TOXICOLOGICAL PROFILE FOR ACROLEIN

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

December 1990

DISCIAIMER

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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.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. 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, and
>
> (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, but no less often than every three years, as required by CERCLA, as amended.

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 significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. 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 and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about acrolein and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). Acrolein (pronounced: acre lean) has been found at 7 of these sites. However, we do not know how many of the 1177 NPL sites have been evaluated for acrolein. As EPA evaluates more sites, the number of sites at which acrolein is found may change. The information is important for you because acrolein may cause harmful health effects and because these sites are potential or actual sources of human exposure to acrolein.

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 substance such as acrolein, 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 ACROLEIN?

Acrolein is a clear or yellow liquid with a disagreeable odor. It burns easily. It changes into a vapor much faster than water does at normal temperatures. When heated to high temperatures, it can change into a vapor very quickly. Near hazardous waste sites in which acrolein is not properly stored, acrolein might be found in the air, water, or soil. Acrolein does not stay in the air or water for very long. Acrolein that enters the air as a vapor changes into other chemicals within days. Acrolein dissolves easily in water. Within days, some of the acrolein in water changes into a vapor and enters the air. The acrolein left in the water is changed into other chemicals, which are rapidly broken down. Acrolein that enters the soil is washed out in water and changes into a vapor, and it is oxidized; we do not know how long this takes.

Acrolein is used to make other chemicals and pesticides and is found in some livestock feeds and pesticides. Small amounts of acrolein can be formed and can enter the air when organic matter such as trees and other plants, including tobacco, are burned and also when fuels such as gasoline and oil are burned. Please refer to Chapters 3, 4, and 5 for more information.

1. PUBLIC HEALTH STATEMENT

1.2 HOW MIGHT I BE EXPOSED TO ACROLEIN?

If you live near a hazardous waste site in which acrolein is not stored properly, you could be exposed to acrolein from breathing air or drinking water. Because acrolein easily changes into a vapor, you are more likely to be exposed from breathing air than from drinking water. A child playing in this hazardous waste site could be exposed by drinking water that contains small amounts of acrolein, by eating soil that contains acrolein, or by getting soil on his or her skin.

You could be exposed to acrolein in many other ways that have nothing to do with hazardous waste sites. Acrolein can be formed by the breakdown of many pollutants found in outdoor air. Burning tobacco and other plants forms acrolein, and you breathe acrolein when you smoke tobacco or are near someone who is smoking. You also breathe acrolein when you are near automobiles, because burning gasoline forms acrolein, which enters the air. If you live near an oil or coal power plant, you breathe small amounts of acrolein. Acrolein is formed when fats are heated. Small amounts of acrolein may also be found in foods such as fried foods, cooking oils, and roasted coffee. You could breathe acrolein if you work in an industry that uses acrolein to make other chemicals.

There is very little information on the levels of acrolein that are usually in outside air, but they are probably low. However, in several large cities acrolein has been measured at levels of 9 parts acrolein in one billion parts air (9 ppb). The levels in inside air can be much higher if you smoke tobacco. For example, in a car with three people smoking and the windows closed, you could breathe in 300 ppb.

Acrolein has not been found in drinking water and is not commonly found in surface waters such as lakes and streams. The background levels of acrolein in these waters or in soil are not known. Although we know acrolein is in certain foods, the amount that is in the foods that you eat is not known.

Please refer to Chapter 5 for more information on how you might be exposed to acrolein.

1.3 HOW CAN ACROLEIN ENTER AND LEAVE MY BODY?

If you breathed acrolein, most of it would enter your body within minutes. If you swallowed acrolein or spilled it on your skin, some of it would probably enter your body, but we do not know how much or how fast. Once in your body, acrolein changes into other chemicals called metabolites. This probably occurs within minutes or hours. Some of these metabolites leave your body in your urine. It is not known how long this takes. For further information on how acrolein can enter and leave your body, see Chapter 2.

1.4 HOW CAN ACROLEIN AFFECT MY HEALTH?

How a chemical affects your health depends on how much you are exposed to and for how long. As the level and length of your exposure increase, the effects are likely to become more severe. If you breathed low levels of acrolein for a short time, your eyes might water and your nose and throat might become sore. These effects disappear within minutes after the exposure stops. However, if you were exposed to higher levels, your lungs might be affected more severely and for a longer time. Breathing very high levels of acrolein might affect your lungs so severely that you might die. We do not know if eating food or drinking water containing acrolein affects your health. No one knows if breathing or eating acrolein or spilling it on your skin causes birth defects, affects fertility, or causes cancer. For further information on the health effects of acrolein in animals and humans, see Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The levels of acrolein in air, drinking water, and food associated with known human and animal health effects other than cancer are summarized in Tables l-l through l-4. As shown in Table l-l, acrolein irritates your eyes, nose and throat as the exposure level increases from 0.17 parts acrolein in one million parts air (0.17 ppm = 170 ppb) to 0.43 ppm. As shown in Table l-2, exposure to higher levels of acrolein can cause death in animals. If the animal does not die, severe changes in the lungs and lower airways will occur. Lung effects also occur in animals exposed to low levels of acrolein. You can smell acrolein at levels above 0.16 ppm. So, you would probably smell acrolein and notice eye, nose, and throat irritation before it harms your lungs. Minimal Risk Levels (MRLs) are also included in Tables l-1 and l-3. These MRLs were derived from human and animal data for both short-term and long-term exposure, as described in Chapter 2 and in Tables 2-l and 2-2. The MRLs provide a basis for comparison to levels that people might encounter in air or in food or drinking water. If a person is exposed to acrolein at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Since these levels are based on information currently available, there is always some uncertainty associated with them. Also, since the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or levels of risk of cancer. Tables l-3 and l-4 show how little we know about how acrolein in water or food affects your health. Further information on levels of acrolein associated with effects is in Chapter 2.

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

We know of no test to determine whether you have been exposed to acrolein. For more detailed information, see Chapters 2 and 6.

TABLE 1-1. Human Health Effects from Breathing Acrolein*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
0.00005		Minimal Risk Level (see Section 1.5 for discussion).
0.17	40 minutes	Eye irritation.
0.26	40 minutes	Nose irritation.
0.43	40 minutes	Throat irritation.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
0.000009		Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).
		The health effects of long-term exposure of humans to air containing specific levels of acrolein are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.
**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-2. Animal Health Effects from Breathing Acrolein

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
0.1	5 days	Increased risk of infection in mice.
1.7	5 days	Changes in the appearance of the lower airway in mice.
3.7	9 days	Death in monkeys.
4.0	10 days	Death in male rats.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
0.4	13 weeks	Changes in the appearance of the upper airway in rats.
0.7	6 weeks	Changes in the lungs of guinea pigs.
0.7	6 weeks	Changes in the lungs of monkeys.
4.0	9 weeks	Severe changes in the lower airway of rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Acrolein*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects of short-term exposure of humans to food containing acrolein are not known.
Levels in Water		The health effects of short-term exposure of humans to water containing acrolein are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects of long-term exposure of humans to food containing acrolein are not known.
Levels in Water (ppm) 0.02		Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Acrolein

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects*
		The health effects of short-term exposure of animals to food containing acrolein are not known.
Levels in Water (ppm)		
80	3 days	Death in rats.
9	13 days	Miscarriages in rabbits.
36	13 days	Stomach ulcers in rabbits.
72	13 days	Birth defects in rats.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects of long-term exposure of animals to food containing acrolein are not known.
Levels in Water (ppm)		
4	24 months	Decreased number of blood cells in rats.
24	18 months	Death in mice.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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

The Environmental Protection Agency (EPA) recommends that the level of acrolein in lakes and streams be limited to 0.32 parts of acrolein per million parts of water for the prevention of possible human health effects from drinking water or eating fish or shellfish contaminated with acrolein. The EPA has restricted the use of all pesticides containing acrolein and has also identified acrolein as a toxic waste. The EPA requires that companies that make, transport, treat, store, or dispose of acrolein comply with the regulations of a federal hazardous waste management program. The EPA has also proposed standards that limit the amount of acrolein put into publicly owned wastewater treatment plants. EPA requires that releases or spills of 1 pound or more be reported to the National Response Center. The Food and Drug Administration (FDA) has determined that levels of acrolein used to prepare modified food starch must not be more than 0.6%.

The Occupational Safety and Health Administration (OSHA) has set a limit of 0.1 ppm acrolein in workroom air to protect workers during an 8-hour shift over a 40-hour workweek. The National Institute for Occupational Safety and Health (NIOSH) recommends that the concentration in workroom air be limited to 0.1 ppm averaged over an 8-hour shift.

1.8 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 give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in the recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to acrolein. Its purpose is to present levels of significant exposure for acrolein based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of acrolein and (2) a depiction of significant exposure levels associated with various adverse health effects.

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 data in this section are 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, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund 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) are of interest to health professionals and citizens alike. Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of

extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these 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

2.2.1.1 Death

The only available information regarding lethal effects in humans after inhalation exposure to acrolein was provided by Gosselin et al. (1979), who described a case of a 4-year-old boy exposed to smoke containing acrolein from an overheated fryer for 2 hours; the boy's 2-year-old brother also died; however, no details were reported. After 24 hours, death occurred by asphyxia. The autopsy revealed massive cellular desquamation of the bronchial lining and miscellaneous debris in the bronchial lumen. Also, multiple pulmonary infarcts were observed. The information provided by this case report must be considered qualitative only, since smoke components other than acrolein may have contributed to the pathology.

Exposure of rats to concentrations of acrolein in the air higher than 7 ppm for short periods of time (<l hour) caused death in approximately l-11 days (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). In all cases, death was attributed to severe effects on the respiratory tract including obstruction of trachea and bronchi, and pulmonary edema and hemorrhage. A single exposure to a low concentration of acrolein and repeated exposures to lower concentrations (3-4 ppm) caused death in rats and monkeys before the 10th day of exposure (Carpenter et al. 1949; Kutzman et al. 1984, 1985; Lyon et al. 1970). The cause of death was not reported for the rats, but in monkeys it was attributed to respiratory congestion. The data in experimental animals clearly indicate that the respiratory system is a primary target of acrolein exposure following inhalation and show an inverse relationship between the exposure concentration and the time it takes for death to occur after acute duration exposures. Furthermore, the information provided by animal data regarding cause of death is in good agreement with observations made in humans after accidental exposure (Champeix et al. 1966; Gosselin et al. 1979). Reliable values for lethality in experimental animals after inhalation exposure to acrolein are presented in Table 2-l and Figure 2-l.

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 30 min/d				130 (LC_{50})	Skog 1950
2	Rat	62 d 5 d/wk 6 hr/d		1.4		4.0[a]	Kutzman et al. 1985
3	Rat	1 d 4 h/d				8	Carpenter et al. 1949
4	Rat	1 d 10 min/d				327 (LC_{50})	Catilina et al. 1966
5	Monkey	6 wk 5 d/wk 8 hr/d		0.7		3.7[a]	Lyon et al. 1970
Systemic							
6	Human	1 d 40 min/d	Derm/Oc Resp Resp		0.17[b,c] (eye irrit) 0.26[b] (nose irrit) 0.43[b] (throat irrit)		Weber-Tschopp et al. 1977
7	Human	1 d 5-10 min	Derm/Oc		0.81 (eye irrit)	1.22 (eye irrit)	Sim and Pattle 1957
8	Human	1 d 1 hr/d	Resp Derm/Oc		0.3 (decr resp rate) 0.3 (eye irrit)		Weber-Tschopp et al. 1977
9	Rat	5 d 4 hr/d	Hepatic Other		4.0 (decr rel wt) 4.0 (decr body wt)		Murphy et al. 1964
10	Rat	1 d 10 min/d	Resp			327 (epithelial destruction)	Catilina et al. 1966
11	Rat	9 d 4 hr/d	Hepatic		3.9 (decr rel wt)		Murphy et al. 1964

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
12	Rat	1 d 4 hr/d	Resp		12 (resp irrit)		Murphy et al. 1964
13	Rat	1 d 30 min/d	Resp Derm/Oc			130 (lung hemorrhage) 130 (sev irrit)	Skog 1950
14	Rat	20-81 hr	Hepatic	1.0	2.1[a] (incr wt)		Murphy et al. 1964
15	Mouse	1 d 30 min/d	Resp		2.9 (RD_{50})		Nielsen et al. 1984
16	Mouse	1 d 10 min/d	Resp		1.41 (RD_{50})		Steinhagen and Barrow 1984
17	Mouse	5 d 6 hr/d	Resp		1.7[a] (RD_{50})		Buckley et al. 1984
18	Mouse	1 d 10 min/d	Resp		1.03 (RD_{50})		Steinhagen and Barrow 1984
19	Mouse	4 d 3 hr/d	Resp		1.7 (RD_{50})		Kane and Alarie 1977
20	Gn pig	1 d 2 hr/d	Resp	0.6			Murphy et al. 1963
21	Gn Pig	1 d 60 min/d	Resp		17 (decr resp rate)		Davis et al. 1967
Immunological							
22	Mouse	5 d 3 hr/d			0.1[a] (decr resistance)		Aranyi et al. 1986
23	Mouse	1 d 8 hr/d			3 (decr resistance)		Astry and Jakab 1983

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Death							
24	Rat	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970
25	Mouse	5 wk 1 hr/d		44			Watanabe and Aviado 1974
26	Gn Pig	6 wk 5 d/wk 8 hr/d		3.7			Lyon et al. 1970
27	Hamster	13 wk 5 d/wk 6 hr/d		4.9			Feron et al. 1978
28	Monkey	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970
Systemic							
29	Rat	13 wk 5 d/wk 6 hr/d	Resp Cardio Hemato Renal	1.4 4.9	0.4[a,d] (metaplasia) 4.9 (incr hrt wt) 4.9 (incr kdy wt)	4.9 (lung hemorrhage)	Feron et al. 1978
30	Rat	6 wk 5 d/wk 8 hr/d	Resp Renal Derm/Oc Other	3.7 3.7	0.7 (lung inflammation) 3.7 (decr bw gain)		Lyon et al. 1970
31	Rat	3 wk 5 d/wk 6 hr/d	Resp Other		3.0 (epithelial dysplasia) 3.0 (decr bw gain)		Leach et al. 1987

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
32	Rat	62 d 5 d/wk 6 hr/d	Resp Cardio Hepatic Other	 1.4 1.4	0.4 (inflammation) 4.0 (incr heart wt) 4.0 (incr liver wt) 4.0 (decr bw gain)	4.0[a] (squamous metaplasia)	Kutzman et al. 1984
33	Rat	>60<180d 7 d/wk 24 hr/d	Resp Other		0.55 (incr lung wt) 0.55 (decr bw gain)		Bouley et al. 1975
34	Rat	62 d 5 d/wk 6 hr/d	Resp Other		1.4 (lung hyperplasia) 4.0 (decr bw gain)	4.0 (lung edema and decr func)	Costa et al. 1986
35	Rat	62 d 5 d/wk 6 hr/d	Resp Cardio Renal Other	 	1.4 (bronchiolar inflammation) 4.0 (incr heart wt) 4.0 (incr kdy wt) 4.0 (decr bw gain)	4.0 (bromchiolar necrosis)	Kutzman et al. 1985
36	Gn Pig	90 d 7 d/wk 24 hr/d	Resp Cardio Hepatic	0.22 1.8 0.22	1.0 (lung inflammation) 1.0 (liver inflammation)		Lyon et al. 1970
37	Gn Pig	6 wk 5 d/wk 8 hr/d	Resp Hemato Renal Derm/Oc Other	 3.7 3.7 3.7 3.7	0.7[a] (lung inflammation)		Lyon et al. 1970
38	Hamster	13 wk 5 d/wk 6 hr/d	Resp Cardio Hemato Hepatic Renal Derm/Oc Other	0.4 1.4 4.9 1.4 1.4	1.4 (epithelial inflammation) 4.9 (incr hrt wt) 4.9 (incr PCV) 4.9 (incr kdy wt) 4.9 (sens irrit) 4.9 (decr bw gain)	4.9 (tracheal metaplasia)	Feron et al. 1978

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
39	Monkey	6 wk 5 d/wk 8 hr/d	Resp Hemato Hepatic Renal Derm/Oc Other	 3.7 3.7 3.7 0.7	0.7[a] (lung inflammation) 3.7 (eye irrit) 3.7 (decr bw gain)	3.7 (lung hemorrhage)	Lyon et al. 1970
40	Monkey	90 d 7 d/wk 24 hr/d	Resp Cardio Derm/Oc Other	 1.8 1.8	1.8 (tracheal hyperplasia) 1.0 (eye irrit)	 1.8 (sev eye irrit)	Lyon et al. 1970
Immunological							
41	Rat	3 wk 5 d/wk 6 hr/d		3.0			Sherwood et al. 1986
42	Rat	3 wk 5 d/wk 6 hr/d		3.0			Leach et al. 1987
Neurological							
43	Rat	62 d 5 d/wk 6 hr/d			4.0 (incr brain wt)		Kutzman et al. 1984
44	Rat	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970
45	Gn Pig	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970
46	Hamster	13 wk 5 d/wk 6 hr/d		4.9			Feron et al. 1978

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Neurological							
47	Monkey	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970
Reproductive							
48	Rat	>60<180d 7 d/wk 24 hr/d		0.55			Bouley et al. 1975
CHRONIC EXPOSURE							
Death							
49	Hamster	52 wk 5 d/wk 7 hr/d		4			Feron and Kruysse 1977
Systemic							
50	Rat	10-18 mo 7 d/wk 1 hr/d	Resp Other	8	8 (hyperplasia)		Le Bouffant et al. 1980
51	Hamster	52 wk 5 d/wk 7 hr/d	Resp Other		4 (epithelial metaplasia) 4 (decr bw gain)		Feron and Kruysse 1977

[a]Presented in Table 1-2.
[b]Presented in Table 1-1.
[c]Used to derive an acute inhalation MRL of 0.00005 ppm, which is presented in Table 1-1; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).
[d]Used to derive an intermediate inhalation MRL of 0.000009 ppm, which is presented in Table 1-1; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1000 (10 for extrapolation from animals to humans, 10 for human variability, and 10 for use of a LOAEL).

bw = body weight; Cardio = cardiovascular; d = day; decr = decreased; Derm/Oc = dermal/ocular; func = function; Gn Pig = guinea pig; Hemato = hematological; his = histology; hr = hour; hrt = heart; incr = increased; irrit = irritation; kdy = kidney; LC_{50} = concentration in the air that caused death to 50% of the animals; mo = month; PCV = packed cell volume; RD_{50} = concentration in the air that caused 50% reduction in respiratory rate; rel = relative; Resp = respiratory; sens = sensory; sev = severe; wk = week; wt = weight.

