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MARTIN MARIETTA

Safety Analysis Report Update Program

GUIDANCE ON HEALTH EFFECTS OF TOXIC CHEMICALS

February 1994

SAR UPDATE

Issued by:

Central Safety Evaluation Team

MARTIN MARIETTA ENERGY SYSTEMS, INC.
Oak Ridge, Tennessee

Prepared for the U.S. Department of Energy
under U.S. Government contract DE-AC05-84OR21400

MANAGED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE UNITED STATES
DEPARTMENT OF ENERGY

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ABBREVIATIONS AND ACRONYMS

AbsD	absorbed doses
ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
CH_3CN	acetonitrile (methyl cyanide)
CNS	central nervous system
DOE	U.S. Department of Energy
EEGL	Emergency Exposure Guidance Level
EEL	emergency exposure limit
EMAC	Emergency Management Advisory Committee
EPA	U.S. Environmental Protection Agency
ERPG	Emergency Response Planning Guideline
HxCDD	hexachlorodibenzo-*p*-dioxin
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life or health
ILO	International Labor Office
LC_{50}	lethal concentration to 50% of an exposed population
LC_{LO}	lethal concentration low (lowest lethal concentration)
$LD_{1.2}$	dose lethal to 1.2% of an exposed population
LD_{50}	lethal dose to 50% of an exposed population
LOAEL	lowest observed adverse effect level
MMES	Martin Marietta Energy Systems, Inc.
MMUS	Martin Marietta Utility Systems, Inc.
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NO_x	nitrogen oxide(s)
NRC	National Research Council
ORNL	Oak Ridge National Laboratory
OSHA	Occupational Safety and Health Administration
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCQ	polychlorinated quaterphenyl
PEL	permissible exposure limit
RASH	Rapid Screening of Hazard
RGD	regional gas dose
RPF	relative potency factor
RTECS	Registry of Toxic Effects of Chemical Substances
SAR	Safety Analysis Report
SARUP	Safety Analysis Report Update Program
SCAPA	Subcommittee on Consequence Assessment and Protective Actions (DOE)
SD	Sprague-Dawley (rats)

STEL	short-term exposure limit
STPL	short-term public limit
TCDD	tetrachlorodibenzo-*p*-dioxin
TCDF	tetrachlorodibenzofuran
TLV	threshold limit value
TWA	time-weighted average
WHO	World Health Organization

ACKNOWLEDGMENTS

This report was prepared for the Central Safety Evaluation Team (CSET). Several team members contributed to the technical review of the document. Technical reviews on the behalf of CSET were provided by S. G. Bloom (who also managed the program for CSET), J. T. Jankovic, R. A. Just, J. L. Kasten, K. D. Keith, Jr., and E. R. Wagoner. H. L. Arnold, Jr., served as the CSET representative for this contribution.

Authors of this report include C. B. Foust (Fluorine), G. D. Griffin (Hydrogen Chloride), N. B. Munro (PCBs and Their Combustion Products), and M. L. Socolof (Acetrontrile). Two independent reviews were performed for each chapter. Reviewers include K. A. Davidson, R. H. Ross, and R. A. Young. C. E. Easterly served as the liaison between CSET and the authors and provided technical guidance to the authors.

EXECUTIVE SUMMARY

Martin Marietta Energy Systems, Inc. (MMES), and Martin Marietta Utility Services, Inc. (MMUS), are engaged in phased programs to update the safety documentation for the existing U.S. Department of Energy (DOE)–owned facilities. The safety analysis of potential toxic hazards requires a methodology for evaluating human health effects of predicted toxic exposures. This report provides a consistent set of health effects and documents toxicity estimates corresponding to these health effects for some of the more important chemicals found within MMES and MMUS. The estimates are based on published toxicity information and apply to acute exposures for an "average" individual.

