorbents after purging in a gas stream (water, soil, solid waste samples). Styrene from such samples is measured very sensitively by gas chromatography with flame ionization detection (GC/FID) and very specifically by gas chromatography with mass spectrometric detection (GC/MS). Methods for the determination of styrene in environmental samples have been standardized by the American Society for Testing and Materials (ASTM 1989b), U.S. Environmental Protection Agency (EPA 1986a, 1986b; EPA 1989b, 1989c, 1989d), and National Institute for Occupational Safety and Health (NIOSH 1984). As shown by the data in Table 6-1, relatively low detection limits (0.01 mg/sample, 0.10 µg /L in water, 4 µg /kg in soil, 500 µg /kg in solid waste) can be achieved for the determination of styrene in environmental samples and the accuracy appears to be acceptable for those limited cases in which accuracy data are available. No significant reports were found pertaining to styrene degradation products in environmental samples.

Methods for the determination of styrene in environmental samples are summarized in Table 6-2.

## 6. ANALYTICAL METHODS

### 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of styrene is available. Where adequate information is not available, ATSDR, in conjunction with the 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 styrene.

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. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 6.3.1 Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** Biological monitoring of styrene exposure has been reviewed (Guillemin and Berode 1988). Sensitive and selective methods are available for the qualitative and quantitative measurement of styrene and its two major metabolites, MA and PGA, in samples from exposed individuals after the analytes are separated from their biological sample matrix. The concentration of these metabolites in urine has been found to correlate with average exposure levels in air (Harkonen et al. 1978), and so may be used as a biomarker of exposure. However, measurements of MA and PGA are not specific for this purpose (Bartolucci et al. 1986) and these metabolites can result from the metabolism of other organic substances, particularly ethylbenzene (Baselt 1988b). As noted in Chapter 5 for studies of the general population, styrene has been identified in adipose tissue at concentrations of 8-350 ng/g (Stanley 1986), in blood at a mean concentration of 0.4 µg /L (Antoine et al. 1986) and in exhaled breath at mean concentrations of 0.7-1.6 µg /L. Levels of MA and PGA in biological samples from the general population probably are below the detection limits of methods that are currently used (Baselt 1988a). However, it is likely that normal background levels of these metabolites in unexposed individuals are too low to be of any significance. Although new and improved methods for the determination of styrene and its metabolites in biological samples need not have a high priority, additional work on standardization of these methods for use in biological samples accompanied by additional studies involving interlaboratory comparisons of recovery, accuracy, and precision data would be useful.

As discussed in Section 2.5.2, clinical means have been proposed to indicate exposure to styrene. In general, these are not sufficiently sensitive, specific, or well characterized. The most common symptom of

## 6. ANALYTICAL METHODS

exposure, impairment of central nervous system function, is not at all unique to styrene. Neither cytogenetic monitoring of peripheral lymphocytes nor unscheduled DNA synthesis have been sufficiently well characterized as biomarkers of exposure to styrene.

There is currently some information that can be used to correlate levels of biomarkers of exposure to styrene in biological media with adverse health effects. Central nervous system depression has been correlated with a urinary MA concentration of 800 mg/L or higher and a decrement in psychomotor performance in association with a concentration of 1,200 mg/L or more (Harkonen et al. 1978). The styrene concentrations in air producing these effects and urinary MA levels were relatively high. Studies to determine if effects at lower levels of exposure could also be correlated to metabolite levels in urine would be valuable. However, the design of studies involving controlled inhalation exposures in humans is precluded by the potential carcinogenicity of styrene.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** In an occupational setting the medium that is of most concern for human exposure to styrene is air, although at Superfund sites contaminated groundwater may pose a greater danger. Methods are well developed for the determination of styrene in water and air with excellent selectivity and sensitivity (ASTM 1989a; EPA 1989f, 1989g, 1989i; NIOSH 1984). Methods for the determination of styrene in soil and waste samples have been available for a shorter length of time and require additional testing and validation (EPA 1986b, 1986c).

The detection limits for styrene in environmental media cited in Table 6-2 (0.01 mg/sample, typically 10 L) (NIOSH 1984), 0.04 µg /L in water (EPA 1989i), 4 µg /kg in soil (EPA 1986c) are low enough to enable the determination of styrene in any environmental medium likely to pose a hazard to health based upon information currently available in the literature. These detection limits are probably below most ambient background levels of styrene.

Sampling methodologies for compounds such as styrene continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction and purification procedures (Green and LePape 1987). It is desirable to have means to measure organic compounds such as styrene in situ in water and other environmental media without the need for sampling and extraction procedures to isolate the analyte prior to analysis.