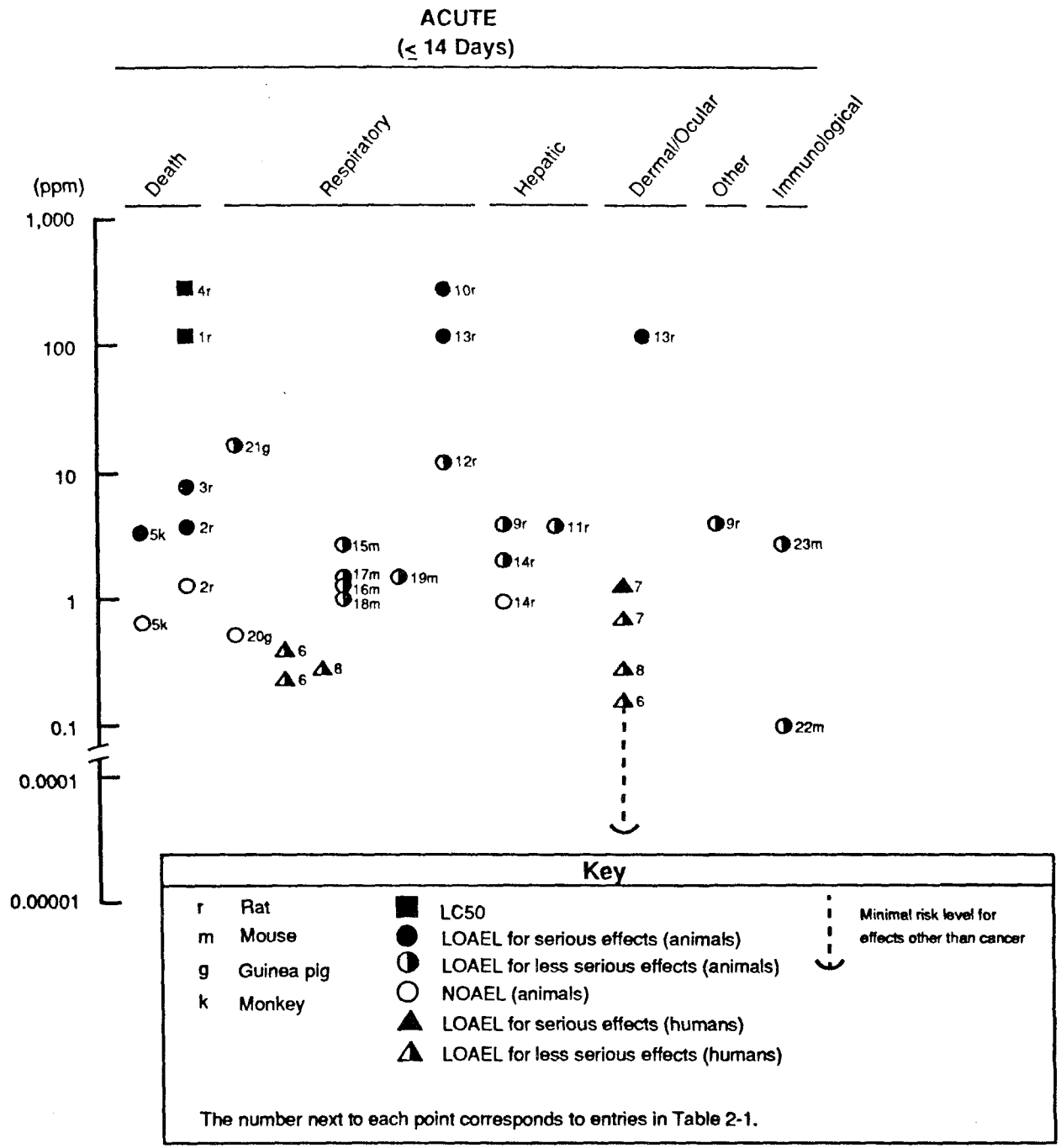


FIGURE 2-1. Levels of Significant Exposure to Acrolein - Inhalation

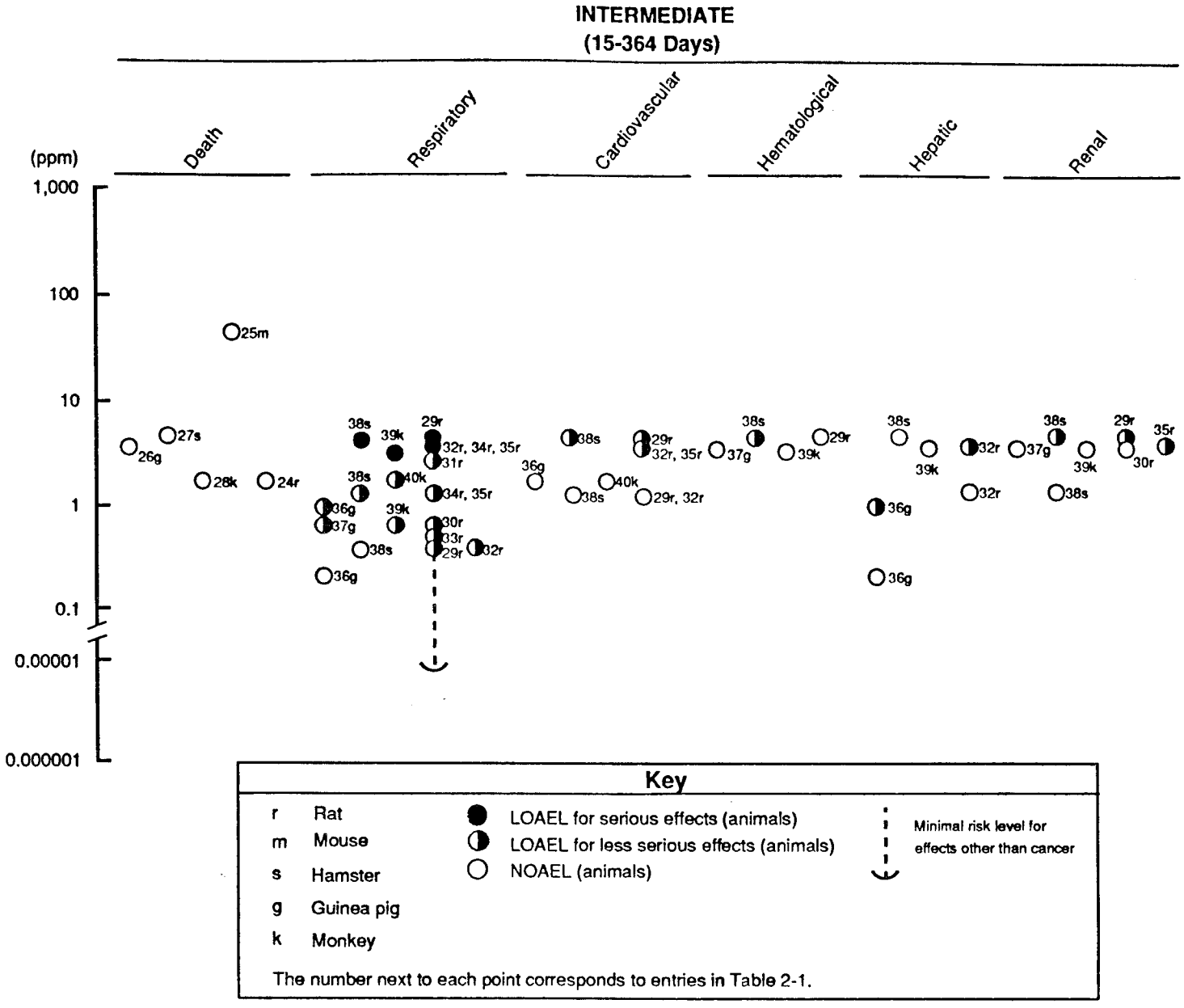
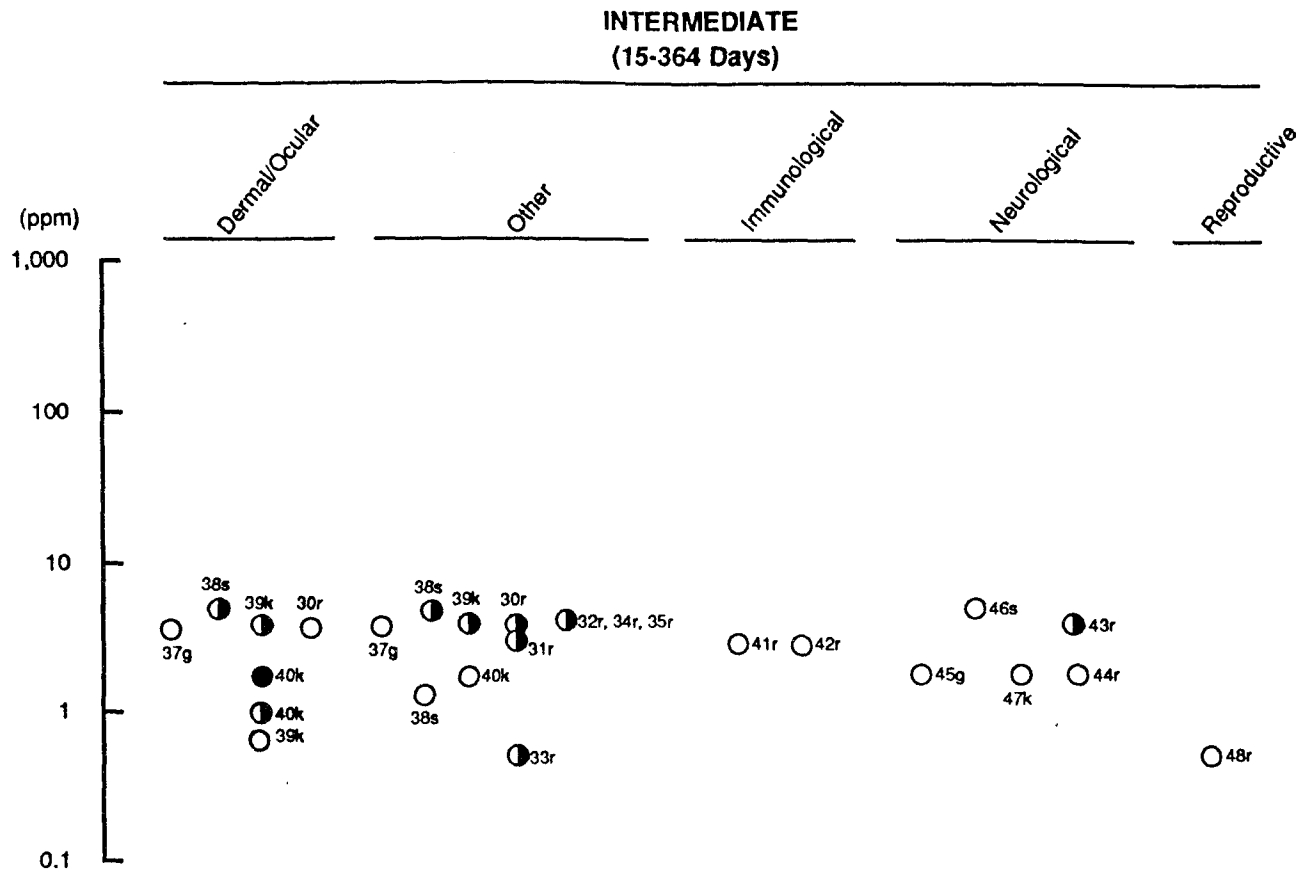


FIGURE 2-1 (Continued)



Key			
r	Rat	●	LOAEL for serious effects (animals)
s	Hamster	◑	LOAEL for less serious effects (animals)
g	Guinea pig	○	NOAEL (animals)
k	Monkey		

The number next to each point corresponds to entries in Table 2-1.

FIGURE 2-1 (Continued)

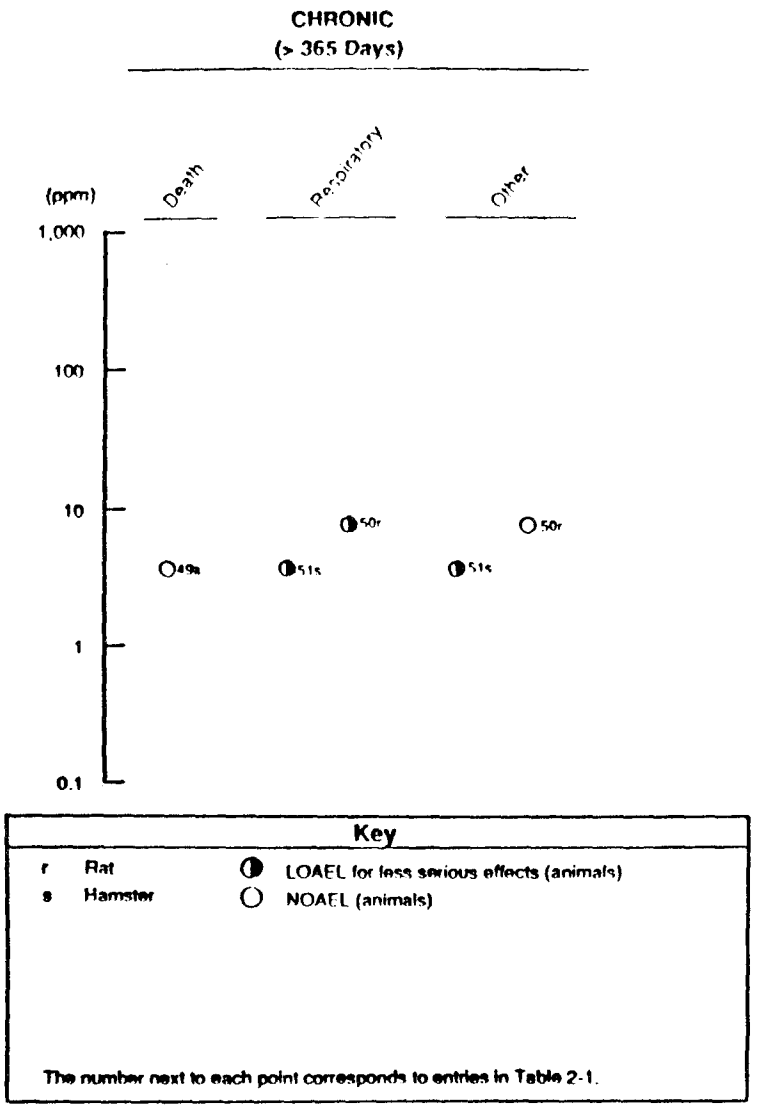


FIGURE 2-1 (Continued)

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans after inhalation exposure to acrolein.

Respiratory Effects. Champeix et al. (1966) reported that a 36-year old male was accidentally exposed to acrolein vapors in the workplace (duration of exposure was not reported, but is presumed to be less than 1 day). The most relevant signs and symptoms noticed were high fever, dyspnea, coughing, foamy expectoration, cyanosis, and pulmonary edema. Eighteen months after the exposure, the chronic pneumopathy, bronchitis, and emphysema persisted. Similar respiratory effects were observed by Bauer et al. (1977) on a 21-year-old male exposed to smoke from an overheated pan for 6 hours. It was assumed that acrolein was the main component of the smoke, although other components may have contributed to the symptoms.

In a study conducted with volunteers, a 20% decrease in respiratory rate was seen after an acute exposure to a low-level concentration of acrolein; throat irritation occurred after 10 minutes (Weber-Tschopp et al. 1977). In the same study, the concentration of acrolein in the air was gradually increased from 0 to 0.6 ppm during 35 minutes and was kept at that level for an additional 5 minutes. In this case, there was a 25% decrease in respiratory rate at 0.6 ppm, and throat irritation was noticed at 0.43 ppm. The significance of the decrease in respiratory rate is not clear, but in animals; particularly rodents, it is considered to represent a reflex response to protect the respiratory tract from toxicants (Alarie 1973). In the case reported by Gosselin et al. (1979), death was presumably caused by inhalation of acrolein from an overheated fryer. Cellular desquamation of the bronchial lining and miscellaneous debris in the bronchial lumen were observed.

Several studies reported acute effects of acrolein in experimental animals; generally, the results confirm information provided by the lethality studies that acrolein is a highly selective respiratory toxicant. Exposure of rodents to low concentrations of acrolein for several minutes induced a reflex decrease in respiratory rate by activation of the sensory nerve endings in the nasal mucosa (Alarie 1973; Davis et al. 1967; Kane and Alarie 1977; Nielsen et al. 1984; Steinhagen and Barrow 1984). In all species examined (mice, rats, guinea pigs, hamsters, and dogs), exposure to concentrations of 1.7 ppm or more induced moderate to severe histological alterations of the respiratory epithelium (Buckley et al. 1984; Catilina et el. 1966; Dahlgren et al. 1972; Feron et al. 1978; Hales et al. 1988; Kilburn and Mackenzie 1978; Murphy et al, 1964; Skog 1950). In addition, low levels of exposure to 0.1-2.5 ppm caused biochemical alterations in the nasal respiratory mucosa of rats, but the toxicological significance of this finding is unclear (Lam et al. 1985). Bronchial responsiveness, assessed by changes in pulmonary resistance, was increased in guinea pigs exposed to

0.3-1.3 ppm acrolein for 2 hours (Leikauf et al. 1989). This increase, however, was not accompanied by a simultaneous increase in neutrophil infiltration, which the authors took to suggest that cells other than neutrophils are responsible for the increase in bronchial responsiveness.

Studies regarding respiratory effects after intermediate duration exposure of humans to acrolein were not located in the available literature. In experimental animals, histological alterations in the respiratory tract appear to be common. Repeated exposures to acrolein concentrations between 0.2 and 5.0 ppm for up to 180 days caused moderate to severe epithelial damage in the bronchi and lungs of rats (Costa et al. 1986; Kutzman et al. 1984, 1985; Lyon et al. 1970), monkeys, guinea pigs, and dogs (Lyon et al. 1970), and rabbits and hamsters (Feron et al. 1978). In general, as indicated in Table 2-l and Figure 2-1, the severity of the effects increased as the concentration of acrolein increased. An intermediate MRL was derived from the less serious LOAEL identified in the Feron et al. (1978) study.

Studies regarding the respiratory effects of chronic exposure to acrolein in humans were not located in the literature. In the chronic exposure study in rats (Le Bouffant et al. 1980), occasional emphysematous areas were seen in the alveoli after 18 months of exposure to 8 ppm acrolein; however, the animals were only exposed to acrolein vapors for 1 hour/day, 7 days/week. Hamsters exposed to 4.0 ppm acrolein 7 hours/day, 5 days/week for 52 weeks developed inflammation and epithelial metaplasia in the nasal cavity, with a few animals exhibiting exudation in the lumen (Feron and Kruysse 1977). Approximately 20% of the animals killed at week 81, after a recovery period of about 6 months, still showed treatment-8 , related effects in the nasal cavity.

The overall evidence from acute, intermediate, and chronic duration studies in experimental animals indicates that the respiratory system is a target for acrolein. These results agree with the clinical picture observed in a case of accidental human exposure to acrolein, in which the respiratory effects were prevalent and persisted for several months after exposure (Champeix et al. 1966). Furthermore, from the animal data available, no species appears to be especially sensitive to acrolein since similar effects were seen in all species tested with comparable acrolein concentrations. The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Cardiovascular Effects. As previously indicated, studies regarding cardiovascular effects in humans after intentional inhalation exposure to acrolein were not located in the literature. No cardiovascular effects we observed in a case of accidental exposure to acrolein vapors (the concentration of acrolein or the duration of exposure was not reported) (Champeix et al. 1966).

2. HEALTH EFFECTS

In experimental animals, the cardiovascular system does not appear to be a target for acrolein. Nonspecific inflammatory lesions in the heart were reported in rats, dogs, monkeys, and guinea pigs after intermediate duration exposure to similar concentrations of acrolein (Lyon et al. 1970). Also, an increase in relative heart weight was observed in hamsters and rats exposed to 4.9 ppm of acrolein (Feron et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in animals or humans after inhalation exposure to acrolein.

Hematological Effects. As previously mentioned, no studies regarding hematological effects in humans after inhalation exposure to acrolein were located in the literature. No remarkable hematological alterations were described in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

The weight of evidence indicates that the hematological system is not asensitive indicator of acrolein toxicity in laboratory animals. In general, intermediate duration exposure had no adverse hematological effects in rats, guinea pigs, dogs, male hamsters, and monkeys (Feron et al. 1978; Lyon et al. 1970). Increased numbers of erythrocytes, hemoglobin, and lymphocytes were observed in female hamsters exposed at 4.9 ppm (Feron et al. 1978). No acute or chronic studies were located regarding hematological effects of acrolein. The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to acrolein.

Hepatic Effects. No studies regarding hepatic effects in humans after inhalation exposure to acrolein were located in the literature. No hepatic alterations were described in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

In general, the liver does not appear to be a target organ for acrolein in experimental animals. Effects reported in rats after acute exposure to low concentrations (4-8 ppm) of acrolein consisted of increases in enzyme activities and changes in liver/body weight ratio; however, these changes could represent adaptive responses (Murphy 1965; Murphy et al. 1964). One report was found describing liver necrosis (minute foci without a specific pattern) in 3 of 9 rats after intermediate duration exposure to 1.0 ppm acrolein, but this effect was not noticed at a higher concentration (Lyon et al. 1970). As seen in Table 2-l and Figure 2-1, no adverse liver effects were seen in hamsters, rabbits, monkeys, dogs, and guinea pigs exposed to 4.9 ppm acrolein or less. The highest NOAEL values and all reliable LOAEL

values for hepatic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

Renal Effects. No studies regarding renal effects in humans after inhalation exposure to acrolein were located in the literature. A normal urinalysis was reported in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

Renal effects in guinea pigs, dogs, and monkeys were described as nonspecific (Lyon et al. 1970). An increase in amorphous material in the urinary sediment was observed in rats, hamsters, and rabbits after intermediate-duration exposure to 4.9 ppm acrolein (Feron et al. 1978). However, without further characterization of the sediment, the significance of this finding is unclear. The overall evidence suggests that the kidney is not a target for acrolein. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Dermal/Ocular Effects. Volunteers had eye irritation after exposure to 0.6 ppm acrolein for 7.5 minutes or to 0.17 ppm for approximately 1 hour (Weber-Tschopp et al. 1977). Lacrimation occurred within 20 seconds in individuals exposed to 0.81 ppm, and within 5 seconds at 1.22 ppm (Sim and Pattle 1957). Human data summarized by Kane and Alarie (1977) show that concentrations of acrolein between 0.5 and 5 ppm caused lacrimation and various degrees of eye irritation in exposure periods of 10 minutes or less. Reliable LOAELs for dermal/ocular effects in humans are presented in Table 2-l and Figure 2-l. Data from the Weber-Tschopp et al. (1977) study were used as a basis for an acute inhalation MRL.

The dermal/ocular effects observed in experimental animals are qualitatively similar to those described in humans. Concentrations of acrolein higher than 1.0 ppm (1.8-3.7 ppm) caused eye irritation in dogs and monkeys, but guinea pigs and rats appeared to be less sensitive, since 3.7 ppm had no noticeable effect (Lyon et al. 1970). No histological evaluation of the eye was conducted, but other reports indicate that ocular discharges are commonly seen (Murphy et al. 1964; Skog 1950). The highest NOAEL values and all reliable LOAEL values for dermal/ocular effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Other Systemic Effects. Data regarding other systemic effects in humans after inhalation exposure to acrolein were not located in the literature. Decreased body weights and increased adrenal weights after acute exposures were reported in rats (Murphy et al. 1964). In intermediate duration studies, depressed body weight gains were reported in rats, hamsters, monkeys, and rabbits (Bouley et al. 1975; Feron et al. 1978 Kutzman et al. 1985; Leach et al. 1987; Lyon et al. 1970). In the absence of information regarding food intake, the significance of these findings is unclear.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to acrolein.

Short-term exposures to acrolein reduced bactericidal activity of the respiratory tract in experimental animals (Aranyi et al. 1986; Astry and Jakab 1983; Bouley et al. 1975). It is conceivable, however, that this is not a true immunological effect but results from the destruction by acroleir of the respiratory epithelium and its inherent defense mechanisms. The immunotoxicity of acrolein after inhalation exposure was tested in rats using several immunoassays (Leach et al. 1987; Sharwood et al. 1986). Negative results were obtained with exposures up to 3 ppm for 3 weeks in both studies. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to acrolein.

Concentrations of acrolein between 22 and 249 ppm for 10 minutes induced a dose-related decrease in substance P and calcitonin gene-related peptide in nerve terminals innervating the trachea of rats (Springall et al. 1990). No change was seen in total nerve distribution and number or in vasoactive intestinal peptide. Springall et al. (1990) indicate that acrolein may induced release of peptides that could play a role in the physiological response to irritants.