The health effects (toxicological endpoints) used in this report are (1) the **detection threshold**, (2) the **no observed adverse effect level**, (3) the **onset of irritation/reversible effects**, (4) the **onset of irreversible effects**, and (5) a **lethal exposure**, defined to be the 50% lethal level. An irreversible effect is defined as a significant effect on a person's quality of life, e.g., serious injury. Predicted consequences are evaluated on the basis of concentration and exposure time.

Although accepted toxicological standards have been developed for radiological exposures, industrial hygiene applications, and emergency response applications, accepted methods for safety analysis applications generally do not exist for chemically toxic materials. Safety Analysis Reports (SARs) must often consider short-term releases, lasting from a few seconds to a few hours, where inhalation is usually the most significant exposure pathway. In order to compare results from different accidents, it is desirable to have a consistent set of biological response endpoints corresponding to specific health effects. These endpoints must be technically accurate and informative to non-health professionals such as managers and engineers. This report provides guidance for selected chemicals.

This first edition of the report presents acute toxicity estimates for four chemicals: (1) acetonitrile, (2) fluorine, (3) hydrogen chloride, and (4) polychlorinated biphenyls (PCBs) and their combustion products. Planned later editions are expected to include 20 additional chemicals: (5) hydrogen fluoride, (6) oxides of nitrogen (NO, NO_2, N_2O_2), (7) uranium hexafluoride, (8) soluble and insoluble uranium, (9) nitric acid, (10) chlorine, (11) chlorine trifluoride, (12) sulfur dioxide, (13) sulfuric acid, (14) carbon tetrachloride, (15) lithium hydride/deuteride, (16) lithium carbonate, (17) toluene 4-diisocynate, (18) potassium hydroxide, (19) sodium/potassium alloy (NaK), (20) acetic acid, (21) hydrogen peroxide, (22) perchloroethylene, (23) phosgene, and (24) ingestion of soluble and insoluble uranium.

Readers interested in obtaining current versions of this report are encouraged to request inclusion of their names on the distribution list. For information, contact Clay Easterly (telephone 615-574-6254) or Robert Just (615-574-6497).

1

INTRODUCTION

1. INTRODUCTION

This report was prepared to document the accident-related toxicity of some of the important chemicals used or stored in facilities at the U.S. Department of Energy (DOE) sites operated by Martin Marietta Energy Systems, Inc. (MMES). The results are also applicable to the gaseous diffusion plant facilities operated by Martin Marietta Utility Services, Inc. (MMUS), and to other facilities with potential exposure to these chemicals. These results will be used primarily in Safety Analysis Reports (SARs), which focus on accidents and acute exposures. Thus, the main thrust is on acute toxicological responses, primarily to inhalation and to dermal (skin) and ocular (eye) exposures. (Other analyses, such as the Annual Environmental Monitoring Reports, identify chronic effluents and estimate long-term impacts to members of the public. Workers are systematically evaluated for chronic hazardous exposures by the Industrial Hygiene and Health Physics programs.)

Although accepted toxicological standards have been developed for radiological exposures, industrial hygiene applications, and emergency response applications, accepted methods for safety analysis applications generally do not exist for chemically toxic materials. SARs must often consider short-term releases, lasting from a few seconds to a few hours, where inhalation is usually the most significant exposure pathway. In order to compare results from different accidents, it is desirable to have a consistent set of biological response endpoints corresponding to specific health effects. These endpoints must be technically accurate and informative to non-health professionals such as managers and engineers. This report provides guidance for selected chemicals.

Typically, accidents result in exposures that are minutes to hours long. Moreover, they almost always are limited to single events, rather than involving continuous exposure in a work environment, and hence the exposure criteria are not governed by analysis of chronic exposures. In performing safety analyses for a large number of facilities and processes, it is important to have a consistent set of biological response endpoints so that impacts from accident scenarios involving different hazardous chemicals can be compared on a relative basis. A common set of five acute health-based toxicological endpoints was identified as being necessary for the MMES Safety Analysis Report Update Program (SARUP). Realistically, it is impossible to exactly compare any two chemicals because no two chemicals exert identical toxicological effects; however, that fact should not be used as an impediment to the development of a rational process designed to evaluate accidents and to develop appropriate safety controls.