In regard to methods for determining parent styrene and degradation products in environmental media the following conclusions may be drawn: Because styrene can be detected instrumentally and determined in air and normal water samples with totally adequate selectivity and sensitivity, no additional data are needed at this time. A moderate need exists to improve methodologies to determine styrene in soil, sludges, and solid wastes. Styrene degradation products are a different matter in that little information is available on their determination in environmental samples. In air these

## 6. ANALYTICAL METHODS

compounds should consist predominantly of photochemical oxidation products, whereas in water and soil samples they are expected to be biodegradation products. Additional research is needed on the determination of these materials.

### 6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of styrene and other volatile organic compounds in blood. These methods use purge-and-trap methodology and magnetic mass spectrometry which gives detection limits in the low parts per trillion range.

Research is underway at the Cooperative Institute for Research in Environmental Sciences (CIRES) at the University of Colorado, Boulder, to improve methods for the analysis of styrene and related compounds in environmental samples, particularly atmospheric samples.

Studies are also underway that would improve the means for determining styrene, its metabolites, and related compounds in biological samples and environmental media. Improvements continue to be made in chromatographic separation and detection. Problems associated with the collection of styrene on a sorbent trap, followed by thermal desorption, may be overcome with direct purging to a capillary column with whole column cryotrapping (Pankow and Rosen 1988). Current activities in the areas of supercritical fluid extraction (King 1989) and supercritical fluid chromatography (Smith 1988) include focus on compounds such as styrene and its metabolites in biological samples and environmental media. Fourier transform infrared flow cell detectors are sensitive and selective for the detection of compounds such as styrene that have been separated by supercritical fluid chromatography (Wieboldt et al. 1988). Immunoassay methods of analysis are very promising for the determination of various organic pollutants and toxicants, and it is reasonable to assume that styrene, and particularly its metabolites, are candidates for this type of analysis.

## 7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for styrene by various national and state agencies. These values are summarized in Table 7-1.

## 7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Styrene

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
IARC	Carcinogenic classification	Group 2B <sup>a</sup>	IARC 1987
<u>NATIONAL</u>			
Regulations:			
a. Air:			
OSHA	PEL TWA STEL	50 ppm (215 mg/m <sup>3</sup> ) 100 ppm (425 mg/m <sup>3</sup> )	OSHA 1989 (29 CFR 1910.1000) Table Z-1-A
b. Water:			
EPA ODW	MCLG MCL	0.1 mg/L <sup>b</sup> 0.1 mg/L	EPA 1991
	Monitoring for unregulated contaminants	Yes	EPA 1987b
EPA OWRS	General permits under NPDES	Yes	40 CFR 122, Appendix D, Table V
	General Pretreatment Regulations for Existing and New Sources of Pollution	Yes	40 CFR 403
	Hazardous substance Reportable quantity	Yes 1,000 pounds	40 CFR 116 40 CFR 117.3
c. Other:			
EPA OERR	Reportable quantity	1,000 pounds	EPA 1989a (40 CFR 302.4)
EPA OSW	Groundwater monitoring list (Appendix IX)	Yes	EPA 1987c (40 CFR 264)
EPA OTS	Toxic chemical release reporting rule	Yes	EPA 1988a (40 CFR 372)
	Preliminary assessment information rule	Yes	EPA 1982 (40 CFR 712.30)
FDA	Food additive-synthetic flavoring substance	Yes	21 CFR 172.515
	Indirect food additive - adhesives, styrene block polymers	Yes	21 CFR 175.105, 177.181
	Component of polymers in paper in contact with dry food	Yes	21 CFR 176.180
	Residual styrene monomer limit in polystyrene intended for use in contact with food	1% by weight	21 CFR 177.1640
Guidelines:			
a. Air:			
ACGIH	TLV TWA STEL	50 ppm (215 mg/m <sup>3</sup> ) 100 ppm (425 mg/m <sup>3</sup> )	ACGIH 1988
NIOSH	IDLH TWA (10 hr) Ceiling (15 min)	5,000 ppm 50 ppm 100 ppm	NIOSH 1985
b. Water:			
EPA ODW	Health Advisories		EPA 1987a
	One-day (child)	22.5 mg/L	
	Ten-day (child)	2 mg/L	
	Longer-term (child)	2 mg/L	
	(adult)	7 mg/L	
	Lifetime	0.14 mg/L	