In intermediate duration studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970), the neurological effects identified consisted of increases in the brain/body weight ratio and nonspecific inflammatory responses in sections of the brain (it is not clear from the original papers whether sections refer to anatomical areas or to histological preparations). These effects were noticed in rats, guinea pigs, dogs, and monkeys at comparable concentrations of acrolein. Based on the evidence available, it does not appear that the nervous system is a target for acrolein.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to acrolein.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to acrolein.

2. HEALTH EFFECTS

A single study was identified regarding the reproductive effects of inhaled acrolein. Bouley et al. (1975) exposed male and female rats to 0.55 ppm acrolein continuously for 26 days and reported that exposure did not affect the number of pregnancies or the number and weights of the fetuses. Although Bouley et al. (1975) examined the most relevant indices and an adequate number of animals were tested, the use of only one dose level diminishes the impact of the reproductive assessment derived from this study.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to acrolein.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans after inhalation exposure to acrolein.

Only two studies in animals were located that examined the carcinogenic potential of acrolein after inhalation exposure. Feron and Kruysse (1977)exposed hamsters to a single acrolein concentration of 4.0 ppm for 7 hours/day, 5 days/week for 52 weeks and found no evidence of respiratory tract tumors or tumors in other tissues and organs. However, this study is considered to be of too short duration to determine carcinogenicity. Le Bouffant et al. (1980) exposed rats for lo-18 months to 8 ppm acrolein for 1 hour/day, 7 days/week and reported no evidence of tumors in the respiratory tract or in other tissues and organs.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans after oral exposure to acrolein.

The oral LD_{50} for rats was reported as 46 mg/kg, with a range of 39-56 mg/kg (Smyth et al. 1951). However, a single oral dose of l0-25 mg/kg in rats was lethal to over 40% of the animals (Draminski et al. 1983; Sakata et al. 1989; Sprince et al. 1979). Loss of reflexes occurred after 3 hours, and increased lethargy gradually led to death. Most of the animals died 3-8 hours after dosing (Sprince et al. 1979). Furthermore, increased maternal mortality was observed in rats treated with 10 mg/kg/d and in rabbits treated with 4 mg/kg/d during gestational days 7-19 (Hoberman 1987; King 1982). In contrast, no increase in deaths was observed in a two-generation reproductive study, in which rats were treated by gavage with 7.2 mg/kg/d (King 1984). Similarly, the overall survival rate was not affected in rats chronically exposed to 2.5 mg/kg/d and in dogs exposed to 2 mg/kg/d (Long 1987; Long and Johnson 1988). Decreased survival was, however, reported in

male mice chronically treated with 4.5 mg/kg/d acrolein by gavage (Long and Johnson 1989). Chronic exposure of rats to 36 mg/kg/d or less of acrolein via the drinking water did not affect mortality (Lijinsky and Reuber 1987). From these limited data, presented in Table 2-2 and Figure 2-2, it appears that acrolein is more lethal if administered via gavage than via drinking water. This is probably the result of the dose being administered all at once rather than throughout the day. although intubation errors or aspiration of the injected bolus cannot be ruled out. Another factor that must be considered is the stability of acrolein in drinking water.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects in humans after oral exposure to acrolein. However, studies were located regarding these endpoints in several species of animals. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No histopathological changes were observed in the respiratory systems of rats after intermediate-duration exposure to 7.2 mg/kg/d (King 1984). Similarly, no changes were observed during histopathological examination of respiratory tract tissues from rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) chronically exposed to 2.5, 4.5, or 2 mg/kg/d, respectively.

Cardiovascular Effects. Histopathological examination of the cardiovascular system revealed no effects after intermediate-duration exposure to acrolein in rats or after chronic exposure in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987).

Gastrointestinal Effects. Rats administered a single gavage dose of 25 mg/kg of acrolein in saline showed severe gastrointestinal effects that included multifocal ulceration of the forestomach and glandular stomach 48 hours after dosing. The areas of ulceration showed severe inflammation, focal hemorrhage, and edema (Sakata et al. 1989). Gastric mucosa ulcerations were also observed in rabbits exposed to 4 mg/kg/d during gestational days 7-19 (Hoberman 1987). Similar findings were reported in rats after an intermediate-duration exposure to 5.4 mg/kg/d (King 1984). No significant gastrointestinal effects of acrolein exposure, however, were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic dosing with 2.5, 4.5, or 2 mg/kg/d, respectively.

Hematological Effects. No hematological effects were observed in rats after intermediate-duration exposure to 7.2 mg/kg/d acrolein (King 1984). In contrast, hematocrit values were decreased in rats exposed to 0.05 mg/kg/d acrolein or more for 6 months (Long and Johnson 1988). The values

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

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	Gd 7-19 1x/d		6		10 (14/40 died)	King 1982
2	Rat	(W)	ND				46 (LD_{50})	Smyth et al. 1951
3	Rat	(G)	1x				11.2[a]	Sprince et al. 1979
4	Rat	(G)	1x				25	Sakata et al. 1989
5	Rabbit	(G)	Gd 7-19 1x/d		2		4	Hoberman 1987
Systemic								
6	Rat	(G)	1x	Gastro			25 (stomach ulceration)	Sakata et al. 1989
7	Rat	(G)	Gd 7-19 1x/d	Other	3.6	6 (decreased body wt gain)		King 1982
8	Rabbit	(G)	Gd 7-19 1x/d	Gastro Other	2	0.5 (decreased body wt gain)	4[b] (gastric ulceration)	Hoberman 1987
Developmental								
9	Rat	(G)	Gd 7-19 1x/d		6		10[c] (decreased litter wt, increased skeletal anomalies)	King 1982
10	Rabbit	(G)	Gd 7-19 1x/d		0.5		1 (fetal resorptions)	Hoberman 1987

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
Reproductive								
11	Rat	(G)	Gd 7-19 1x/d		10			King 1982
12	Rabbit	(G)	Gd 7-19 1x/d		0.5		1[d] (fetal resorptions)	Hoberman 1987
INTERMEDIATE EXPOSURE								
Death								
13	Rat	(G)	115 d 1x/d		7.2			King 1984
Systemic								
14	Rat	(G)	115 d 1x/d	Resp	7.2			King 1984
				Cardio	7.2			
				Gastro	4	5.4 (stomach ulcerations)		
				Hemato	7.2			
				Musc/skel	7.2			
				Hepatic	7.2			
				Renal	7.2			
				Derm/Oc	7.2			
				Other	5.4	7.2 (decreased body wt in F_0 generation)		
Reproductive								
15	Rat	(G)	115 d 1x/d		7.2			King 1984
CHRONIC EXPOSURE								
Death								
16	Rat	(W)	104-124 wk 5 d/wk		36			Lijinsky and Reuber 1987

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
Death								
17	Rat	(G)	24 mo 7d/wk 1x/d		2.5			Long and Johnson 1988
18	Mouse	(G)	18 mo 7d/wk 1x/d		2.0		4.5[e]	Long and Johnson 1989
19	Dog	(C)	12 mo 7d/wk 1x/d		2.0			Long 1987
Systemic								
20	Rat	(G)	24 mo 7d/wk 1x/d	Resp	2.5			Long and Johnson 1988
				Cardio	2.5			
				Gastro	2.5			
				Hemato	0.05[f]	0.5[g] (decreased monocytes in females)		
				Musc/skel	2.5			
				Hepatic	2.5			
				Renal	2.5			
				Derm/Oc	2.5			
				Other	2.5			
21	Mouse	(G)	18 mo 7d/wk 1x/d	Resp	4.5			Long and Johnson 1989
				Cardio	4.5			
				Gastro	4.5			
				Hemato	4.5			
				Musc/skel	4.5			
				Hepatic	4.5			
				Renal	4.5			
				Derm/Oc	4.5			
				Other	0.5	2.0 (decreased body wt gain)		

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
22	Dog	(C)	12 mo 7d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/Oc Other	2.0 2.0 2.0 2.0 2.0 2.0 2.0 2.0 2.0			Long 1987
Reproductive								
23	Rat	(G)	24 mo 7d/wk 1x/d		2.5			Long and Johnson 1988
24	Mouse	(G)	18 mo 7d/wk 1x/d		4.5			Long and Johnson 1989
25	Dog	(C)	12 mo 7d/wk 1x/d		2.0			Long 1987
Cancer								
26	Rat	(W)	104-124 wk 5d/wk				36 (CEL)	Lijinsky and Reuber 1987

[a]Converted to an equivalent concentration of 80 ppm in water for presentation in Table 1-4.
[b]Converted to an equivalent concentration of 36 ppm in water for presentation in Table 1-4.
[c]Converted to an equivalent concentration of 72 ppm in water for presentation in Table 1-4.
[d]Converted to an equivalent concentration of 9 ppm in water for presentation in Table 1-4.
[e]Converted to an equivalent concentration of 24 ppm in water for presentation in Table 1-4.
[f]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.0005 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). This MRL has been converted to an equivalent concentration in water (0.02 ppm) for presentation in Table 1-3.
[g]Converted to an equivalent concentration of 4 ppm in water for presentation in Table 1-4.

(C) = capsule; Cardio = cardiological; CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; (G) = gavage; Gastro = gastrological; Gd = gestation day; Hemato = hematological; mo = month; Musc/skel = musculoskeletal; ND = no data; Resp = respiratopy; (W) = water; wk = week.

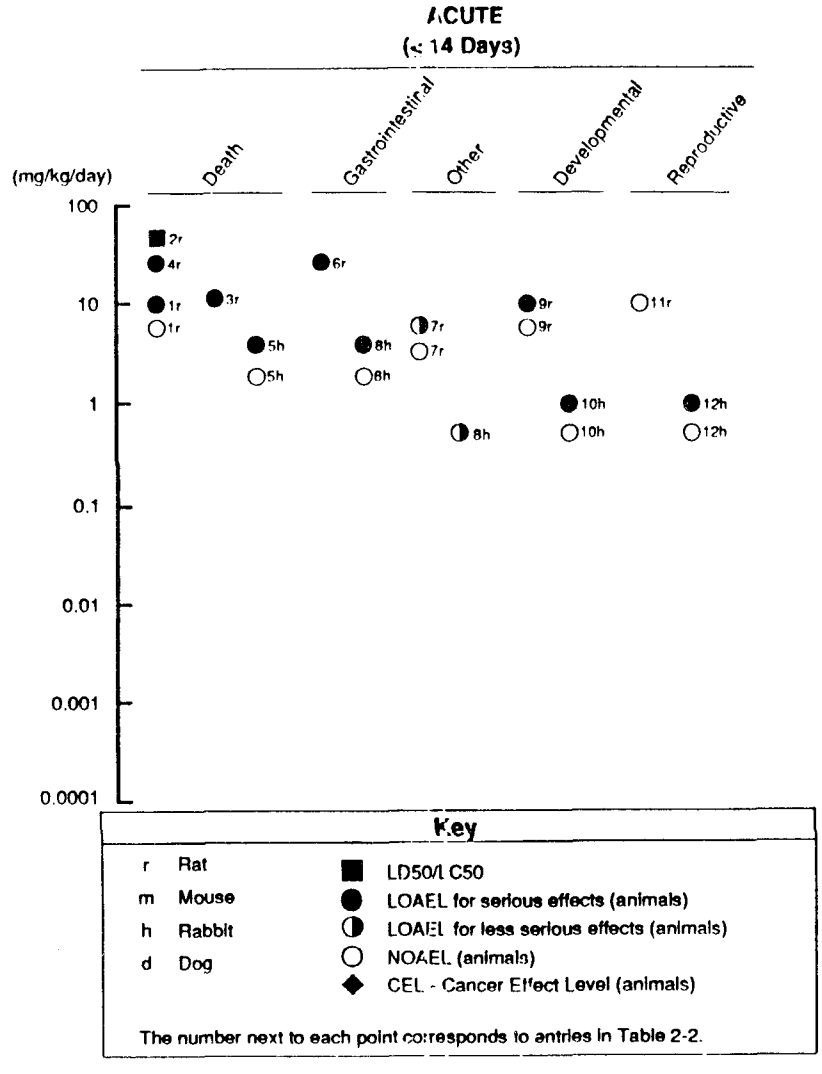


FIGURE 2-2. Levels of Significant Exposure to Acrolein - Oral

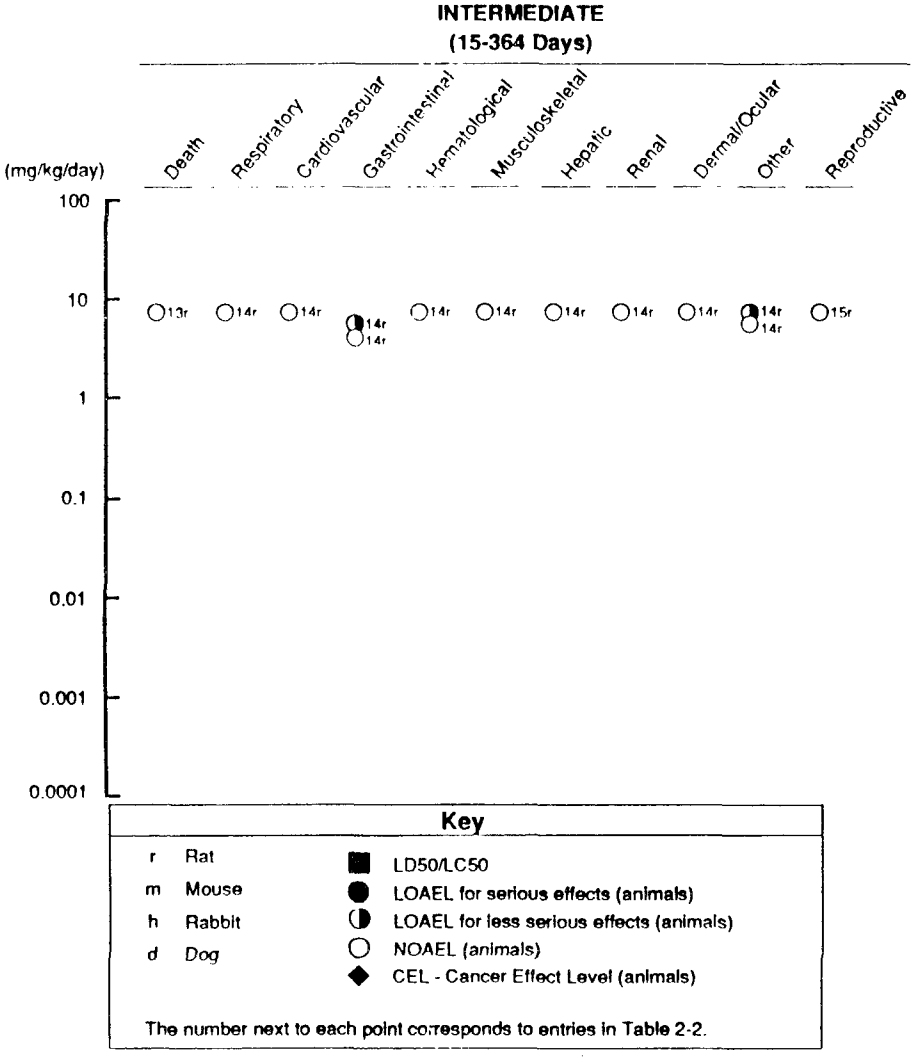


FIGURE 2-2 (Continued)

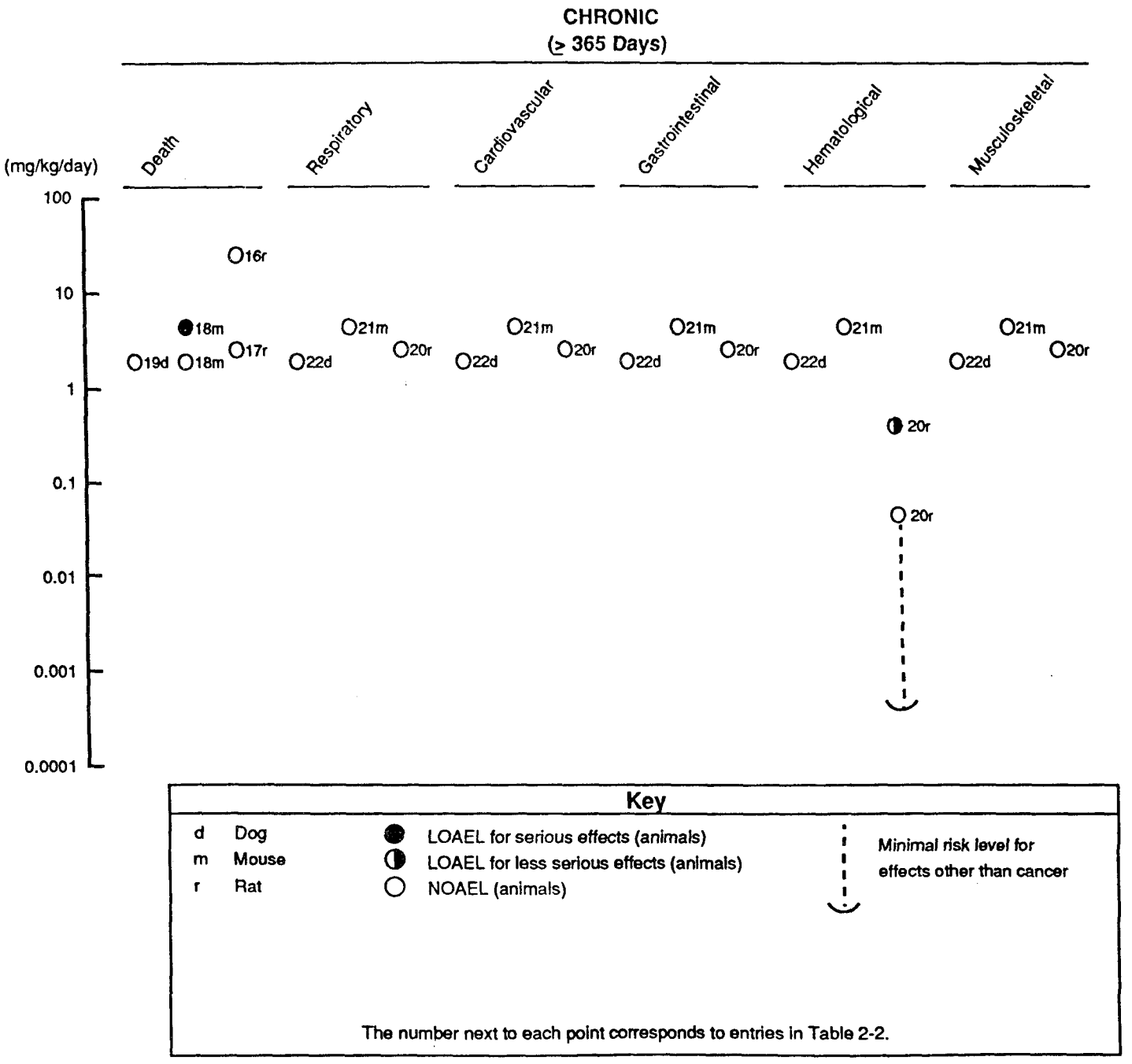


FIGURE 2-2 (Continued)

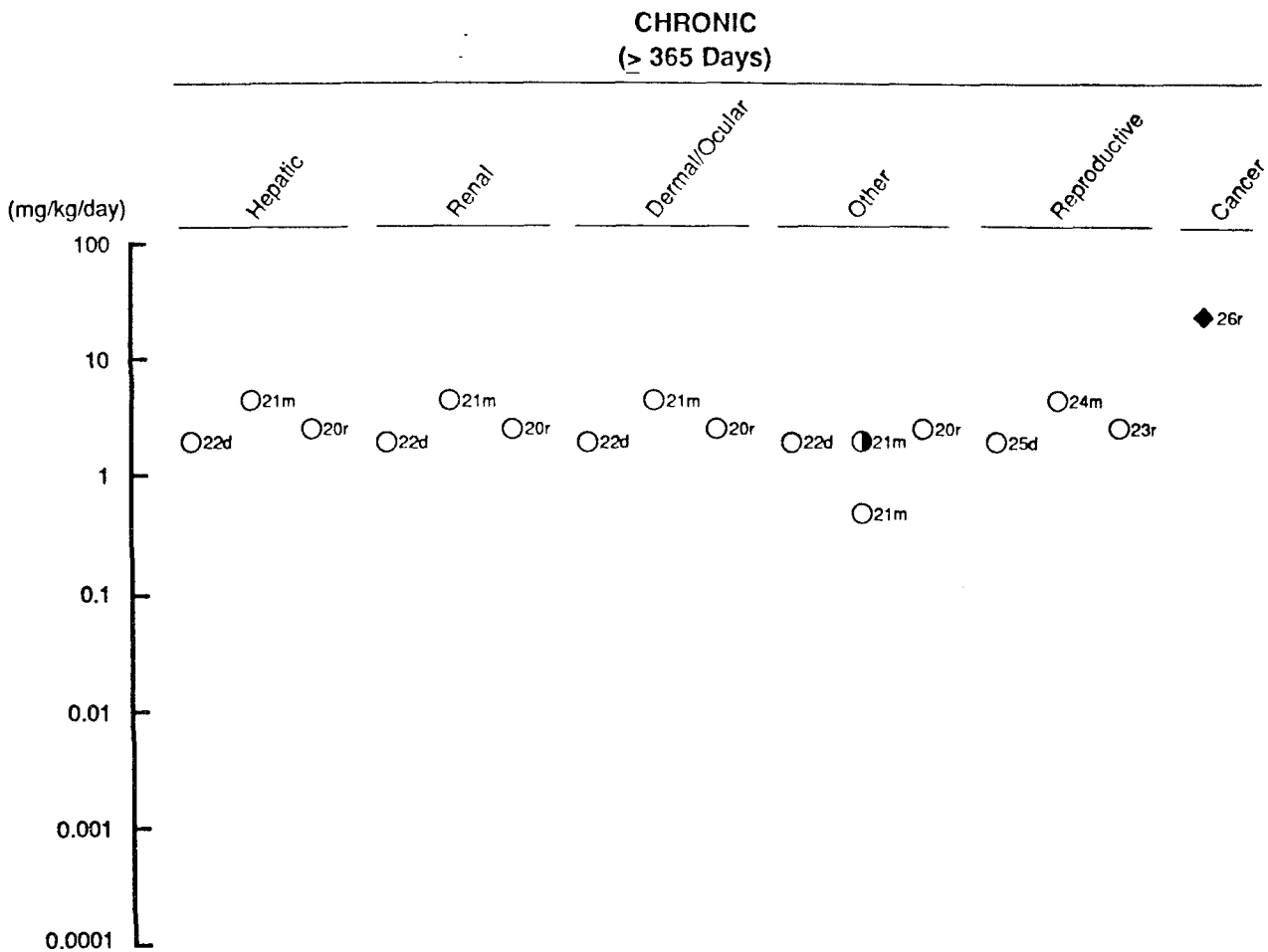


FIGURE 2-2 (Continued)

returned to normal at 24 months when the study was terminated. Furthermore, decreased monocytes were reported in female rats after 24 months of exposure to 0.5 mg/kg/d acrolein. The NOAEL value was 0.05 mg/kg/d and was used for the derivation of a chronic oral MRL of 0.0005 mg/kg/d as described in the footnote to Table 2-2. No pathological changes were found after hematological analysis of blood from mice or dogs chronically exposed to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively (Long and Johnson 1988, 1989).