The materials evaluated in this report are a compilation of priority chemicals identified as having the potential to exist in quantities which, if released uncontrollably, could pose a significant hazard to on-site or off-site personnel. Because of resource limitations, priority was placed on the chemicals on the basis of the number of facilities processing a given hazardous

material, the volatility and toxicity of the material, and the quantity of material present. This report contains information on the following chemicals: (1) acetonitrile, (2) fluorine, (3) hydrogen chloride, and (4) polychlorinated biphenyls (PCBs) and their combustion products. Work is in progress on 20 additional chemicals: (5) hydrogen fluoride, (6) oxides of nitrogen (NO, NO_2, N_2O_2), (7) uranium hexafluoride, (8) soluble and insoluble uranium, (9) nitric acid, (10) chlorine, (11) chlorine trifluoride, (12) sulfur dioxide, (13) sulfuric acid, (14) carbon tetrachloride, (15) lithium hydride/deuteride, (16) lithium carbonate, (17) toluene 4-diisocynate, (18) potassium hydroxide, (19) sodium/potassium alloy (NaK), (20) acetic acid, (21) hydrogen peroxide, (22) perchloroethylene, (23) phosgene, and (24) ingestion of soluble and insoluble uranium. As sections on additional chemicals are completed, or as important new information becomes available, this report will be revised.

Results for each of the subject chemicals are reported in separate sections. Each section contains a summary designed to be used directly by consequence analysts for typical applications. This summary is followed by a brief description of the physical and chemical properties of the element or compound, including a discussion of possible reaction products in ambient air, information on the combustibility of the material, and identification of the possible combustion products. (In some cases, toxicity analyses of the chemicals and their oxidation/hydrolysis products are contained in the same section. The Table of Contents and the section titles indicate which, if any, by-products are discussed in the section.) Following the discussion of physical and chemical characteristics is a summary of the existing human health toxicity information and, if appropriate, a summary of the animal toxicity data. These data are then analyzed to determine the following health-based toxicological endpoints based on acute exposure and, where possible, the time course of these endpoints. Information on delayed effects of acute exposure (e.g., reproductive, immunological, carcinogenic) is usually not available, but where information is available, it is summarized.

1. Detection threshold. Detection by human sensory organs is often considered important in accident scenarios because it provides the basis for indicating whether or not human detection could result in evacuation or other protective measures. For some materials, detection is not through the sense of smell but results from irritation.

2. No observed adverse effect level (NOAEL). In some cases, where insufficient data exist, this may be a no observed effect level (NOEL). The rationale for the use of this level is to identify a concentration or dose below which there are no observed adverse toxicological effects. For exposures below this level no further analyses need be performed.

3. Onset of irritation/reversible effects. A minimum level of health impact provides a sensitive measure for acute effects. Identification of this concentration or absorbed dose is also important because the range between this level and the next

level, onset of irreversible effects, represents a very low hazard and is helpful information for engineering analyses.

4. Onset of irreversible effects. This level identifies the onset of significant and permanent health impacts. Its main function is to provide a level between perhaps very subtle and transitory effects (identified as irritation/reversible effects) and lethality. An irreversible effect is defined as a significant effect on a person's quality of life, e.g., serious injury. In most cases, the effect will be somatic; however, it is possible that genetic effects could occur.

5. Lethal exposure level (50% lethality). It is important and necessary to identify potentially lethal chemical hazards. The inclusion of other measures such as LD_{10} or LD_{01} may be more satisfactory for some applications than the use of the LD_{50} measure; however, the information necessary to identify these levels is rarely available. If more detailed lethality information than LD_{50} is available, it is discussed.