## 7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
c. Other:			
EPA	Carcinogenic Classification (under review by EPA)	Group B2/C <sup>c</sup>	EPA 1989b
	Cancer slope factor	0.03 (mg/kg/day) <sup>-1</sup>	EPA 1988b
	RfD (oral)	0.2 mg/kg/day	IRIS 1989
<b>STATE</b>			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1989
Connecticut		4.30 mg/m <sup>3</sup> (8 hr)	
Indiana		3.45 µg/m <sup>3</sup> (annual)	
Indiana (Indianapolis)		2.17 mg/m <sup>3</sup> (8 hr)	
Kansas		1.75 µg/m <sup>3</sup> (annual)	
Kansas (Kansas City)		3.45 µg/m <sup>3</sup> (annual)	
Massachusetts		115.81 µg/m <sup>3</sup> (24 hr)	
		1.75 µg/m <sup>3</sup> (allowable ambient level)	
Nevada		5.12 mg/m <sup>3</sup> (8 hr)	
New York		0.716 mg/m <sup>3</sup> (1 yr)	
North Carolina		42.5 mg/m <sup>3</sup> (15 min)	
		1.30 mg/m <sup>3</sup> (24 hr)	
North Carolina (Forsyth County)		1.34 mg/m <sup>3</sup> (24 hr)	
		42.5 mg/m <sup>3</sup> (15 min)	
North Dakota		2.15 mg/m <sup>3</sup> (8 hr)	
		4.25 mg/m <sup>3</sup> (1 hr)	
Rhode Island		30.0 µg/m <sup>3</sup> (annual)	
Vermont		0.512 mg/m <sup>3</sup> (annual)	
Virginia		3.60 mg/m <sup>3</sup> (24 hr)	
b. Water:	Drinking water quality standards		FSTRAC 1988
Arizona		140 µg/L	
Maine		270 µg/L	
Minnesota		140 µg/L	
Massachusetts		0.005 mg/L	ORS 1989
		(guideline)	
Wisconsin		10 µg/L	

<sup>a</sup>Group 2B: possible human carcinogen.

<sup>b</sup>EPA proposed an MCLG and an MCL of 0.1 mg/L based on a Group C carcinogen classification and an MCLG of zero and an MCL of 0.005 mg/L based on a Group B2 carcinogen classification.

<sup>c</sup>Group B2: probable human carcinogen; Group C: Possibly carcinogenic to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfD = Reference Dose; STEL = Short Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average



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## 9. GLOSSARY

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

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

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

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

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

**Carcinogen** -- A chemical capable of inducing cancer.

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

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

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

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

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

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

## 9. GLOSSARY

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

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

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

**In Vivo** -- Occurring within the living organism.

**Lethal Concentration<sub>(Lo)</sub> (LC<sub>Lo</sub>)** -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)** -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(Lo)</sub> (LD<sub>Lo</sub>)** -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)** -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)** -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

**No-Observed-Adverse-Effect Level (NOAEL)** -- The dose of chemical at which there were no statistically or biologically significant increases in frequency

## 9. GLOSSARY

or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ( $K_{ow}$ )** -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.  
**Permissible Exposure Limit (PEL)** -- An allowable exposure level in workplace air averaged over an 8-hour shift.

**$q_1^*$**  -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The  $q_1^*$  can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  for air).

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

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

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

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

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

## 9. GLOSSARY

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

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

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

**Toxic Dose (TD<sub>50</sub>)** -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Uncertainty Factor (UF)** -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

## APPENDIX A

## USER'S GUIDE

## Chapter 1

## Public Health Statement .

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance. The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

## Chapter 2

## Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

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

## LEGEND

## See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

## APPENDIX A

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

- (2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.
- (3) Health Effect the major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAEL's and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column.
- (6) Exposure Frequency / Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "c").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

## APPENDIX A

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOEL of 10 ppm.

- (10) Reference The complete reference citation is given in Chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis. In experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See LSE Figure 2-1**

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

- (13) Exposure Duration the same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect these are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