Musculoskeletal Effects. Extensive histopathological examination in rats after intermediate-duration exposure also included the musculoskeletal system (King 1984). No changes were found. Similar results were obtained in rats (Long and Johnson 1988), mice (Long and Johnson 1989), and dogs (Long 1987) chronically exposed to acrolein.

Hepatic Effects. Smyth et al. (1951) administered acrolein to rats in drinking water at concentrations ranging between 0.17 and 1.5 ppm for 30 days. The authors reported that altered liver or kidney weights occurred with all concentrations of acrolein; however, the investigators did not indicate whether the alterations were increases or decreases. Furthermore, it is unclear if the altered organ weight occurred in the liver and/or kidneys. No liver effects were observed upon gross pathological or histological examinations in rats after intermediate-duration exposure to 7.2 mg/kg/d acrolein (King 1984). Similarly, no changes were found in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively.

Renal Effects. Altered kidney weights were reported by Smyth et al. (1951) in rats given acrolein in doses that ranged between 0.17 and 1.5 ppm in the drinking water. It is unclear from the report whether there was an alteration in kidney weight or liver weight or both. The investigators did not indicate whether the effects were increases or decreases in organ weights, No histopathological changes were reported in kidneys of rats after intermediate-duration exposure to 7.2 mg/kg/d (King 1984) or in rats (Long and Johnson 1988), mice (Long and Johnson 1989), and dogs (Long 1987) after chronic exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively. Negative results were also obtained from the urinalysis of exposed animals.

Dermal/Ocular Effects. No treatment-related dermal/ocular effects were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) chronically exposed to acrolein.

Other Systemic Effects. Decreased body weight gains were reported in rats treated with 6 mg/kg/d (King 1982) and in rabbits treated with 4 mg/kg/d acrolein during gestation days 7-19 (Hoberman 1987). In a preliminary study, decreased body weight gain was also observed in rabbits treated with 0.5 mg/kg/d acrolein.

Statistically significant decreases in total serum protein, albumin, and calcium were observed in dogs given 2 mg/kg/d acrolein for 12 months (Long 1987). However, the toxicological significance of this finding is not clear, since no effects were observed in any organs or tissues upon gross pathological or histological examination.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to acrolein.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to acrolein.

Slow response to stimuli, body sag, loss of elevation reflexes, and poor body tone were observed in rats exposed to a single oral dose of 11.2 mg/kg acrolein (Sprince et al. 1979). The usefulness of this study in assessing the neurotoxic effects of oral exposure to acrolein is limited. It is difficult to determine whether these observed effects are direct toxicological effects attributed to acrolein treatment or nonspecific responses of animals in extremis.

2.2.2.5 Developmental Effects

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

Developmental effects have been observed in animals after oral exposure. Increased incidences of skeletal anomalies and delayed ossification and decreased mean fetal weight and total litter weights were observed in the offspring of rats exposed to 10 mg/kg/d (King 1982). This dosage, however, was toxic to the dams, resulting in maternal deaths. In a preliminary dose-range finding study, exposure of rabbits to 1 mg/kg/d or more resulted in dose-related increased incidences of fetal resorption (Hoberman 1987); however, fetal mortality was not affected in the primary study, in which rabbits were exposed to 2 mg/kg/d or less during gestation. No explanation for the discrepancy was provided. The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are 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 acrolein.

Exposure of rats to 10 mg/kg/d acrolein during pregnancy had no effect on the number of implantations or resorptions or on the ratio of live/dead

fetuses per litter (King 1982). No evidence of acrolein reproductive toxicity was found in a two-generation study in which rats of each generation were exposed to 7.2 mg/kg/d for 100-120 days prior to mating and then for 15 days during mating (King 1984). Similarly, no effects on fertility were found in rabbits exposed to 2 mg/kg/d acrolein during pregnancy (Hoberman 1987). However, in the preliminary dose-range study, a dose-related increase in embryonal resorptions was observed after exposure of dams to 1 mg/kg/d or more. No explanation for this discrepancy was given in the study. No fetuses were alive in the litters of dams that were administered 4 mg/kg/d acrolein. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category 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 or animals after oral exposure to acrolein.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to acrolein.

Limited evidence of the carcinogenicity of acrolein in animals is provided by the long-term study of Lijinsky and Reuber (1987). In this study, groups of male rats were given acrolein in the drinking water at concentrations that provided doses of 0, 5.6, 14, or 36 mg/kg/day, 5 days/week for 104-124 weeks. A control group of females was also kept. One group of females was also given the highest dose on the same schedule as the males. The only indication of a carcinogenic effect of acrolein was the incidence of neoplasms of the adrenal cortex in female rats. Five of 20 rats treated with the highest acrolein dose had adenomas and two had hyperplastic nodules of the adrenal cortex. According to the authors, this type of tumor is rare in untreated female rats of the strain used (F344); the historical incidence is approximately 5% (there was one reported in concurrent controls). The increased incidence of adrenocortical tumors was only marginally significant as judged by the Fisher Exact Test. Because only 20 rats per group were used, this study cannot be considered a definitive bioassay for carcinogenicity, but the results do suggest a carcinogenic potential. Extensive histopathological examination did not reveal any carcinogenic effects in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after oral exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively, for 12-24 months. However, it must be mentioned that the duration of two of these studies, 18 months in mice and 12 months in dogs, may have precluded the development of neoplasms. It should also be noted that the doses used in these three studies are considerably smaller than those used by Lijinsky and Reuber (1987). The dose of 36 mg/kg/d is presented as a tentative CEL in Table 2-2 and Figure 2-2.

2.2.3 Dermal/Ocular Exposure

2.2.3.1 Death

No studies were located regarding lethality in humans after dermal exposure to acrolein.

In rabbits administered several dilutions of acrolein percutaneously, the LD_{50}s ranged from 160-1000 mg/kg body weight, depending on the vehicle and concentration (Albin 1962). Salaman and Roe (1956) painted the backs of mice with 5 ppm acrolein (in sesame oil) for 10 weeks for a total dose of 12.6 mg and reported that acrolein did not cause mortality.

2.2.3.2 Systemic Effects

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

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to acrolein. When applied locally to the eyes of rabbits, acrolein (dose not reported) increased the heart rate (Basu et al. 1971). However, this effect is most likely due to the painful stimulation of the eye.

Dermal/Ocular Effects. Schonning (1966) described a case of a 57-year-old man who accidentally spilled acrolein over his genital area. Swelling of the penis and scrotum occurred, and after 15 days the genital area was deeply ulcerated and gangrenous. No follow-up information was provided. Lacroix et al. (1976) applied a solution of 10% acrolein in ethanol to 12 volunteers; the skin was biopsied 48 hours later. All subjects exhibited irritation and had papillary edema, and 11 had polymorphonuclear infiltrates. In addition, five cases of epidermal necrosis occurred. No further information was provided.

Accidental exposure to vapors of acrolein produced burns of the cheeks and eyelids in a male subject (Champeix et al. 1966).

Effects such as eye and nose irritation produced by exposure to acrolein vapors are discussed in Section 2.2.1.2.

2.2.3.3 Immunological Effects

Rappaport and Hoffman (1941) reported the case of a male smoker who developed a severe skin reaction on the fingers of his right hand (which he used to hold the cigarette) and on his upper and lower lips. The patient was subjected to numerous allergy tests and found to be sensitive to acrolein from the cigarette.

No studies were located regarding immunological effects in animals after dermal exposure to acrolein.

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

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans after dermal exposure to acrolein.

Salaman and Roe (1956) applied acrolein (in sesame oil) to the backs of mice once a day for 10 weeks. The total dose applied was 12.6 mg (5% solution). The authors reported no tumors at the site of application or at remote sites. These results should be interpreted with caution, since the duration of the study was too short to evaluate carcinogenic potential, and only 15 mice were used.

Levels of significant exposure by the dermal route associated with effects are presented in Table 2-3.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans after inhalation exposure to acrolein.

Egle (1972) exposed anesthetized dogs to concentrations of acrolein between 172 and 262 ppm for a brief period of time (l-3 minutes) and observed that acrolein uptake by the total respiratory tract at ventilatory rates of 6-20 respirations/minute averaged 80-85X of the inhaled dose. Retention was independent of the respiratory rate. The author estimated that only about 20% of the inhaled dose reached the lower respiratory tract. Exposure of the lower respiratory tract alone resulted in 65-70% concentration-independent retention, but decreased slightly with increases in tidal volume from 100 to 160 mL. Although the study by Egle (1972) does not provide information on the disposition of the retained acrolein or on

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

Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	1 d	Derm/Oc			10% (severe skin irritation)	Lacroix et al. 1976
INTERMEDIATE EXPOSURE						
Death						
Mouse	10 wk 1 d/wk		42 mg/kg/d			Salaman and Roe 1956

d = day; Derm/Oc = dermal/ocular; wk = week.

whether the uptake rates represent steady-state values, it indicates that acrolein at relatively high concentrations is effectively removed from inhaled air by both the upper and lower respiratory tracts.

2.3.1.2 Oral Exposure

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

Very little information is known about the absorption of acrolein following oral exposure. Based on toxicological effects observed after oral administration of acrolein, it is assumed to be absorbed through the gastrointestinal tract. However, the rate and extent of absorption are not known.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to acrolein. In cases of accidental dermal exposure (described in Section 2.2.3), effects were restricted to the exposed region of the body, presumably because of the high reactivity of acrolein.

Limited information is available regarding dermal absorption of acrolein in animals. The percutaneous LD_{50} for rabbits ranged from 160 to 1000 mg/kg, depending on the vehicle (Albin 1962). From these limited data, it appears that acrolein is more efficiently absorbed when mineral spirits are used as a vehicle, rather than water.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to acrolein.

2.3.2.2 Oral Exposure

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

In a study conducted by Draminski et al. (1983), the acrolein conjugated metabolite S-carboxyethylmercapturic acid was identified in the urine of rats after oral administration of a single dose of 10 mg/kg of acrolein. This study provides indirect evidence of distribution of acrolein to the liver or kidney, where conjugation most likely occurred.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to acrolein.

2.3.3 Metabolism

Because of the limited information available regarding the metabolism of acrolein in humans and animals after inhalation, oral, and dermal exposures, relevant data are presented below.

In nonbiological cell-free systems, acrolein has been shown to form thiol ethers within seconds when reacted with glutathione or cysteine (Esterbauer et al. 1975, 1976). In cell systems in vitro, such as cultured human bronchial cells and isolated cell preparations from rat liver and kidneys, acrolein has been shown to form conjugates with glutathione, cysteine, and/or N-acetylcysteine (Dawson et al. 1984; Dupbukt et al. 1987; Gurtoo et al. 1981; Zitting and Heinonen 1980). The formation of these conjugates greatly diminished the cytotoxic effects of acrolein, indicating that conjugation may be an important detoxication mechanism. In addition to the evidence provided by the numerous in vitro studies, two reports from the literature demonstrated that acrolein also reacts with glutathione in vivo. In these studies, the acrolein metabolite 3-hydroxymercapturic acid was identified in the urine of rats after a subcutaneous dose of acrolein (Alarcon 1976; Kaye 1973).

Based on experimental results, Pate1 et al. (1980) proposed an in vitro metabolic scheme for acrolein in rat liver and lung preparations. In this scheme, free acrolein can interact with proteins and nucleic acids, and/or with thiol groups such as glutathione. Acrolein can also be transformed into acrylic acid by liver cytosol or microsomes, or it can be oxidized to glycidaldehyde by lung or liver microsomes. Acrylic acid may be incorporated into amino acids, fatty acids, and sterol. Glycidaldehyde can be metabolized to glyceraldehyde, which then can enter the glycolitic pathways. From the scheme proposed by Pate1 et al. (1980), glycidaldehyde appears to be the only chemical that could represent a risk to human health, since it has shown carcinogenic properties in mice and rats when applied dermally (Shamberger 1974; Van Duuren 1967a, 1967b). The metabolic pathway proposed by Pate1 et al. (1980) is shown in Figure 2-3.

2.3.3.1 Inhalation Exposure

No studies were located regarding metabolism in humans after inhalation exposure to acrolein.

Lam et al. (1985) found a dose-related depletion of glutathione in the nasal respiratory mucosa of rats after exposure to 0.1-2.5 ppm of acrolein for 3 hours. This finding is consistent with a chemical reaction leading to the formation of a glutathione-acrolein adduct.

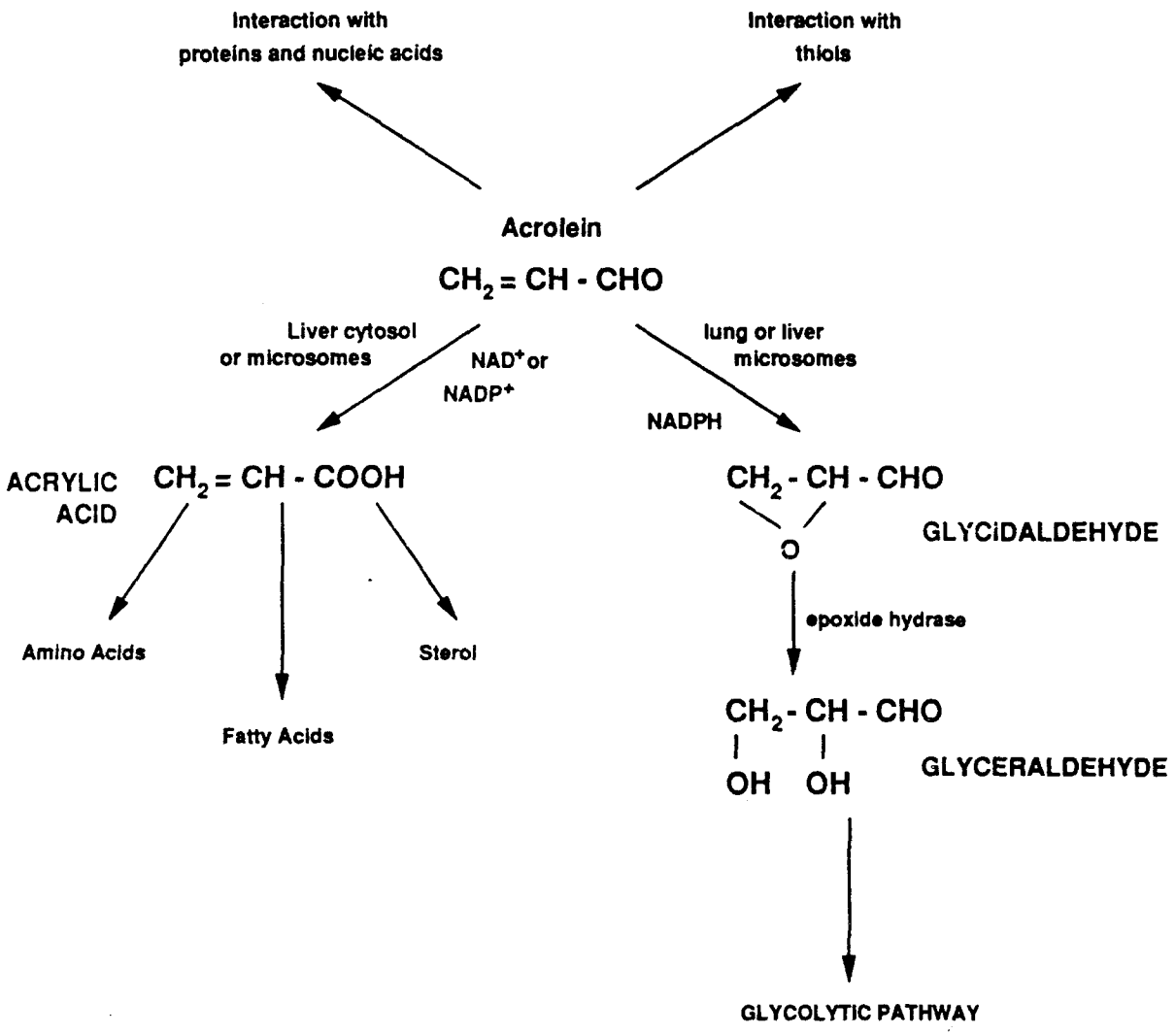


FIGURE 2-3. Proposed Metabolic Scheme for Acrolein In Vitro
Source: Patel et al. 1980

2.3.3.2 Oral Exposure

No studies were located regarding metabolism in humans after oral exposure to acrolein.

Draminski et al. (1983) administered 10 mg/kg of acrolein as a single oral dose to rats and collected the urine during 3 days. Since the metabolite S-carboxyethylmercapturic acid was found in the urine, but S-hydroxypropylmercapturic acid (which should have been formed if acrolein had reacted with glutathione) was not, an alternative pathway was proposed. In this metabolic scheme, acrolein is first metabolized to acrylic acid with subsequent formation of the methyl ester, which is then conjugated with glutathione to form S-carboxyethylmercapturic acid methyl ester. The metabolic pathway postulated by Draminski et al. (1983) is shown in Figure 2-4.

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal exposure to acrolein.

2.3.4. Excretion

2.3.4-l Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to acrolein.

2.3.4.2 Oral Exposure

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

Draminski et al. (1983) reported the presence of the acrolein metabolite S-carboxyethylmercapturic acid in the urine of rats after administration of a single oral dose of 10 mg/kg of acrolein. The percentage of the dose recovered as the metabolite in the urine was not determined.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to acrolein.

2.4 RELEVANCE TO PUBLIC HEALTH

The clinical signs common to humans and animals following acute inhalation exposure to acrolein (e.g., lacrimation, upper respiratory tract

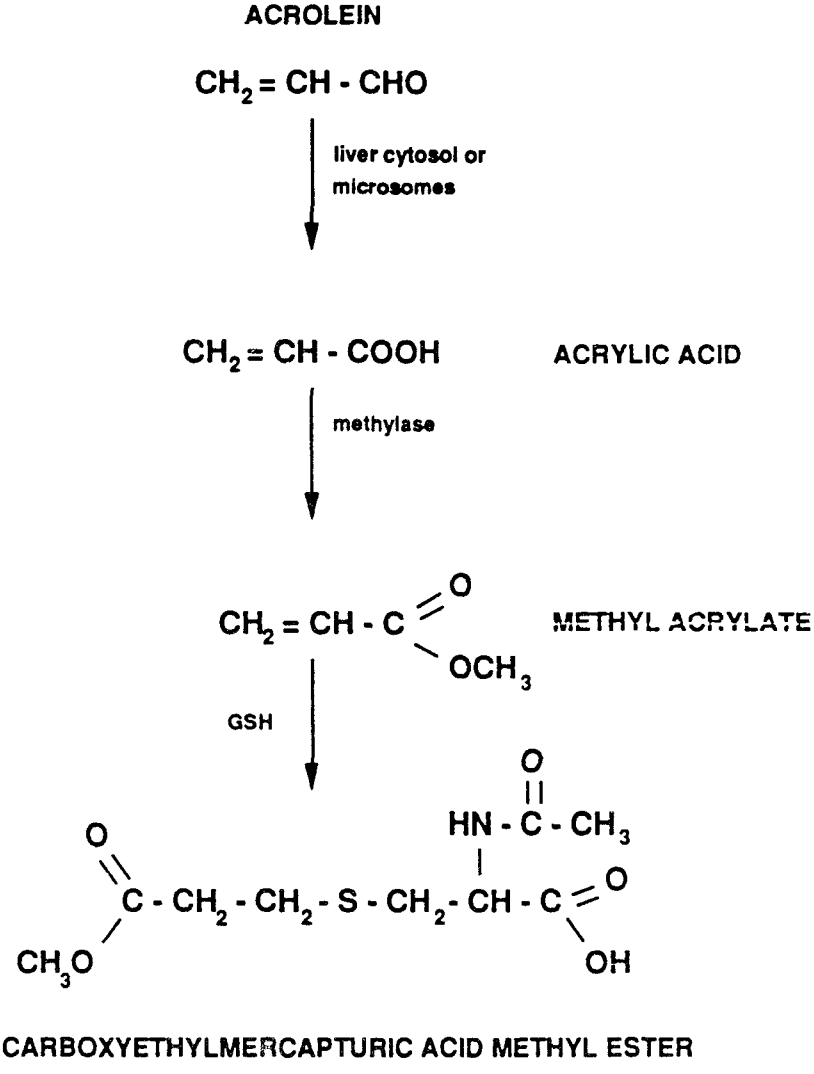


FIGURE 2-4. Proposed Metabolic Scheme for Acrolein In Vivo
Source: Draminski et al. 1983

irritation and congestion, airway occlusion, and death by asphyxiation) point to the respiratory system as the major target of toxicity. Even if death is prevented, some respiratory effects may persist for months. The respiratory systems of animals are also affected following longer-term exposure. Animal data do not suggest that acrolein may have immunological effects; however, exposure to acrolein vapors may result in a decrease in bactericidal activity. No other systems or organs have yet been identified as targets for acrolein, although nonspecific effects have been identified in the livers, kidneys, and brains of animals.

Death. No human fatality due specifically to inhalation of acrolein has been reported. However, based on results obtained with experimental animals, it is reasonable to assume that exposure to relatively high doses of acrolein vapors is lethal to humans. Death has been observed in animals after inhalation, oral, and dermal exposure to acrolein. The cause of death in experimental animals seemed to be respiratory failure caused by the formation of cellular debris, which blocked the tracheal and bronchial lumen and led to asphyxiation. The concentration of acrolein necessary to induce death in animals is inversely related to the duration of exposure (see Table 2-l). The irritative properties of acrolein in the eyes and upper respiratory tract, seen in both humans and animals, will most likely serve as warning long before lethal concentrations can be reached.

Systemic Effects. The only known effects of acrolein exposure in humans are general respiratory congestion and eye, nose, and throat irritation. Studies in humans have shown that eye irritation occurs with concentrations slightly lower than those that produce either nose or throat irritation (Weber-Tschopp et al. 1977). Amoore and Hautala (1983) calculated an odor safety factor for acrolein of 0.61. This value was derived by dividing the threshold limit value (TLV) (0.1 ppm) by the odor threshold (0.16 ppm), and means that approximately 50% of attentive persons can detect the TLV concentration in the air. These irritative effects of acrolein, also observed in animals (Lyon et al. 1970; Murphy et al. 1964; Skog 1950), are temporary and disappear rapidly when exposure ceases. Acrolein stimulates free nerve endings in the cornea1 and nasal epithelium, triggering the reflex response of reduction in the respiratory rate (Alarie 1973). This response is particularly prominent in rodents and is aimed at decreasing the intake of the chemical irritant. The respiratory congestion observed in animals following acute inhalation exposure to acrolein (Catilina et al. 1966) probably results from its irritating properties on mucous membranes. Since acrolein is known to be irritating to mucous membranes of humans, inhalation exposure would probably result in pulmonary congestion in humans. In fact, the case described by Champeix et al. (1966) clearly supports that view. In addition, it shows that serious respiratory alterations, such as emphysema, can persist for several months after the accidental exposure.

No information is available regarding cardiovascular effects in humans following inhalation, oral, or dermal exposure to acrolein. Changes in

blood pressure and heart rate reported in rats (Egle and Hudgins 1974) were shown to be sympathetic-mediated, with pressor effects occurring at lower intravenous doses (0.25 mg/kg), whereas vagal-mediated cardioinhibitory and depressor effects were seen at higher intravenous doses (5 mg/kg). In contrast, no cardiovascular effects were observed in rats after intermediate-duration oral exposure to acrolein (King 1984). Furthermore, no effects were reported after chronic oral exposure in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987). No information was located regarding cardiovascular effects in animals following dermal exposure to acrolein. In the absence of further information, no inference can be made regarding possible cardiovascular effects in humans.

No information is available regarding gastrointestinal effects in humans following inhalation, oral, or dermal exposure to acrolein. A recent report by Sakata et al. (1989) showed that in rats acrolein causes severe gastrointestinal damage when administered by gavage. This effect is due to the strong irritant properties of acrolein on mucosal membranes, and is in complete agreement with the effects produced by acrolein in the respiratory tract when inhaled. This result is supported by similar findings in rabbits treated orally during pregnancy (Hoberman 1987) and in rats after intermediate-duration exposure (King 1984). In contrast, no changes in the gastric mucosa were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic exposure to lower concentrations of acrolein. It is reasonable to assume that if acrolein is ingested by humans, it would cause severe gastrointestinal effects.

No studies were located regarding hematological effects in humans after acrolein exposure, Mostly negative results were obtained in experimental animals after inhalation and oral exposures to acrolein. The only hematological changes were recorded in female rats (increased number of erythrocytes, lymphocytes) after inhalation exposure, but not in males in the same exposure group (Feron et al. 1978). Similarly, female rats had an increased number of monocytes after chronic oral exposure (Long and Johnson 1988). No such changes were found in males. The reason for the apparent sex-related difference is not clear.

No data were located regarding hepatic effects in humans following inhalation, oral, or dermal exposure to acrolein. No serious dose-related effects were noticed in animals exposed to acrolein in the air. Similarly, no toxic effects were observed in the livers of orally exposed animals (King 1984; Long 1987; Long and Johnson 1988, 1989). Furthermore, no data were located regarding hepatic effects in animals following dermal exposure to acrolein. There are insufficient data to predict whether acrolein is hepatotoxic in humans.

Cases of accidental dermal contact with acrolein and studies with volunteers clearly indicate that acrolein is a strong dermal irritant,

causing skin burns. A 10% solution in ethanol applied to the skin caused epidermal necrosis.

Whether systemic effects, other than respiratory, caused by acrolein in animals will occur in humans is difficult to ascertain. It is clear that because of its high chemical reactivity, acrolein will cause damage to all tissues that come in contact with it. However, because the most relevant route of exposure is by inhalation, and because of the strong irritant odor, systemic effects other than respiratory are not likely to be observed in humans.

Immunological Effects. No data were located regarding immunological effects in humans following inhalation, oral, or dermal exposure to acrolein. In experimental animals, the effects of acrolein on the immune system have been evaluated by determining the lethality of bacterial agents to acrolein-exposed animals. The effects have varied, depending on the concentration of acrolein, duration of exposure, and species used. Although the mechanism by which acrolein alters the immune response is not known, the general view is that it decreases the bactericidal activity of the respiratory epithelium by destroying mucosal layers that contain defense mechanisms. Acrolein destroyed ciliated cells in the respiratory tract of rats (Catilina et al. 1966), guinea pigs (Dahlgren et al. 1972), and hamsters (Kilburn and McKenzie 1978). This effect was also induced in rabbit tracheas by tobacco smoke, and acrolein was identified as one of the agents having ciliary-depressant activity (Kensler and Battista 1963). Acrolein suppressed protein synthesis 50% in rabbit alveolar macrophages in vitro (Leffingwell and Low 1979). Increased mortality due to bacterial infection was reported in mice (Astry and Jakab 1983) and rats (Bouley et al. 1975) after exposure to acrolein for 8 hours and 3 weeks, respectively. However, in the study by Bouley et al. (1975), no difference was seen between control and treated animals after 63 days of exposure to acrolein, which probably indicates that immunity can develop after the initial infection; this should be considered in intermediate- and longduration studies. Administration of 5.6 mg/kg acrolein intravenously in mice prior to sensitization with sheep erythrocytes resulted in enhancement of the delayed-type hypersensitivity and antibody forming cells response to the sheep erythrocytes (Kawabata and White 1988). The authors suggest that enhancement of the immune response was produced by acrolein binding to the sulfhydryl groups of cells required for the generation of suppressor T-cells. Based on studies in experimental animals, it is likely that humans accidentally exposed to high concentrations of acrolein by inhalation will have an increased risk of contracting respiratory infections. The effects of long-term exposure to low concentrations of acrolein on the human immune system are not known.

Neurological Effects. No information was identified regarding neurological effects in humans following exposure to acrolein. The only data available in experimental animals described nonspecific brain inflammation after exposure to acrolein in the air (Lyon et al. 1970). In

the absence of further information, no inference regarding possible effects in humans can be made. However, levels in the ambient environment or in air, water, and soil surrounding waste sites are probably not high enough to warrant concern for severe neurological effects.

Developmental Effects. No evidence exists to indicate that acrolein causes developmental effects in humans. However, several studies have been conducted regarding the teratogenic and embryotoxic properties of acrolein in animals. An increased incidence of skeletal anomalies was reported in the offspring of rats that were exposed to 10 mg/kg/d acrolein by gavage during gestation (King 1982) but not in rabbits that were exposed to 2 mg/kg/d during gestation (Hoberman 1987). Increased fetal resorptions were, however, reported in a preliminary dose-range study in rabbits exposed orally during pregnancy, and no live fetuses were found in the group exposed to 4 mg/kg/d acrolein (Hoberman 1987). Acrolein was embryolethal when injected intravenously to pregnant rabbits at doses that had toxic effects in the maternal animals (Claussen et al. 1980). When injected into the yolk sac, acrolein was embryolethal and teratogenic, but at doses considerably higher than intravenous doses. Acrolein induced malformations when injected into the amniotic fluid of pregnant rats (Hales 1982; Slott and Hales 1985). However, when rat embryos were cultured in vitro, acrolein did not induce malformations (Mirkes et al. 1984), but it delayed growth (Schmid et al. 1981). Similar results were found with mouse limb buds cultured in vitro (Stahlmann et al. 1985). Slott and Hales (1986), however, found that acrolein was teratogenic to rat embryos cultured in vitro. Since the range of concentrations used by Slott and Hales (1986) was similar to that used by Schmid et al. (1981), the difference in the results is difficult to interpret but is probably related to differences in incubation procedures or the presence of serum at the time of exposure (Curren et al. 1988; Smith et al. 1990). Although it is not known whether acrolein causes developmental effects in humans, it is possible that, if free acrolein reaches the human embryo, teratogenic effects may develop.

Reproductive Effects. It is not known whether acrolein could cause reproductive effects in humans. A single study was identified regarding the reproductive effects of inhaled acrolein in animals. In this study (Bouley et al. 1975), exposure of rats to acrolein prior to mating did not affect the number of pregnancies or number and weight of the fetuses. Acrolein treatment during pregnancy did not affect the reproductive ability of rats (King 1982). Similarly, no reproductive effects were found in a two-generation oral exposure study in this species (King 1984). Increased fetal resorptions were reported in rabbits exposed orally to 1 mg/kg/d during pregnancy, but no live fetuses were found in the group exposed to 4 mg/kg/d acrolein (Hoberman 1987). Therefore, the potential of acrolein to cause reproductive effects in humans cannot be ruled out.

Genotoxic Effects. No studies were located regarding the genotoxic effects of acrolein in humans or animals by inhalation, oral, or dermal routes. Acrolein was not mutagenic in vivo as judged by the dominant lethal

assay in the mouse (Epstein et al. 1972) or the sex-linked recessive lethal test in Drosophila (Zimmering et al. 1985).

The in vitro genotoxicity of acrolein has been investigated in prokaryotic and eukaryotic organisms and in mammalian cell systems. The overall evidence, presented in Table 2-4, indicates that acrolein is weakly mutagenic without activating systems and nonmutagenic in the presence of activating systems in Salmonella tyohimurium and Escherichia coli. In the yeast, Saccharomyces cerevisiae, acrolein was not mutagenic without activating systems. In mammalian cells, acrolein gave positive results without activating systems. Acrolein inhibited the activity of DNA polymerase as well as DNA and RNA synthesis in rat liver cell nuclei. Acrolein also induced chromosome breakage and sister-chromatid exchange in Chinese hamster ovary cells. DNA damage was seen in human myeloid cells and bronchial cells in culture Acrolein was not mutagenic to normal human fibroblasts in culture, but fibroblasts with a deficient DNA repair system showed a positive mutagenic response (Curren et al. 1988). Acrolein was also a potent inhibitor of the DNA repair enzyme 0^6-methylguanine-DNA methyl transferase. The mechanism by which acrolein induces genotoxicity in mammalian cells is not known but it has been shown that acrolein can form adducts with DNA, such as $1N^2$ -propanodeoxyguanine (Chung et al. 1984; Foiles et al. 1989) and $1N^6$-propanodeoxyadenine (Smith et al. 1990). Because of the limited number of in vivo tests, there is insufficient evidence to predict that acrolein poses a genotoxic threat to humans.

Cancer. Acrolein administered in the water for 104 weeks induced neoplasms in the adrenal cortex of female rats (Lijinsky and Reuber 1987). This type of tumor is rare in untreated rats. The increased incidence over controls was only marginally significant according to the Fisher Exact Test. This study cannot be considered a definitive positive or negative bioassay for carcinogenicity. Long-duration inhalation studies provided no evidence of carcinogenicity in hamsters or rats (Feron and Kruysse 1977; Le Bouffant et al. 1980). Furthermore, no neoplastic effects of chronic oral exposure to acrolein were observed in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987). The same results were found with dermal application and subcutaneous injections of acrolein (Salaman and Roe 1956; Steiner et al. 1943). However, several classes of chemicals structurally or functionally related to acrolein, such as aldehydes and dienes, are alkylating agents and have shown evidence of being animal carcinogens. There is some evidence that glycidaldehyde, a proposed acrolein metabolite, induces skin cancer in mice and rats (Shamberger 1974; Van Duuren 1967a,b). Based on the above and on the lack of epidemiological data, acrolein is considered to have limited animal evidence for carcinogenicity. Based on the overall available evidence, the EPA has classified acrolein as a Group C substance: a possible human carcinogen (EPA 1987c). IARC (1987) has classified acrolein as a Group 3 substance, i.e., a chemical for which there is inadequate evidence for carcinogenicity in humans and animals.

TABLE 2-4. Genotoxicity of Acrolein *In Vitro*

End Point	Species (Test System)	Result: With Activation	Result: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	*Salmonella typhimurium* (plate incorporation)	-	-	Andersen et al. 1972
	S. typhimurium (plate incorporation)	-	-	Florin et al. 1980
	S. typhimurium (plate incorporation)	-	-	Loquet et al. 1981
	S. typhimurium (plate incorporation)	-	-	Bignami et al. 1977
	S. typhimurium (plate incorporation)	-	(+)	Lijinsky and Andrews 1980
	S. typhimurium (plate incorporation)	-	+	Lutz et al. 1982
	S. typhimurium (plate incorporation)	-	+	Eder et al. 1982
	S. typhimurium (plate incorporation)	-	-	Basu and Marnett 1984
	S. typhimurium (plate incorporation)	ND	-	Bartsch et al. 1980
	S. typhimurium (plate incorporation)	ND	(+)	Khudoley et al. 1987
	S. typhimurium (liquid preincubation test)	ND	+	Marnett et al. 1985
	S. typhimurium (liquid incubation method)	ND	+	Foiles et al. 1989
	S. typhimurium (liquid incubation method)	-	(+)	Waegemaekers and Bensink 1984
	Escherichia coli PQ37 (SOS chromotest)	-	-	Von der Hude et al. 1988
	E. coli K-12/343/113 (plate incorporation)	-	ND	Ellenberger and Mohn 1977
	E. coli WPuvrA (plate incorporation)	ND	(+)	Hemminki et al. 1980
	E. coli DNA polymerase deficiency (plate incorporation)	ND	+	Bilimoria 1975
Eukaryotic organisms:				
Fungi:				
Gene mutation	*Saccharomyces cerevisiae* (plate incorporation) N123, S211, S138	ND	-	Izard 1973
Chromosomal aberrations	*S. cerevisiae* MB1072-2B (plate incorporation)	ND	-	Fleer and Brendel 1982
Mammalian cells:				
DNA, RNA synthesis	Rat liver cell nuclei	ND	+	Moule et al. 1971
DNA polymerase activity	Rat liver	ND	+	Munsch et al. 1973, 1974
Chromosome breakage	Chinese hamster ovary cells	+	+	Au et al. 1980
Sister-chromatid exchange	Chinese hamster ovary cells	+	+	Au et al. 1980
DNA damage	Human myeloid cells K562	ND	+	Crook et al. 1986
DNA damage	Human bronchial cells (culture)	ND	+	Grafstrom et al. 1988
DNA repair	Human bronchial cells (culture)	ND	+	Krokan et al. 1985
DNA repair	Human fibroblasts (culture)	ND	-	Curren et al. 1988
DNA repair	Human fibroblasts (xeroderma pigmentation)	ND	+	Curren et al. 1988
Gene mutation	Chinese hamster V79 cells	ND	+	Smith et al. 1990

+ = positive result; - = negative result; (+) = positive or marginal result; ND = no data.

2.5 BIOMARKIXS 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 or cell 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 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 (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 acrolein are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by acrolein 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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Acrolein

A product of the conjugation of acrolein with glutathione, 3-hydroxypropylmercapturic acid, has been identified in the urine of individuals receiving the drug cyclophosphamide (Alarcon 1976; Kaye and Young 1974). Since the same product was identified in the urine of rats administered acrolein subcutaneously (Alarcon 1976), it was thought that levels of 3-hydroxypropylmercapturic acid in the urine could be used to identify exposure to acrolein. However, Alarcon (1976) found no correlation between the dose of cyclophosphamide administered and the amount of 3-hydroxypropylmercapturic acid in the urine of patients. Methods developed to determine levels of acrolein in human tissues and fluids are described in Chapter 6.

2.5.2 Biomarkers Used to Characterize Effects Caused by Acrolein.

No studies were located regarding levels of acrolein or its metabolites in human tissues and fluids associated with effects. No biochemical or histological changes specific for acrolein exposure were identified. Results from a toxicokinetic study suggested that acrolein can react with proteins and nucleic acids in the organism (Pate1 et al. 1980). After transformation into acrylic acid, incorporation into amino acids, fatty acids, and sterols can be expected. However, specific effects associated with these biochemical reactions are not known.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Ansari et al. (1988) showed that acrolein enhances the inhibitory effect that certain industrial chemicals, such as styrene and 1,2-dichloroethane, have on the •l-proteinase inhibitor of human plasma *in vitro*. A decrease in the activity of the •l-proteinase inhibitor may result in an increase in the activity of the lung enzyme neutrophil elastase, which can lead to the development of emphysema. Acrolein has also been shown to increase the pentobarbital- and hexobarbital-induced sleeping time in rats (Jaeger and Murphy 1973). The mechanism, according to the authors, could include changes in the absorption and distribution of the barbiturates, More recent information suggests that the mechanism may involve a covalent reaction between acrolein and cytochrome P-450 leading to inactivation of P-450 resulting in prolonged action of the barbiturates (Lame and Seggall 1987).

Acrolein forms adducts with thiols such as glutathione, cysteine, N-acetylcysteine, and others. Such reaction protects tissues and cells from the cytotoxic effects of acrolein or acrolein-releasing substances (Brock et al. 1981; Chaviano et al. 1985; Dawson et al. 1984; Gurtoo et al. 1983; Ohno and Ormstad 1985; Whitehouse and Beck 1975).

Exposure of mice for 10 minutes to mixtures of sulfur dioxide and acrolein showed that either irritant can alter or block the effect of the

other (Kane and Alarie 1979). Furthermore, when the mice were exposed to mixtures, recovery was much slower than when exposed to the individual chemicals. The authors postulated that a bisulfite-acrolein adducc may be formed. When exposure ceased, this adduct would release acrolein, thus preventing immediate recovery. In addition, Kane and Alarie (1978) exposed mice to mixtures of acrolein and formaldehyde and showed that the respiratory response to mixtures was less pronounced than the response to either chemical alone. This is consistent with a mechanism in which both chemicals act on the same type of physiological receptor (free nerve endings).

2.7 POPUIATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

In general, individuals whose ventilatory function is compromised, such as those with emphysema, or individuals with allergic conditions such as asthma, will be at a higher risk of developing adverse respiratory responses when exposed to a strong respiratory irritant such as acrolein.

2.8 ADEQUATY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 acrolein 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 acrolein.

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.

2.8.1 Existing Information on Health Effects of Acrolein

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to acrolein are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of acrolein. 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.

As seen from Figure 2-5, very little information is available regarding the health effects of exposure of humans to acrolein. Experimental studies

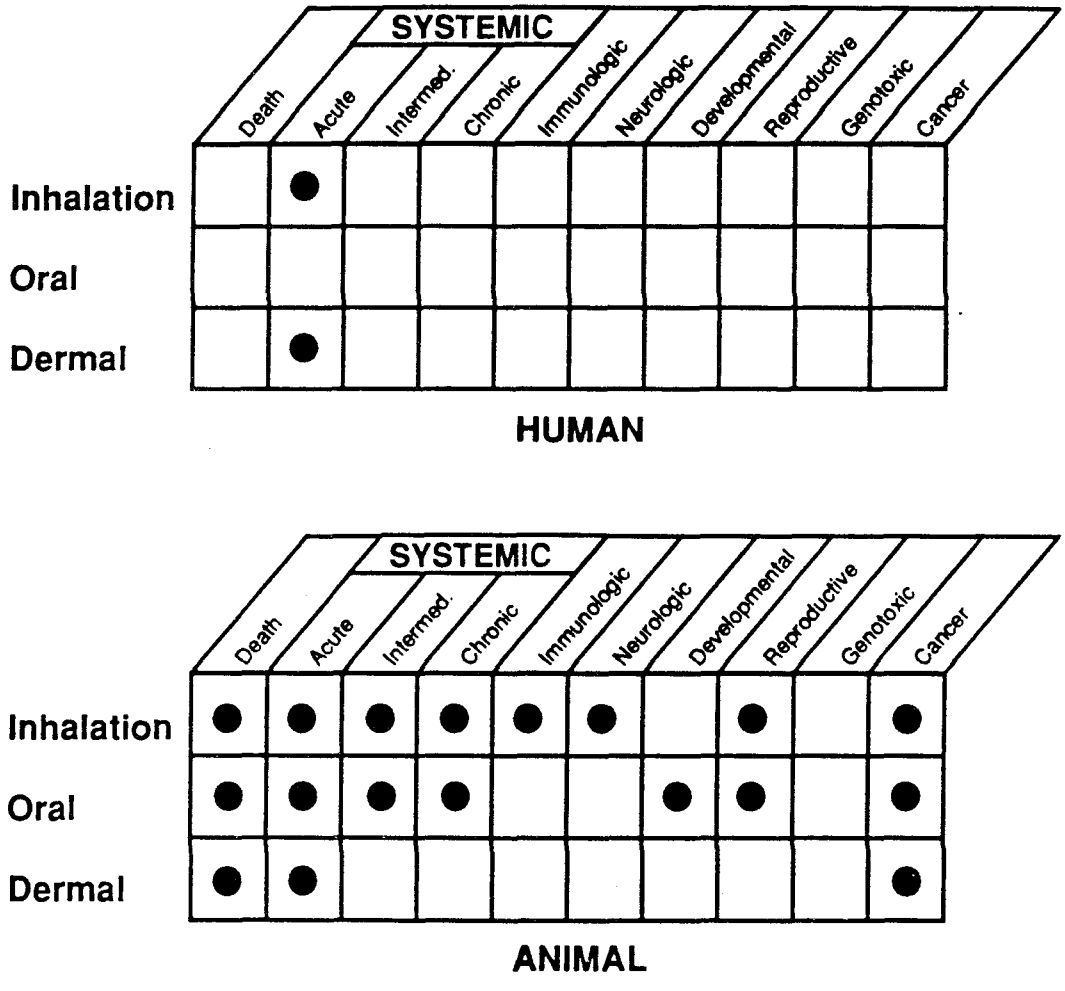


FIGURE 2-5. Existing Information on Health Effects of Acrolein

in humans have attempted to determine the thresholds for eye, nose, and throat irritation. Information on humans accidentally exposed to acrolein also indicates that acrolein irritates the skin, eyes, nose, and throat, and that severe respiratory effects can persist long after exposure occurs.