APPENDIX A

- (18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

# SAMPLE

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

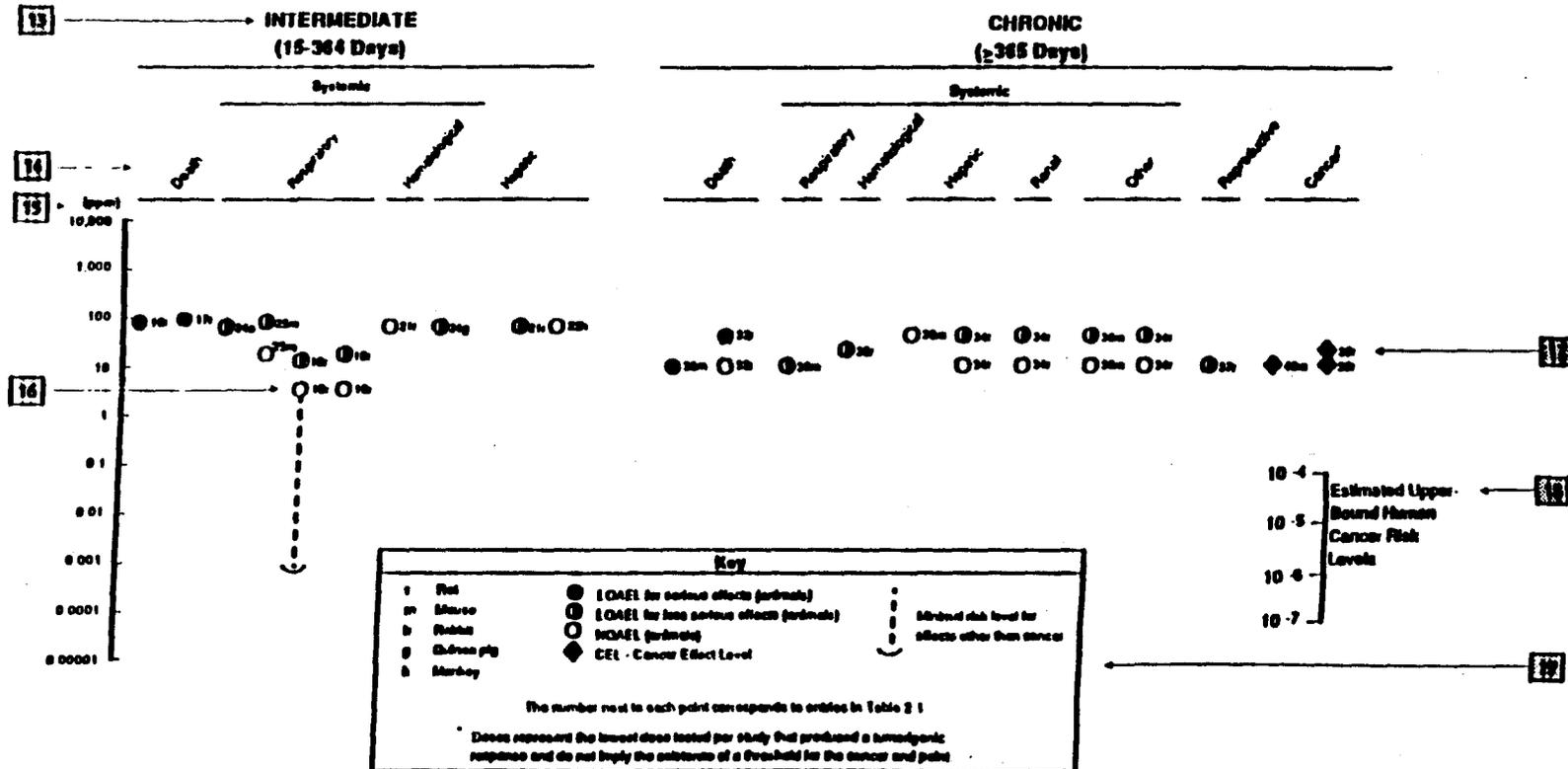
Key to figure <sup>a</sup>	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>2</b> → INTERMEDIATE EXPOSURE							
<b>3</b> → Systemic	<b>5</b> ↓ Rat	<b>6</b> ↓ 13 wk 5d/wk 6hr/d	<b>7</b> ↓ Resp	<b>8</b> ↓ 3 <sup>b</sup>	<b>9</b>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

<sup>a</sup> The number corresponds to entries in Figure 2-1.

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

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

# SAMPLE



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

**APPENDIX A****Chapter 2 (Section 2.4)****Relevance to Public Health**

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

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

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, -chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

## APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

## APPENDIX B

## ACRONYMS, ABBREVIATIONS, AND SYMBOLS USED IN TEXT

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f <sub>1</sub>	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	octanol-soil partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration low
LC <sub>50</sub>	lethal concentration 50 percent kill
LD <sub>Lo</sub>	lethal dose low
LD <sub>50</sub>	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	Mandelic acid

## APPENDIX B

mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSH TIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
PGA	Phenylglyoxlic acid
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	<u>STORAGE</u> and <u>RETRIEVAL</u>
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than

## APPENDIX B

$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
$\%$	percent
$\alpha$	alpha
$\beta$	beta
$\delta$	delta
$\gamma$	gamma
$\mu\text{m}$	micron
$\mu\text{g}$	microgram



## APPENDIX C

## PEER REVIEW

A peer review panel was assembled for styrene. The panel consisted of the following members: Dr. Arthur Gregory, private consultant, Washington, DC; Dr. James Withey, Research Scientist, Environmental Health Center, Ottawa, Ontario, Canada; and Dr. Carroll Snyder, Research Professor/Director, Laboratory of Inhalation Carcinogenesis and Toxicology, New York University, New York, NY. These experts collectively have knowledge of styrene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. A second panel of reviewers was assembled to review the sections on mitigation of effects. This panel consisted of: Dr. Brent Burton, Medical Director, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Alan Hall, Private Consultant, Evergreen, Colorado; and Dr. Alan Woolf, Director of Clinical Pharmacology and Toxicology, Massachusetts Poison Control System, The Children's Hospital, Boston, Massachusetts. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