Data are available for acute and intermediate inhalation exposures that resulted in death of animals. For the most part, these exposures also affected the respiratory tract and the immune response to bacterial agents. An intermediate inhalation exposure study of rats prior to mating and during pregnancy did not result in fetotoxic or teratogenic effects. Limited information is available regarding chronic inhalation exposure.

Data are available for oral doses associated with death and increased mortality in acute, intermediate, and chronic exposure. The developmental and reproductive effects of oral exposure to acrolein have also been investigated. Chronic oral exposure of female rats resulted in neoplasms in the adrenal cortex.

Acrolein applied to the skin of animals results in skin irritation and death if applied in high concentration. Acrolein was not carcinogenic when applied to the skin of mice for 10 weeks.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure to acrolein is irritating to the upper respiratory system and eyes in humans and animals. The respiratory tract is the primary target of acrolein toxicity via inhalation exposure. Desquamation of the respiratory epithelium followed by airway occlusion and asphyxiation was the main reason for acrolein-induced mortality in animals. An MRL for acute inhalation exposure was derived from human data for respiratory effects. No data were located regarding acrolein toxicity in humans after oral exposure. Information regarding acute oral exposure of animals is limited to developmental toxicity studies. These studies have found decreased body weight gain and gastric ulceration in maternal animals, but endpoints of acute oral exposure in nonpregnant animals have not been identified. Therefore, the acute oral data are not sufficient to derive an MRL. Skin contact with acrolein caused irritation, burns, and epidermal necrosis in humans. It is evident, therefore, that the necrotic effects of acrolein occur at the site of primary contact regardless of routes of exposure. The acute lethal levels of acrolein were established after inhalation and oral exposure in rats. Target organs for acrolein toxicity other than at the site of contact, however, were not identified and pharmacokinetic data are insufficient to identify target organs across routes of exposure. Further studies in this direction after exposure via all three routes would be useful. The information is important for populations living near hazardous waste sites who might be exposed to acrolein for brief periods of time.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to acrolein in humans. Inhalation exposure studies in animals provided information on doses and treatment schedules that are lethal and that produce respiratory tract toxicity. The information was sufficient for derivation of an inhalation MRL. Two intermediate-duration oral studies were conducted in rats. One of the studies was limited in size and scope, the other one (two-generation reproductive study) has shown some differences between the first and second generation in clinical signs of acrolein toxicity. Furthermore, the mortality, though attributed to injuries from gavaging, was increased in all exposure groups. The study seemed, therefore, unreliable for MRL derivation. No systemic toxicity was reported in mice after intermediate duration dermal exposure to acrolein. The pharmacokinetic data were insufficient to identify the target organs of acrolein toxicity. Further studies regarding acrolein toxicity especially after oral and dermal routes would be useful. The results would be useful for possible extrapolation to humans and protection of populations around hazardous waste sites who might be exposed to acrolein for prolonged periods of time.

Chronic-Duration Exposure and Cancer. No studies were located regarding toxicity in humans following chronic exposure by any route of exposure. Respiratory toxicity was observed in rats and hamsters after inhalation exposure. However, the design of these inhalation studies was poor (short daily exposure or only one exposure level used), and the data were insufficient for MRL derivation. Chronic oral studies were performed in rats, mice, and dogs. Extensive histopathological examination revealed no effects in any organs, and a chronic oral MRL was derived from the results of hematological analysis in rats. No studies were located regarding acrolein toxicity after dermal exposure in animals. The pharmacokinetic data are insufficient to speculate on possible target organs of acrolein toxicity across routes of exposure. Acrolein has been selected for a general toxicology study by the National Toxicology Program (NTP 1990). This study could provide important information that is needed for the evaluation of health hazards of populations living near hazardous waste sites for a long period of time.

No studies were located regarding the carcinogenicity of acrolein in humans. No carcinogenicity of acrolein was observed in two limited (see above) chronic inhalation studies in animals. Dermal application of acrolein to mice for ten weeks did not induce cancer. However, the length of the study is considered too short for proper evaluation. No carcinogenic effect was found in rats, mice, and dogs following extensive histopathological examinations after chronic oral exposure to acrolein. An increased incidence of adrenocortical adenomas was observed in female rats after oral exposure to acrolein in another study. However, the study was limited in the number of exposed animals and the use of only one dose in exposed females. The carcinogenic potential of acrolein will be evaluated in the NTP study (NTP 1990).

Genotoxicity. No studies were located regarding acrolein genotoxicity in humans. Dominant lethality of acrolein observed in mice indicated a genotoxic potential in mammals. The result is supported by in vitro data that showed mutagenic potential of acrolein in bacterial and mammalian cells without metabolic activation. Further studies in animals would be useful to determine the ability of acrolein to induce chromosomal aberrations after exposure. Cytogenetic analysis of peripheral lymphocytes of workers exposed to acrolein would provide an opportunity to assess its genotoxicity in humans.

Reproductive Toxicity. No studies were located regarding reproductive effects of acrolein in humans. No changes in reproductive organs of rats after intermediate and chronic oral exposures or in mice or dogs after chronic exposures were found during histopathological examination. Conflicting results were obtained in reproductive toxicity studies in animals. No reproductive effects were observed in rats after inhalation exposure or in rats after oral exposure to acrolein. The results of a multigeneration oral exposure study in rats were also negative. Although not reproduced in the main study, the results of a pilot dose-range study indicated increased fetal resorptions in rabbits after oral exposure to acrolein. Furthermore, dominant lethality was induced in mice exposed to acrolein by inhalation. These data indicated possible reproductive effects of acrolein exposure in animals, and further studies would be useful to support these results. No data were located regarding reproductive effects in animals after dermal exposure, and the pharmacokinetic data are insufficient to draw any conclusion. Further studies in animals would be useful for extrapolating the results to human exposure.

Developmental Toxicity. No studies were located regarding developmental effects of acrolein in humans after any route of exposure. The developmental toxicity of acrolein was studied after oral exposure in rats and rabbits. Increased incidences of skeletal anomalies and delayed ossification were observed in rats, and increased fetal resorptions were found in rabbits. Furthermore, the results from parenteral administration indicate that acrolein can cross the placenta, causing malformations and embryolethality in experimental animals. This information is particularly relevant to individuals who are receiving the drug cyclophosphamide, of which acrolein is a metabolite. The developmental effects after inhalation or dermal exposure in animals were not studied. Pharmacokinetic data are insufficient to predict developmental effects after these routes of exposure. Further studies regarding information on developmental toxicity of acrolein after inhalation and dermal exposure would be useful. The information is important for possible extrapolation of results to human exposure.

Immunotoxicity. Information regarding immunological effects of acrolein in humans is not available. Acute and subchronic inhalation studies indicate that acrolein may increase the risk of bacterial infections in the respiratory tract, but a battery of immunotoxicity tests has not been

performed. Such tests provide a more sensitive assessment of possible immunotoxic effects than does histological examination of tissues and organs of the immune system. Since a case of an allergic response to acrolein derived from cigarette smoke was described in humans, sensitization tests could help identify agents causing allergic responses in individuals exposed to tobacco smoke. No information regarding immunological effects in animals after oral or dermal exposure to acrolein were located.

Neurotoxicity. No information was located regarding neurological effects of acrolein in humans. Symptoms of central nervous system depression were observed in rodents after oral exposure to acrolein, but only after lethal concentrations. No such effects were observed in animals after inhalation exposure; the animals died from asphyxia caused by epithelial desquamation and, consequently, respiratory obstruction. No behavioral changes were observed in animals exposed to acrolein by any route. Nonspecific histopathological effects on the brains of animals were found in subchronic inhalation studies. No histopathological changes were observed after oral exposure. No studies regarding neurotoxicity of acrolein after dermal exposure were located. However, the available data do not indicate that the central nervous system is the major target of acrolein toxicity.

Epidemiological and Human Dosimetry Studies. The only information available concerning effects of acrolein in humans comes from a limited number of cases of accidental exposure by the inhalation and dermal routes. In these cases, severe effects were observed in the eyes and respiratory tract mucosa, some effects persisting for several months after the exposure occurred. However, epidemiological studies are not available. Chronic human exposure is not likely to occur because of the strong irritating effects of acrolein. This means that individuals exposed to acrolein would most likely leave the polluted area before acrolein reaches a dangerous concentration. Amoore and Hautala (1983) calculated that the odor safety factor for acrolein is such that lo-50% of attentive persons can detect the TLV concentration (0.1 ppm) in the air. Nevertheless, epidemiology studies of individuals who live in areas where acrolein has been detected, such as polluted urban centers and of workers occupationally exposed to acrolein, even at low doses, would provide information regarding the effects of longterm exposure to tolerable concentrations. This information would be useful for monitoring individuals near hazardous waste sites for preventive purposes.

Biomarkers of Exposure and Effect. No reliable biomarkers of acrolein exposure have been identified. The finding of 3-hydroxypropylmercapturic acid in the urine after exposure to acrolein or cyclophosphamide seemed to be promising for use as an exposure identifier. However, further studies found no correlation between the amount of 3-hydroxypropylmercapturic acid in the urine and the dose of parent compound administered. Further identification of acrolein metabolites in the urine and their correlation with levels of exposure would be useful. Recently, Iype et al. (1987)

presented preliminary results in an abstract regarding the development of an antibody-mediated assay to monitor subjects exposed to acrolein. This assay exploits the possible formation of acrolein-adducted DNA in cells, or the formation of antibodies against such adducts in serum. Such assays could eventually be used for the early detection of respiratory diseases such as emphysema, to which acrolein may be a contributor. Further studies regarding possible biochemical changes after acrolein exposure would be useful.

It has been proposed that acrolein can be transformed metabolically into acrylic acid, which may be incorporated into amino acids, fatty acids, and sterol. However, specific biomarkers of effect for acrolein have not been identified. Studies regarding identification of these biomarkers would be useful.

Absorption, Distribution, Metabolism, Excretion. The only toxicokinetic data of acrolein are from the in vivo absorption study in dogs by Egle (1972) and the oral exposure study in rats by Draminski et al. (1983), from which a possible metabolic pathway was proposed. However, dermal and inhalation exposures may lead to different metabolic pathways and patterns of distribution and excretion, which could account for differences in the degree of toxicity exhibited by different routes of exposure. The metabolism of acrolein in vitro seems to be well understood, especially the reaction with thiol groups. This reaction represents an important mechanism for the protection of cells and tissues from the cytotoxic effects of acrolein. Determining the urinary excretion of acrolein conjugates in control volunteers and in individuals known to have been exposed to polluted environments could provide information concerning absorption and excretion of the xenobiotic. The use of human cell systems in culture might be considered a useful alternative to studying the metabolic fate of acrolein.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of acrolein in vivo. Differences in the toxicokinetics of a chemical among species may account for differences in toxic responses. The potential for acrolein to produce toxic effects has been investigated in rats, mice, dogs, guinea pigs, hamsters, rabbits, and monkeys, but the animal species that serves as the best model for extrapolating results to humans remains unknown. Although virtually no information is available regarding the toxicokinetics of acrolein in humans, analysis of the urine of individuals accidentally exposed to the chemical or living in polluted urban areas would provide valuable information on absorption and excretion rates if the exposure to acrolein was known.

2.8.3 On-going Studies

Several on-going studies regarding acrolein have been identified from the National Technical Information Service (NTIS 1988).

S. Cohen and R. Smith, University of Nebraska, Omaha, NE, are investigating the mechanism by which acrolein induces damage in the bladder epithelium of rats, in vivo and in vitro. Their studies include short-term and long-term bioassays. Similar studies are being performed by C. Irving and co-workers, Veterans Administration Medical Center, Memphis, TN. At Massachusetts General Hospital, Boston, MA, C. Hales is conducting research on the mechanism by which acrolein produces pulmonary edema and how it interacts with skin burns to induce lung injuries. The experimental animals include dogs and sheep.

At the American Health Foundation, New York, NY, P. Foiles and S. Hecht, sponsored by the NCI, are attempting to develop sensitive immunoassays in mice for the detection of acrolein-DNA adducts in animals and eventually in humans exposed to the chemical. Dr. Foiles and his collaborators are pursuing 32_P post-labeling methods for the detection of acrolein modified DNA. C. Sevilla, Proteins International, Rochester, MN, is attempting to develop monoclonal antibodies for acrolein-DNA adducts. These antibodies will be used in clinical and research monitoring of levels of the adduct in human DNA samples.

P. Mirkes, University of Washington, Seattle, WA, is continuing his investigation on the teratogenic properties of the metabolites of the drug cyclophosphamide, of which acrolein is one. The studies are being performed in rat embryos cultured in vitro. R. Okita, Medical College of Wisconsin, Milwaukee, WI, is studying the effects of acrolein on the activity of the enzyme NAD+-dependent prostaglandin dehydrogenase in the lungs of rabbits and guinea pigs. His studies are aimed to better characterize this enzyme and the function of prostaglandins and other eicosanoid derivatives in pulmonary function. Acrolein has been selected for a general toxicology study by the National Toxicology Program (NTP 1990).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of acrolein are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of acrolein are presented in Table 3-2.

TABLE 3-1. Chemical Identity of Acrolein

	Value	Reference
Chemical name	Acrolein	
Synonyms	Acraldehyde acrylaldehyde allyl aldehyde 2-propenal propylene aldehyde	SANSS 1988
Trade names	Aqualin, MAGNACIDE H®	Bennett 1981, 1982
Chemical formula	C_3H_4O	CAS 1988
Chemical structure	$CH_2 = CH - CHO$	SANSS 1988
Identification numbers:		
CAS Registry	107-02-8	CAS 1988
NIOSH RTECS	AS1050000	RTECS 1988
EPA Hazardous Waste	P003	HSDB 1988
OHM-TADS	7216793	OHM-TADS 1988
DOT/UN/NA/IMCO	UN 1092	HSDB 1988
IMCO	3.1	HSDB 1988
HSDB	177	HSDB 1988
NCI	Not available	

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

TABLE 3-2. Physical and Chemical Properties of Acrolein

Property	Value	Reference
Molecular weight	56.06	Hess et al. 1978
Color	Colorless or yellowish	Hess et al. 1978
Physical State	Liquid	Hess et al. 1978
Melting point	-86.9°C	Weast 1983
Boiling point	52.5-53.5°C	Weast 1983
Density at 20°C	0.8389 g/m^3	Riddick et al. 1986
Specific gravity, 20/4°C	0.8410	Weast 1983
Odor	Disagreeable, choking odor, pungent	Hawley 1981; Windholz 1983
Odor threshold:		
Water	0.11 ppm	Amoore and Hautala 1983
Air	0.16 ppm	
Solubility:		
Water at 20°C	206,000 mg/L	Hess et al. 1978
Organic solvents	Miscible with lower alcohols, ethers, hydrocarbons, acetone, benzene	Tweedy and Houseworth 1976
Partition coefficients:		
Log octanol/water	-0.01	Hansch and Leo 1985
Log K_{oc}	51-270	Irwin 1988
Vapor pressure at 20°C:	220 mmHg	Hess et al. 1978
Henry's law constant:		
at 20°C	3.06 x 10^{-5} atm-m^3/mol	Snider and Dawson 1985
Autoignition temperature	234°C	Hess et al. 1978
Flashpoint	-18°C (open cup)	Hess et al. 1978
	-26°C (closed cup)	Hess et al. 1978
Flammability limits in air	2.8-31 volume %	Hess et al. 1978
Conversion factors:		
ppm (v/v) to mg/m^3 in air at 25°C	1 ppm (v/v) = 2.29 mg/m^3	
mg/m^3 to ppm (v/v) in air at 25°C	1 mg/m^3 = 0.44 ppm (v/v)	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Acrolein is manufactured as an end-use product and as an unisolated intermediate in the production of acrylic acid. Acrolein is manufactured by air oxidation of propylene via the following reaction (Hess et al. 1978):

$$CH_3CH=CH_2 + 0_2 \rightarrow CH_2=CHCHO + H_20$$

Companies that currently produce acrolein as an unisolated intermediate are: BASF Corp., Freeport, TX; Hoechst Celanese Corp., Clear Lake, TX; Rohm and Haas, Deer Park, TX; and Union Carbide, Taft, LA (Nemec and Bauer 1978; SRI 1988; USITC 1988). During 1988, these companies produced a combined total of 1.1 billion pounds of acrylic acid (USITC 1988). Based on this figure, the production volume of unisolated acrolein in the United States during 1988 has been estimated to be 0.9 billion pounds, assuming 100% yield of acrylic acid from acrolein. Where less than 100% yield of acrylic acid is achieved, the unreacted acrolein is probably recycled back into the reaction chamber. Between 1959 and 1980, Shell Chemical Co. in Norco, TX, produced acrolein for captive consumption in the manufacture of glycerin. Production of acrolein at this facility ceased when the plant was shut down (CMR 1981). A 4-5% increase in the production of acrylic acid is expected through 1991 (CMR 1987), and a corresponding increase in the production of unisolated acrolein is expected. In 1978, domestic manufacturing plants produced approximately 354 million pounds of acrolein (Anderson 1983). Approximately 308 million pounds were produced as an unisolated intermediate in acrylic acid production, 24 million pounds were used in the manufacture of glycerin, 20 million pounds were used in the manufacture of methionine and related compounds, and 2 million pounds were used for miscellaneous purposes.

4.2 IMPORT

During 1972, United States imports and exports of acrolein were negligible (HSDB 1988). No further information regarding the import or export of this compound was located.

4.3 USE

The largest single use for acrolein is as an unisolated intermediate in the manufacture of acrylic acid, most of which is converted to its lower alkyl esters. Acrolein is also used as a herbicide and algicide in irrigation waters and drainage ditches; as a biocide in cooling water towers and water treatment ponds; in the control of algae, weeds, and mollusks in recirculating process water systems; to control microbial growth in feed lines used in subsurface wastewater injection; as a slimicide in the paper industry; as a biocide in oil wells and liquid petrochemical fuels; in the cross-linking of protein collagen in leather tanning; as a tissue fixative in histological samples; as a starting material in the manufacture of Union

Carbide's ERL-4221 bis-epoxide (which is used to make electrical insulators); in the manufacture of colloidal forms of metals; in the production of perfumes; as a warning agent in methyl chloride refrigerant; and as an intermediate in the manufacture of methionine and its hydroxy analogue, glutaraldehyde, ally1 alcohol, •-picoline, and tetrahydrobenzaldehyde (Hawley 1981; Hess et al. 1978; IARC 1985; Windholz 1983). Isolated, refined acrolein is used mainly as a biocide and intermediate in the production of methionine and its methoxy analogue, which are protein supplements used in poultry feed. Acrolein has been used to make modified food starch, synthetic glycerine, acrolein homopolymer, several copolymers (e.g., with acrylic acid, acrylonitrile, and acrylic esters), as well as polymers formed by reaction with formaldehyde, guanidine hydrochloride, and ethylene diamine. It has also been used in military poison gas mixtures (IARC 1985).

4.4 DISPOSAL

Prior to implementing land disposal of waste residues (including waste sludge), environmental regulatory agencies should be consulted for guidance on acceptable disposal practices (HSDB 1988). Materials containing concentrated acrolein may be incinerated by: rotary kiln incineration, with a temperature range of 820-1,600°C and a residence time of seconds; fluidized bed incineration, with a temperature range of 450-980°C and a residence time of seconds; and liquid injection', with a temperature range of 650-1600°C and a residence time of 0.1-2 seconds (HSDB 1988). Materials containing small amounts of acrolein may be disposed of by neutralization (if needed), followed by secondary biological treatment or by submerged combustion (to concentrate the waste) followed by incineration (Hess et al. 1978; OHM-TADS 1988). On-site combustion is an option for disposal if the spill site is in a very remote, inaccessible area, and there is danger of subsequent discharge if other methods of disposal are attempted. Local, state, and federal (RCRA) approval must be obtained before burning on site (OHM-TADS 1988).

Acrolein has been identified as a hazardous waste by the Environmental Protection Agency, and the disposal of this compound is regulated under the federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations concerning disposal of hazardous wastes through land treatment, landfilling, incineration, thermal treatment, chemical/physical/biological treatment, underground injection, and deep sea injection are provided in the Code of Federal Regulations (40 CFR 190 to 399). Release of acrolein in wastewater is regulated under the Clean Water Act by the National Pollutant Discharge Elimination System (NPDES). Information regarding effluent guidelines and standards for acrolein may be found in 40 CFR 122, 40 CFR 125, 40 CFR 413, 40 CFR 4.23, and 40 CFR 433. Pursuant to RCRA Section 3004(g)(5), EPA has proposed to restrict the land disposal of acrolein (Federal Register 1989b). Acrolein may be land

disposed only if prior treatment standards have been met, or if disposal occurs in units that satisfy the statutory no migration standard (Federal Register 1989b). Proper guidelines and standards are outlined in the Federal register (1989b).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Acrolein may be released to the environment in emissions and effluents from its manufacturing and use facilities, in emissions from combustion processes (including cigarette smoking and combustion of petrochemical fuels), from direct application to water and wastewater as a slimicide and aquatic herbicide, as a photooxidation product of various hydrocarbon pollutants found in air (including propylene and 1,3-butadiene), and from land disposal of some organic waste materials. Acrolein is a reactive compound and is unstable in the environment.

In ambient air, the primary removal mechanism for acrolein is predicted to be reaction with photochemically generated hydroxyl radicals (half-life 15-20 hours). Products of this reaction include carbon monoxide, formaldehyde, and glycolaldehyde. In the presence of nitrogen oxides, peroxynitrate and nitric acid are also formed. Small amounts of acrolein may also be removed from the atmosphere in precipitation. Insufficient data are available to predict the fate of acrolein in indoor air. In water, small amounts of acrolein may be removed by volatilization (half-life 23 hours from a model river 1 m deep), aerobic biodegradation, or reversible hydration to β-hydroxypropionaldehyde, which subsequently biodegrades. Half-lives less than l-3 days for small amounts of acrolein in surface water have been observed. When highly concentrated amounts of acrolein are released or spilled into water, this compound may polymerize by oxidation or hydration processes. In soil, acrolein is expected to be subject to the same removal processes as in water. This compound can be highly mobile in soil; however, volatilization and degradation processes are expected to attenuate movement through soil.

Data regarding the monitoring of acrolein in the environment are limited. During the 196Os, acrolein was detected at concentrations averaging between 5 and 8 ppb in air samples collected in Los Angeles, CA. These data provide insight regarding maximum atmospheric levels of acrolein in urban areas during this period. During 1976, acrolein levels in air samples collected in Edison, NJ, were not detectable in 14 of 19 samples and averaged 0.31 ppb in the 5 positive samples. No data indicated that acrolein is a contaminant of drinking water supplies. The EPA STORET data indicate that acrolein occurs at a low frequency in wastewater streams, ambient surface water, and groundwater in the United States. In the only report of acrolein occurrence in municipal landfill leachate, 170 ppb acrolein was detected in leachate from one site in Wisconsin. The contract laboratory statistical database indicates that acrolein has been found in soil samples at 1 of 357 sites at a mean concentration of 6.5 ppb, and in water samples at 3 of 357 hazardous waste sites at concentrations ranging between 10.3 and 51,000 ppb; however, no distinction was made between groundwater and surface water samples. The National Priority List Technical Data Base indicates that acrolein has been detected at 7 of 1177 National Priority List (NPL) sites; the frequency of these sites within the United States can be seen in Figure 5-l (View 1989). However, the level of

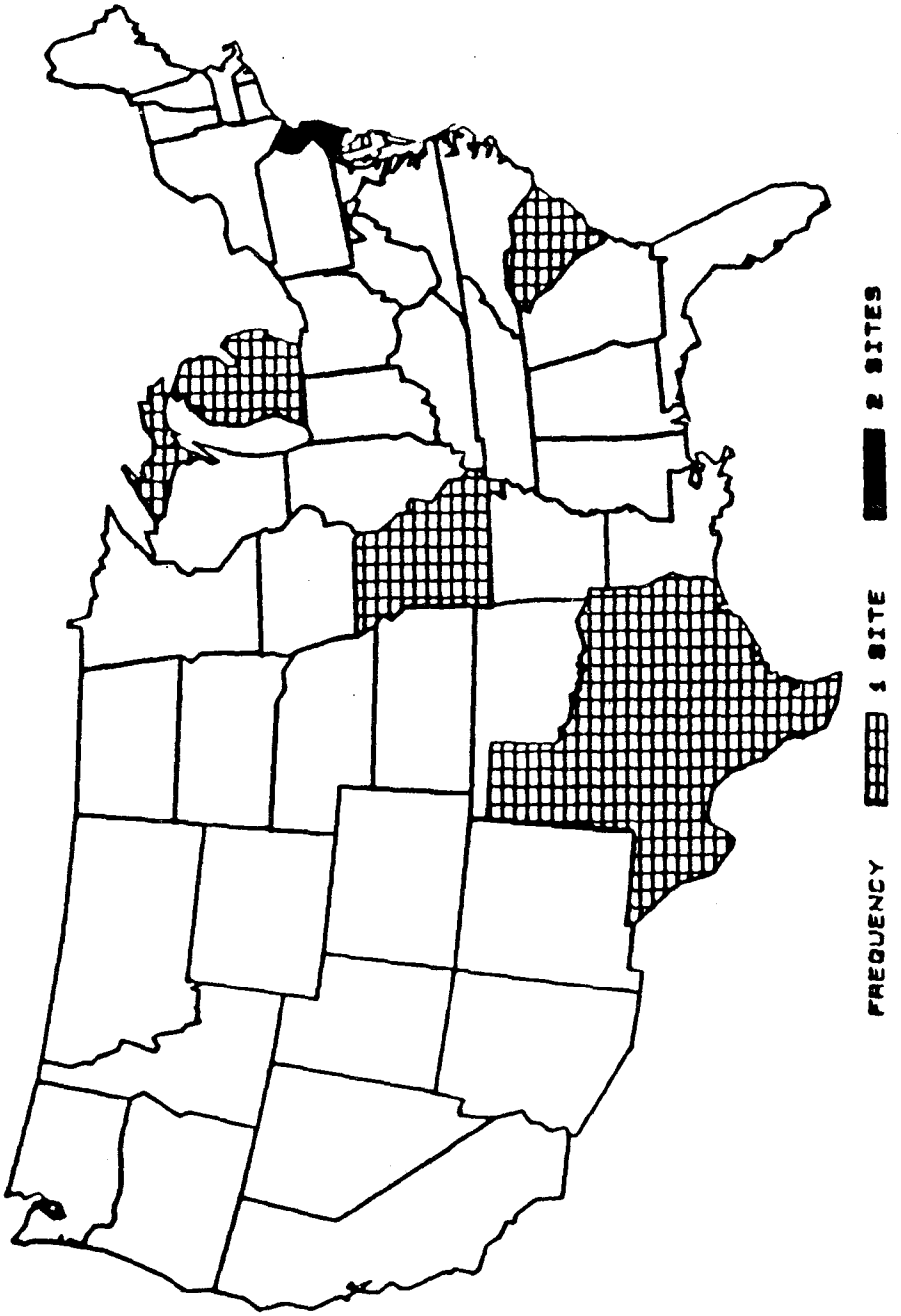


FIGURE 5-1. Frequency of Sites with Acrolein Contamination

contamination or the media in which this compound was found was not reported. Acrolein is a gaseous constituent of cigarette smoke and has been detected at levels equivalent to 3-220 µg per cigarette. Acrolein is formed when fats are heated. It has also been found in foods and food products such as raw cocoa beans, volatiles from cooked mackerel and white bread, and vegetable oils, wine, whiskey, and lager beer. Sufficient data are not available to establish the level of acrolein typically found in these items.

Monitoring data indicate that the general population may be exposed to acrolein through inhalation of contaminated air and through ingestion of certain foods. One of the most important sources of acrolein exposure may be via the heating of fats contained in all living matter. Because of the lack of recent, comprehensive monitoring data, the average daily intake of acrolein and the relative importance of each source of exposure cannot be determined. Estimating the typical level of exposure to acrolein is complicated because acrolein is a common contaminant of tobacco smoke, and there is wide variation among individuals regarding the frequency and level of exposure to tobacco smoke.

There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all the occupations in which work-related exposure to acrolein occur. It appears that occupational exposure can occur via inhalation and dermal contact.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Potential sources of atmospheric release of acrolein include: emissions from facilities involved in the manufacture or use of products containing acrolein; volatilization from treated waters and contaminated waste streams; formation as a photooxidation product of various hydrocarbon pollutants such as propylene, 1,3-butadiene, and other diolefins (Graedel et al. 1978; Maldotti et al. 1980); and emissions from combustion processes. Specific combustion sources include exhaust gas from engines powered by gasoline, diesel or other petrochemical fuels, power plants, burning vegetation (i.e., forest fires), combustion of cellulose materials such as wood, cotton, tobacco, and marijuana, and combustion of polyethylene plastics (Hodgkin et al. 1982; Jonsson et al. i985; Lipari et al. 1984). Acrolein is also a pyrolysis product of polyethylene, animal fats and vegetable oils, cellophane, plastics, and paraffin wax (Boettner and Ball 1980; EPA 1980; Potts et al. 1978; Tanne 1983; Wharton 1978). The concentrations of acrolein in emissions from various combustion and pyrolysis processes are listed in Table 5-l.

Recent estimates of the atmospheric loading rate of acrolein from sources in the United States were not located. Anderson (1983) estimated

TABLE 5-1. Acrolein in Emissions from Combustion

Source	Concentration	References
Auto exhaust gas:		
Gasoline engine	Not detected to 12.1 ppm (detection limit 0.01 ppm) 0-7.79% of total aldehydes, excluding acetone	Lipari and Swarin 1982; Nishikawa et al. 1987a; Seizinger and Dimitriades 1972; Sigsby et al. 1987; Zweidinger et al. 1988
Diesel engine	0.05-0.3 ppm	IARC 1985; Seizinger and Dimitriades 1972
Ethanol engine	Not detected (detection limit 0.01 ppm)	Lipari and Swarin 1982
Cigarette smoke	3-220 µg/cigarette	Hoffman et al. 1975; Horton and Guerin 1974; Magin 1980; Manning et al. 1983
Marijuana smoke	92-145 µg/cigarette	Hoffman et al. 1975; Horton and Guerin 1974
Smoke from burning:		
Wood	50 ppm	Einhorn 1975
Cotton	60 ppm	
Kerosene	<1 ppm	
Emissions from woodburning fireplaces	21-132 mg/kg wood	Lipari et al. 1984
Emissions from power plants:		
Coal-fueled	0.002 lb aldehydes/1000 lbs fuel	Natusch 1978
Gas-fueled	0.2 lb aldehydes/1000 lbs fuel	
Oil-fueled	0.1 lb aldehydes/1000 lbs fuel	
Pyrolysis of polyvinyl chloride food-wrap film during hot wire cutting	27-151 ng/cut	Boettner and Ball 1980
Emissions from the combustion of polyethylene foam	2-23 ppm	Potts et al. 1978
Pyrolysis of polyethylene foam	76-180 ppm	Potts et al. 1978
15 cm above heated cooking oil	2.5-30 mg/m^3	EPA 1980b

the total loading rate of acrolein in 1978 to be 91,450 pounds from facilities involved in its production and use as a chemical intermediate. Loading rates from various industrial sources were as follows: acrylic acid manufacturers, 15,175 pounds; refined acrolein and glycerin manufacturers, 55,660 pounds; methionine manufacturers, 18,150 pounds; and miscellaneous intermediate uses, 2420 pounds. These loading rates were based on a total production volume of 350 million pounds for acrolein in 1978, with 87% of this volume consumed in the production of acrylic acid and its derivatives.

5.2.2 Water

Acrolein may be released to water in effluents from its manufacturing plants and use facilities (see Section 4.3 for specific information regarding uses) and from its direct application to water as an aquatic herbicide (IARC 1985; Lue-Hing et al. 1981; WSSA 1983). Data regarding the amount of acrolein released to United States waters were not located.

5.2.3 Soil

The occurrence of acrolein in soil at one hazardous waste site in the United States and leachate from one municipal landfill in Wisconsin provides evidence that this compound has been released to soil as the result of land disposal of some organic wastes. No data were located regarding the amount of acrolein released to soil.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Acrolein is relatively unstable in the atmosphere; therefore, transport within the atmosphere is expected to be limited. The relatively high vapor pressure of acrolein [220 mm Hg at 20°C (Eisenreich et al. 1981; Hess et al. 1978)] suggests that this compound will not partition from the vapor phase to particulates in the atmosphere. Occurrence of acrolein in rainwater (Grosjean and Wright 1983; Nishikawa et al. 1987b) indicates that this compound may be removed from the atmosphere by washout.

Volatilization is expected to be a significant removal process for any acrolein released to surface waters. Based on a measured Henry's Law constant of 3.06 x 10^{-5} atm-m^3/mol at 20°C, the volatilization half-life from a model river 1 m deep, flowing 1 m/set with a wind speed of 3 m/sec was estimated to be 23 hours using the method of Thomas (1982). Veith et al. (1980) measured a bioconcentration factor (BCF) of 344 for acrolein in bluegill sunfish; however, this may be an overestimate, since total 14C was measured in the fish, which may have resulted in the measurement of acrolein metabolites. A BCF of 0.6 was estimated for acrolein using a linear regression equation based on a log octanol/water partition coefficient (K_{ow}) cf -0.01 (Bysshe 1982; Hansch and Leo 1985). These BCFs, as well as the relatively high water solubility of this compound, suggest

that acrolein does not bioconcentrate significantly in aquatic organisms. Using a linear regression equation based on log K_{ow} data (Lyman 1982), an adsorption coefficient (K_{oc}) of 24 was estimated, which suggests that adsorption of acrolein to suspended solids and sediments in water would not be significant. Irwin (1988) reports a range of experimental K_{oc}, of 51-270 for adsorption of acrolein to two soils. The relatively low experimental and estimated K_{oc} values suggest that acrolein will be highly to moderately mobile in soil and that this compound has the potential to leach significantly (Swann et al. 1983). However, the adsorption of acrolein to soil has been shown to be irreversible (Irwin 1988). Irreversible sorption, biodegradation, hydration, and volatilization of acrolein in soil can be expected to significantly retard the leaching of acrolein through soil.

The relatively high vapor pressure of acrolein and its volatility from water suggest that this compound will evaporate rapidly from soil surfaces and that volatilization is probably a major removal process from soil. The relatively low K_{oc} value for acrolein indicates high mobility in soil and suggests that this compound has the potential to leach significantly (Swann et al. 1983). Degradation processes and volatilization, however, are expected to significantly retard movement of acrolein through soil.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The dominant removal process for acrolein in ambient air is predicted to be reaction with photochemically generated hydroxyl radicals in the troposphere. The atmospheric half-life for acrolein is estimated to be 15-20 hours, based on experimentally determined hydrox 1 reaction rate constants ranging between 1.90 x $l0^{-11}$ and 2.53 x $l0^{-11}$ cm^3/molecules-sec at 25-26°C and an average ambient hydroxyl radical concentration of 5.0 x $l0^5$ molecules/cm^3 (Atkinson 1985). Products of this reaction include carbon monoxide, formaldehyde, and glycolaldehyde. In the presence of nitrogen oxides, products include peroxynitrate and nitric acid (Edney et al. 1986). Direct photolysis in the ambient atmosphere occurs but is expected to be of minor importance. Gardner et al. (1987) reported that the quantum yields for irradiation of acrolein at low air pressures were 0.0066 at 313 nm and 0.0044 at 334 nm. The authors used a computer analysis of their photodissociation data to estimate the half-life of acrolein to be 10 days in the lower troposphere and less than 5 days in the upper troposphere. Experimental data indicate that reaction of acrolein with ozone ($k = 2.8 \times 10^{-19}$ cm^3/molecules-see at 25°C; half-life = 59 days) or nitrate radicals ($k = 5.9 \pm 2.8 \times 10^{-16}$ cm^3/molecules-seC at 25°C; half-life - 16 days) in the troposphere would be too slow to be environmentally significant (Atkinson 1985; Atkinson et al. 1987). The fate of acrolein in indoor air is expected to be different from its fate in outdoor air because of differences in the concentrations of oxidants in indoor air compared to outdoor air and the possibility of other mechanisms of removal.

5.3.2.2 Water

Low concentrations of acrolein may degrade in natural water by either aerobic biodegradation or reversible hydration to β-hydroxypropionaldehyde, which subsequently undergoes aerobic biodegradation (Bowmer and Higgins 1976; Callahan et al. 1979; Tabak et al. 1981). Acrolein applied to surface waters at application rates suggested for herbicidal use can persist up to 6 days (WSSA 1983). Bowmer and Higgins (1976) measured acrolein removal in both laboratory water and in field experiments using irrigation channels. In buffered laboratory water, acrolein reached its equilibrium apparently with β-hydroxypropionaldehyde in approximately 300 hours (92% β-hydroxypropionaldehyde, 8% acrolein); in irrigation channels, acrolein removal was complete. Half-lives were reportedly less than 1 to 3 days in surface water, but values were for the combined effect of degradation and volatilization (Bowmer and Higgins 1976; Bowmer et al. 1974). Kissel et al. (1978) measured acrolein removal in buffered laboratory water and natural river water using both chemical analysis methods and bioassays. Complete hydrolysis (which according to the authors includes hydration to 3-hydroxypropanol) occurred within 150 hours, 120-180 hours, and 5-40 hours in buffered solutions at 22°C and pH 5, 7, and 9, respectively. Based on fish kill bioassays in natural river water at pH 8.1, greater than 93% degradation of acrolein occurred within 6 days.

Jacobson and Smith (1990) studied the dissipation of acrolein, applied at the highest recommended rate according to the label, to achieve a 15 ppm concentration for a 2-hour duration in an irrigation canal and a lateral of the canal which was infested with aquatic plants. The dissipation halflives for acrolein in the irrigation and lateral canals were 275 and 64 minutes, respectively. No acrolein residues were detected (detection limit, 0.01 ppm). No residues of 3-hydroxypropanol were detected (detection limit, 2.0 ppm) in any of the water samples from either canal. These data suggest that acrolein will not persist for moderate or long periods of time in aerobic aquatic environments and that hydration of acrolein may not be an important degradation pathway for acrolein (Jacobson and Smith, 1990).

The ultraviolet (UV) spectrum of acrolein in hexane shows moderate absorption of UV light in the environmentally significant range (wavelengths greater than 290), suggesting that acrolein might undergo photolysis in natural waters; however, hydration of acrolein destroys the chromophores that absorb W light (Callahan et al. 1979), and the equilibrium appears to be far on the side of the hydration product. Thus, the potential for direct photolysis of acrolein in natural waters is probably slight. Oxidation of small amounts of acrolein in natural waters would not be environmentally significant; however, highly concentrated acrolein solutions (i.e., spills) may be polymerized by oxidation or hydration processes (Callahan et al. 1979). Insufficient data are available regarding anaerobic biodegradation to establish the significance of this process as a removal mechanism or to determine the rate at which such a process would proceed. This information

would be particularly useful in determining the fate of acrolein under conditions frequently encountered in groundwater and in landfills,

5.3.2.3 Soil

Experimental data specifically pertaining to the degradation or transformation of acrolein in soil were not located. Results of studies in aquatic systems suggest that acrolein, at low concentrations, may be subject to aerobic biodegradation in soil or transformation via hydration followed by aerobic biodegradation of the hydrated product (see Section 5.3.2.2). Since acrolein is a very reactive compound, abiotic processes, such as oxidation, may be the most important degradation processes.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The atmospheric concentrations of acrolein have been measured in several locations, and the most comprehensive monitoring studies are discussed below. Altshuller and McPherson (1963) and Renzetti and Bryan (1961) determined that acrolein levels in air samples collected in Los Angeles, CA, during 1960-61 averaged between 5 and 8 ppb. Air samples collected in the Los Angeles Basin over a 12-week period during 1968 contained levels ranging between none detected to 18 ppb, although most values ranged between 0.9 and 9 ppb (IARC 1985). Since Los Angeles is a high-density population center with a variety of emission sources and a smog problem related to high traffic density, air monitoring data from this area may provide insight regarding the maximum atmospheric levels of acrolein in urban areas. However, these data are considered too old to provide useful information on current ambient levels of acrolein. In a somewhat more recent survey (although still very outdated), acrolein was detected in 5 of 19 air samples collected in Edison, NJ, during 1976. Positive samples contained acrolein at levels between 0.19 and 0.44 ppb, with a mean concentration of 0.31 ppb (Brodzinsky and Singh 1982). These data are insufficient for determining the level at which acrolein typically occurs in ambient air.

5.4.2 Water

Data from the EPA STORET Data Base indicate that acrolein has a low frequency of occurrence in wastewater streams, ambient surface water, and groundwater in the United States (EPA 1988b; Staples et al. 1985). Acrolein has not been found as a contaminant of drinking water (EPA 1980; Krill and Sonzogni 1986; Otson 1987). Grosjean and Wright (1983) detected acrolein, in combination with acetone, at a concentration of 0.05 ppt in rainwater collected in Los Angeles, CA; however, these compounds were not detected in rainwater samples collected in four less densely populated sites in California. The Contract Laboratory Statistical Database reports that acrolein has been detected in water at 3 of 357 hazardous waste sites in

the United States at mean concentrations ranging from 10.3-51,000 ppb (VIAR 1987). However, this database made no distinction between groundwater and surface water monitoring data. In the only report of acrolein occurrence in municipal landfill leachate, acrolein was detected at a concentration of 170 ppb in 1 of 5 leachate samples collected from sites in Wisconsin (Sabel and Clark 1984).

5.4.3 Soil

The Contract Laboratory Statistical Database reports that acrolein was detected in soil at 1 of 357 hazardous waste sites in the United States, at a mean concentration of 6.5 ppb (VIAR 1987). The National Priority List Technical Data Base (View 1989) indicates that acrolein was detected at 5 of 1177 National Priority List (NPL) sites; however, the database does not contain media concentration data. Acrolein was identified in sediment/ soil/water samples collected from Love Canal in Niagara Falls, NY (Hauser and Bromberg 1982); however, no quantitative data were available.

5.4.4 Other Media

Acrolein has been identified in foods and food components such as raw cocoa beans, chocolate liquor, souring salted pork, fried potatoes and onions, raw and cooked turkey, and volatiles from cooked mackerel, white bread, raw chicken breast, ripe arctic bramble berries, heated animal fats and vegetable oils, and roasted coffee (Cantoni et al. 1969; EPA 1980, 1985; IARC 1985; Umano and Shibamoto 1987). Sufficient data are not available to establish the level of acrolein typically encountered in these foods. Trace ievels of acrolein have been found in wine, whiskey, and lager beer (IARC 1985). Further information regarding the occurrence of acrolein in food and related products is provided by EPA (1980).

Acrolein is a gaseous constituent of tobacco and marijuana smoke, occurring in both mainstream and sidestream smoke (Ayer and Yeager 1982; Hoffmann et al. 1975; Holzer et al. 1976; Rylander 1974; Weber-Tschopp et al. 1976). The level of acrolein in sidestream smoke has been found to be notably higher (12 times higher) than in mainstream smoke (Triebig and Zober 1984). The amount of acrolein emitted in tobacco smoke varies depending upon the kind of cigarette, smoking conditions, puff volume, puff rate, nature, and type of tobacco, as well as a number of other extraneous factors (Holzer et al. 1976). Smoke from various cigarettes have been found to contain 3-220 pg acrolein per cigarette (Hoffmann et al. 1975; Horton and Guerin 1974; Magin 1980; Manning et al. 1983). Smoke from a marijuana cigarette was also found to contain 92-145 μg/cigarette (HofEmann et al. 1975; Horton and Guerin 1974). Studies performed to determine the concentration of acrolein in smoke-filled rooms (Rylander 1974; Triebig and Zober 1984; Weber-Tschopp et al. 1976) indicate that the concentration of acrolein in indoor air is highly dependent upon such factors as the number of cigarettes smoked, rate at which the cigarettes are smoked, size of the room, number of people in the room, and type of ventilation. Acrolein

levels measured in various settings where people were smoking are: cafe, 30-100 ppb; train, l0-120 ppb; car with three smokers (windows open), 30 ppb (avg.); car with three smokers (windows closed), 300 ppb (avg.); restaurant, 3-13 ppb; tavern, 5-18 ppb; and cafeteria, l-10 ppb (Triebig and Zober 1984).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to acrolein through inhalation of contaminated air, inhalation of cigarette smoke, and through ingestion of certain foods. Widespread exposure occurs due to the formation of acrolein during the heating of fats. Because of the lack of recent comprehensive monitoring data, the average daily intake of acrolein and the relative importance of each source of exposure cannot be determined. Primary factors influencing the level of exposure to acrolein via inhalation are: location (urban versus rural), duration and frequency of exposure to tobacco smoke, concentration of tobacco smoke, duration and frequency of exposure to high concentrations of vehicle exhaust (e.g., in parking garages, in heavy traffic), occupational exposure, and downwind distance of residence or work site relative to stationary point sources. Primary factors influencing the level of exposure to acrolein via ingestion are diet and volume of intake, which is typically related to age and sex.

According to a National Occupational Exposure Survey (NOES) by NIOSH between 1981 and 1983, an estimated 1300 workers in the United States are occupationally exposed to acrolein (NIOSH 1988). This is a tentative estimate and is subject to change as further information regarding trade name compounds becomes available. There is potential for exposure to acrolein in many occupational settings as the result of its varied uses and its formation during the combustion and pyrolysis of materials such as wood, petrochemical fuels, and plastics. As a result, it would be difficult to list all the occupations in which work-related exposure to acrolein occurs. Acrolein has been detected in workplace air at a number of locations (Ahrenholz and Egilman 1983; Apol 1982; IARC 1985; Tharr and Singal 1986; Trietman et al. 1980; Woskie et al. 1988). Acrolein concentrations of 0.057-0.085 ppm were detected during system testing conducted as part of a submarine overhaul in Portsmouth Naval Shipyard in Portsmouth, NH (Tharr and Singal). Ahrenholz and Egilman (1983) reported less than 0.0044-0.18 ppm acrolein in the wire line department of Rubbermaid Inc. in Wooster, OH, and Apol (1982) reported less than 0.06 ppm in molding areas of Gerlinger Casting Corp in Salem, OR.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

Those segments of the general population with potentially high exposure to acrolein from exogenic sources include people who come in frequent or prolonged contact with tobacco or marijuana smoke, people who are occupationally exposed, and people who live or work near dense traffic areas, in smoggy areas (e.g., Los Angeles), or downwind from stationary

point sources. Patients ingesting the drug cyclophosphamide are at risk for exposure to acrolein, a metabolite of the drug. It is not known, however, if such patients would be at risk for potentially high exposure to acrolein as a result of taking the drug.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 acrolein 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 acrolein.

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 Identification of Data Needs

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the partitioning of a chemical in the environment. Physical and chemical property data are available for acrolein, but extensive experimental descriptions necessary for evaluating the accuracy of the data are lacking.

Production, Use, Release, and Disposal. Data regarding the production methods for acrolein are adequate; however, data regarding current production volumes and use patterns are lacking. Production data may be difficult to obtain, since many companies desire to maintain their confidentiality. Use, release, and disposal information is useful for determining where environmental exposure to acrolein may be high. Determining the percentage of acrolein used as a captive intermediate (i.e., consumed in closed processes in which the compound is not isolated) rather than as an isolated, refined product is important in estimating the amount of release to the environment from stationary, noncombustion-related sources. An estimate of the amount of acrolein released from stationary sources would be useful in establishing the relative importance of each source of acrolein. Even if information on the production, use, and disposal of acrolein were available, the amounts released would be difficult to estimate, since major factors contributing to its occurrence in the environment are its formation as a product of the photochemical degradation of other atmospheric pollutants and its release in emissions from a wide variety of combustion processes.

5. POTENTIAL FOR HUMAN EXPOSURE

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxics Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Environmental Fate. Experimental data pertaining to the persistence of acrolein in soil and groundwater are lacking. Studies on volatilization from soil surfaces, anaerobic biodegradation in soil and simulated groundwater, and aerobic biodegradation in simulated groundwater would be useful in establishing the likelihood of exposure near hazardous waste disposal sites resulting from volatilization from soil surfaces or from groundwater contamination.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of acrolein from environmental media. Since acrolein has been detected in ambient air and in food and beverages (ppb levels), it is important to determine if acrolein can be absorbed by humans from environmental samples. However, the chemical structure of acrolein makes it a highly reactive molecule, which presumably is why its effects are, for the most part, restricted to the area of exposure (i.e., respiratory system for inhalation exposure or localized skin damage for dermal exposure). The limited information available regarding absorption parameters of acrolein in experimental animals indicates that acrolein is easily retained in the respiratory airways; however, virtually no information is available regarding absorption by the gastrointestinal tract or skin. Therefore, based on the data available, it is likely that inhalation of contaminated air will result in irritation of the eyes and respiratory tract.

Food Chain Bioaccumulation. A bioconcentration factor (BCF) was measured for acrolein that indicates that this compound would not bioaccumulate significantly in fish. This conclusion is supported by monitoring data that indicate that acrolein is not a common contaminant of biota in United States waters. No information was available on the bioaccumulation of acrolein in organisms at other trophic levels. Monitoring for the accumulation of acrolein in organisms from several trophic levels would be useful in estimating the levels of acrolein to which humans are exposed through dietary intake.

Exposure Levels in Environmental Media. Limited, mostly outdated, data were available regarding the detection of acrolein in the environment. Information on exposure to acrolein in air in urban areas, rural areas, near hazardous waste disposal sites, as well as in water (specifically, drinking water supplied from groundwater downgradient from hazardous waste disposal sites and contaminated surface waters) and soil at waste disposal sites

would be useful. Monitoring air and water over a l-year period would provide some indication of seasonal variations.

Exposure Levels in Humans. The database for both workplace exposure and ambient exposure is neither comprehensive nor current. Therefore, it is not possible to calculate a reliable estimate of average daily intake or intake resulting from occupational exposure. Even if this information was available, determination of the average daily intake of acrolein would be complicated by the variability in the frequency and amount of exposure to cigarette smoke and other acrolein sources. The development of a program for monitoring environmental media would provide information for estimating exposure levels in humans. Market basket surveys or total diet studies similar to those conducted by the United States Food and Drug Administration would provide data on typical levels of exposure via dietary intake. These kinds of studies are designed to determine the dietary intake of 16- to 19-year-old males, toddlers (2-year-old), and infants. In addition to workplace monitoring data, occupational exposure may be estimated from detailed examination of the uses of acrolein and the various processes in which acrolein is formed. For instance, since acrolein is a product of the combustion of wood, polyethylene, and petrochemical fuels, fire fighters could be exposed to elevated levels of acrolein. However, determining typical levels of exposure in this occupation would be difficult because of the variability in e kinds of materials consumed in fires.

Exposure Registries. An exposure registry is not available for acrolein. The development of an exposure registry would provide a useful reference tool in assessing exposure levels and frequency of exposure. In addition, a registry would allow an assessment of the variations in exposure concentrations due to such variable factors as geography, season, regulatory actions, presence of hazardous waste landfills, or manufacture and use facilities. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition related to current exposure levels.

5.7.2 On-going Studies

The U.S. Department of Energy is sponsoring a study which is being performed by R. Zinskind and J. Stoheley at Science Applications, Inc. in La Jolla, CA, to determine the concentration of acrolein in exhaust gas from diesel tractors and other vehicles (NTIS 1988). NIOSH is updating its estimates of occupational exposure in the National Occupational Exposure Survey (NOES) by taking into account additional information concerning exposure to trade name compounds. No other pertinent on-going studies were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring acrolein 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 acrolein. 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 acrolein 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 a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Data regarding the analytical methods used in the determination of acrolein in biological samples are limited. Boor and Ansari (1986) developed a method capable of detecting nanogram (ng) quantities of acrolein in biological samples. In this method, a derivatizing agent, 2,4-dinitrophenylhydrazine (DNP), is incubated with liver or kidney homogenate for a short period of time. The acrolein-DNP adduct is then extracted from the sample with chloroform. Analysis for acrolein is accomplished by elution on a reverse phase column using high performance liquid chromatography (HPLC), and detection of the adduct by UV absorbency. Interferences due to the coincidental elution of DNP adducts of ketones or aldehydes other than acrolein are not ruled out by this method of analysis.

Derivatization methods for the measurement of acrolein levels in biological media should be used with caution based upon data for analysis for acrolein in aqueous solutions (Kissel et al. 1978). Methods that utilized derivatives (DNP and 7-hydroxyquinoline) combined with calorimetric *or* fluorimetric detection were not specific for acrolein and consistently did not correlate with those obtained from bioassays. Certain direct methods of detection (nuclear magnetic resonance (NMR), fluorescence, and differential pulse polarography) gave the best correlation to the bioassay results (see discussion of analysis of environmental samples in Section 6.2).

Alarcon (1976) developed a method for quantitifying 3-hydroxypropylmercapturic acid (MCA), a known metabolite of acrolein, in urine. This method involves acidification of the urine to convert MCA to S-(3-hydroxypropyl)-L-cysteine. The amount of S-(3-hydroxypropyl)-L-cysteine can then be quantitated using an automated amino acid analyzer.

Acrolein in biological samples can be detected using a technique developed to determine volatile organic compounds in fish (Hiatt 1983). In this method, homogenized fish are transferred to a special vessel and the

volatile organic compounds are vacuum distilled into a cold trap. The sample is introduced into a cryogenic focusing trap, and the acrolein in the sample is detected by a mass spectrometer (MS). This method can be used in conjunction with HPLC or gas chromatography (GC) to determine the amount of acrolein in the sample.

6.2 ENVIRONMENTAL SAMPLES

Acrolein can be determined in air samples using NIOSH method 2501 (NIOSH 1984). In this method, a known volume of air is pumped through a tube containing a support coated with the derivatizing agent 2-(hydroxymethyl)piperidine. The derivative is eluted from the tube with toluene, and analyzed by GC using a nitrogen specific detector (NSD). Variations of this procedure have also been reported. Rietz (1985) used DNP as a derivatizing agent on the adsorbent tube, and made a final analysis using HPLC coupled to a UV detector. Acrolein has also been trapped for analysis by bubbling air through an aliquot of ethanol, adding methoxylamine hydrochloride to form a derivative, and then brominating the resulting adduct to allow increased detector sensitivity. Quantitation is achieved by GC using an electron capture detector (ECD) (Nishikawa et al. 1986). A summary of these techniques, along with methods for other environmental samples, are presented in Table 6-l. Interferences due to coincidental elution of derivatives of the compounds is a potential problem of these techniques.

Derivatization methods for the measurement of acrolein levels in environmental media should be used with caution based upon data for analysis for acrolein in aqueous solutions (Kisel et al. 1978). In a comparison of chemical analytical methods to bioassays, results obtained using methods utilizing derivatives (DNP and 7-hydroxyquinoline) combined with calorimetric or fluorimetric detection were not specific for acrolein and consistently did not correlate with those obtained from bioassays. Certain direct methods of detection (nuclear magnetic resonance (NMR), fluorescence, and differential pulse polarography) gave the best correlation to the bioassay results (see Table 6-l).

The analysis of acrolein in wastewater and water-miscible wastes or soils with low levels of contamination can be performed using EPA methods 603 and 8030, respectively (EPA 1982a, 1986b). In closely related techniques, an aliquot of water is subjected to a purge and trap protocol, and the sample is thermally desorbed onto a GC for analysis and quantitation. For waste samples not miscible with water or for soil samples with high levels of contamination, the sample can first be extracted with ethanol. The extract is diluted with water and then subjected to the purge and trap analysis described above (EPA 1986b). Coincidental elution of compounds with acrolein may lead to interferences in these methods. Ogawa and Fritz (1985) developed a method for the identification of acrolein in water. A known volume of water is passed over a column of

TABLE 6-1. Analytical Methods for Determining Acrolein in Environmental Samples

Method/Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy[a]	Reference
NIOSH 2501/Air	Collection on tube with 2-(hydroxymethyl)piperidine[b] coated on XAD-2 resin, desorbed by toluene extraction.	GC - NSD[c]	2 µg	NS	NIOSH 1984
EPA 603/Wastewater[d]	Purge at 85°C and trap onto methyl silicone/2,6-diphenylene oxide adsorbent, thermal desorption.	GC - FID	0.6 µg/L	96%	EPA 1982a
EPA 8030/Solid Waste[e]	Purge and trap onto adsorbent, rapid adsorbent, rapid heating desorption	GC - FID	NS	NS	EPA 1986
Air	Trap in ethanol solution, add methoxylaminehydrochloride[b], brominate.	GC - ECD[c]	<4 ppb	81-96%	Nishikawa et al. 1986
	Trap on XAD-2 resin coated with 2-(hydroxymethyl)piperidine[b], desorb with toluene.	GC - NSD[c]	NS	NS	Kennedy et al. 1984
	Trap on XAD-2 resin coated with 2,4-DNP[b], elute adduct with acetonitrile.	HPLC - UV[c]	0.01 mg/m^3	5 mg/m^3	Rietz 1985
Water	Trap on Zeolite ZSM-5 column, elute with acetonitrile, derivatize with 2,4-DNP.	HPLC - UV[c]	<10 µg	98%	Ogawa and Fritz 1985
	Nondirect measurement of aldehyde signal compared to signal for a calibrated sealed external TMS standard.	NMR	5000 ppm	NS	Kissel et al. 1978
	Dilution of sample with deionized water.	Fluorescence spectrometer	>20 ppm	NS	Kissel et al. 1978
	Dilution of sample with deionized water, addition of phosphate buffer and EDTA.	Differential pulse polarography	>30 ppb	NS	Kissel et al. 1978

TABLE 6-1 (Continued)

Method/Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy[a]	Reference
Personal Air	Trap on carbon coated with hydroquinone, desorb with 1,2-dichloroethane.	GC	0.02 ppb	>75%	Hurley and Ketcham 1978
Rain	Add to collected sample methoxylaminehydrochloride[b], brominate.	GC - ECD[c]	0.4 ng/mL	90-101%	Nishikawa et al. 1987b

[a]Defined as the percent recovery of a blank sample.
[b]Derivatizing agent.
[c]Derivative analyzed.
[d]EPA method 603 is the preferred method for quantitative analysis; method 624 can be used to screen samples for acrolein.
[e]Incorporates EPA method 5030.

2,4-DNP = 2,4-dinitrophenylhydrazine; ECD = electron capture detector; EDTA = ethylenediaminetetraacetic acid; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; NMR = nuclear magnetic resonance; NS = not stated; NSD = nitrogen specific detector; TMS = tetramethylsilane; UV = ultraviolet.

zeolite that traps the acrolein. The column is then eluted with acetonitrile, and derivatization using DNP follows. By following this procedure, a sample that can be analyzed by HPLC is obtained. Other derivatizing agents that have been used successfully for the monitoring of acrolein in the environment include dimedon, phenylhydrazone, 4-hexylresorcinol, and 3-methyl-2-benzothiazolone (Altshuller and McPherson 1963; Peltonen et al. 1984).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 acrolein 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 acrolein.

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 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure of acrolein has been identified (see Section 2.5). There are methods that can detect acrolein as well as its metabolite 3-hydroxypropylmercapturic acid. The methods used for the analysis of acrolein, however, can be susceptible to interferences. Methods that positively identify acrolein or one of its derivatives would eliminate the problems associated with specificity of the technique.

No biomarker that can be associated quantitatively with effect has been identified (see Section 2.5). Thus, there are no analytical methods for the determination of biomarkers of effect for acrolein.

Methods for Parent Compound and Degradation Products in Environmental Media. Suitable methods for the determination of acrolein in environmental samples exist. Nevertheless, new methodologies for the determination of acrolein have been reported. These methods can offer increased sensitivity and greater ease of performance. Further testing and evaluation of these methods would be useful in establishing the most powerful and practical techniques for routine analysis of acrolein in environmental samples.

6.3.2 On-going Studies

No on-going studies concerning the determination of acrolein in environmental media or biological materials were identified.

7. REGULATIONS AND ADVISORIES

National and international guidelines, as well as state regulations, pertinent to human exposure to acrolein are summarized in Table 7-l.

Acrolein is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum, wood, and carbon black.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Acrolein

Agency	Description	Value	Reference
WHO	Carcinogenic classification	Group 3[a]	IARC 1987
	National		
Regulations:			
a. Air:			
OSHA	PEL ceiling	0.1 ppm (0.25 mg/m^3)	29 CFR 1910.1000
b. Water:			
EPA OSW	Hazardous waste constituent	No data	EPA 1982b 49 CFR 261
c. Nonspecific media:			
EPA	Extremely hazardous substances emergency planning and release notification requirements	1 pound	EPA 1987a 40 CFR 300 and 355
	Threshold planning quantity	500 pounds	EPA 1987a 49 CFR 300 and 355
FDA	Food starch limitation	0.6%	FDA 1988 21 CFR 172.892
EPA	Pesticide classification	Restricted use	EPA 1982c 40 CFR 162.31
Guidelines:			
a. Air:			
ACGIH	TLV TWA	0.1 ppm (0.25 mg/m^3)	ACGIH 1988-89
	STEL	0.3 ppm (0.8 mg/m^3)	ACGIH 1988-89
NIOSH	IDLH	0.1 ppm (0.25 mg/m^3)	NIOSH 1985
b. Water:			
EPA OWRS	Ambient water quality criteria		EPA 1987b
	Ingesting water and organisms	0.32 mg/L	EPA 1980b
	Ingesting organisms only	0.78 mg/L	EPA 1980b
c. Other:			
EPA	Carcinogenic classification	Group C[b]	EPA 1987c
	State		
Regulations:			
a. Air:			
Connecticut	Acceptable ambient air concentrations	5 µg/m^3 (8 hr)	NATICH 1987
Florida-Tampa		2.5 µg/m^3 (8 hr)	NATICH 1987
North Carolina		80.0 µg/m^3 (15 min)	NATICH 1987
North Dakota		2.5 µg/m^3 (8 hr)	NATICH 1987
North Dakota		8.0 µg/m^3 (1 hr)	NATICH 1987
Nevada		6.9 µg/m^3 (8 hr)	NATICH 1987
New York		0.83 µg/m^3 (1 yr)	NATICH 1987
South Carolina		1.25 µg/m^3 (24 hr)	NATICH 1987
Virginia		4.0 µg/m^3 (24 hr)	NATICH 1987
Kentucky		1 mg/m^3 (8 hr)	State of Kentucky 1986

[a]Group 3: Inadequate evidence for carcinogenicity in humans and animals.
[b]Group C: Possible human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; STEL = Short-Term Exposure Limit; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization.

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9. GLOSSARY

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

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

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

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

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

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

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

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

In Vivo -- Occurring within the living organism.

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

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

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

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

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

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

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

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

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

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

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

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

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

ql* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually pg/L for water, mg/kg/day for food, and pg/m3 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.

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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.

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

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

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

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

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

APPENDIX: PEER REVIEW

A peer review panel was assembled for acrolein. The panel consisted of the following members: Dr. John Egle, Department of Pharmacology and Toxicology, Medical College of Virginia; Dr. Raymond Smith, Department of Pathology and Microbiology, University of Nebraska Medical Center; and Dr. Samuel Cohen, Department of Pathology and Microbiology, University of Nebraska Medical Center. These experts collectively have knowledge of acrolein's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has 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 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 Agency for Toxic Substances and Disease Registry.