Not all of these endpoints can be determined for all of the chemicals of interest. In such cases, the most similar available endpoint is identified (e.g., NOEL vs NOAEL). The important issue is to attempt to identify a common set of endpoints for each material so that it is possible to compare different facilities on a relative basis. Because there is generally a lack of data on the wide range of individuals who may be exposed in an accident situation, the basis for the five endpoints is the average person. It is recognized that some members of the population may be more susceptible to certain toxic exposures than others. However, most of the human data are based on the average individual. Calculations in this manual are based on the average or typical adult male individual with a body mass of 73 kg at a light activity level with a breathing rate of 25 L/min, according to the International Commission on Radiological Protection.[1] Averaging times for human exposures are discussed separately in each section.

The Subcommittee on Consequence Assessment and Protective Actions (SCAPA) of the DOE Office of Emergency Planning and Operations has suggested an approach employing similar health effects but using a simpler means to estimate biological responses as a function of concentration and exposure time. It compares peak 15-min average concentrations with Emergency Response Protection Guidelines (ERPGs), which are considered applicable to exposures up to 1 h. Therefore, the SCAPA approach may be overly conservative for exposures less than 1 h and will be nonconservative for exposures greater than 1 h. Moreover, ERPG values exist for only a few chemicals, and SCAPA develops alternatives based on other

[1]International Commission on Radiological Protection, *Human Respiratory Model for Radiological Protection*, ICRP Pub. 66, *Annals of the ICRP* 24 (1–4), 1994 (in press).

published guidelines. However, most of these other guidelines do not apply to accidents, and the method used by SCAPA to develop the alternative ERPG values is not based on the individual characteristics of the chemical. This is in contrast to the biological-response estimates used in this report.

The methods and goals of this effort differ from those in a related effort in Emergency Response Planning. In Emergency Response Planning, there is a need to keep things relatively simple; consequently, only three levels are usually chosen, as in the ERPGs under development by the American Industrial Hygiene Association. Furthermore, the levels for Emergency Response Planning are chosen to represent accident conditions and provide decision points for go/no-go plans to alert or evacuate affected zones. ERPGs are based on 1-h exposures to a fixed concentration for a given level of assumed human activity and body size, and therefore cannot provide the level of detail desired in the more analytic Safety Analysis approach. Nonetheless, ERPGs represent a valued asset; they are used as benchmarks and in some cases have been adopted for use in this report.

The estimates of health effects provided in this report are intended to be used only in assessing the consequences of postulated accidents in support of the SAR program. This information will be used to determine the adequacy of the controls used to manage the risk of the operation being evaluated. The toxicity estimates are *not* intended to be used as acceptable exposure levels for occupational personnel or members of the public. Furthermore, the guidelines in this section are *not* intended for use in developing emergency exposure levels.

For additional technical information, contact Clay Easterly at 615-574-6254 (FAX 615-576-7651). For programmatic information, contact Robert Just at 615-574-6497 (FAX 615-576-4705).

2

ACETONITRILE

2. ACETONITRILE

2.1 SUMMARY

Acetonitrile is a colorless liquid with an ether-like odor and burning sweetish taste. It has a high evaporation rate, and contact with strong oxidizers may cause fires and explosions. The combustion of acetonitrile may release hydrogen cyanide, nitrogen oxides, carbon dioxide, and carbon monoxide. A discussion of the toxicity of hydrogen cyanide is included in this report; the effects of the nitrogen oxides are addressed in a separate toxicity report.

Human and animal studies suggest that acetonitrile is metabolized by hepatic enzymes to release cyanide, which causes the major acute toxic effects. The toxic effects of acetonitrile are similar to those of hydrogen cyanide because of similar mechanisms of action—i.e., the formation of cyanide. Acute clinical systemic effects from inhalation exposure to acetonitrile are observed in various organ systems: nervous, respiratory, cardiovascular, and gastrointestinal. Related effects include nausea, vomiting, headache, severe lassitude, weakness, respiratory depression, chest or abdominal pain, shock, convulsions, coma, seizures, and death. The effects may appear several hours after exposure has ceased. Dermatologic effects occur from skin contact with liquid acetonitrile causing mild erythema of short duration. The liquid may also cause burns to skin and eyes upon contact. Local effects of vapor exposure including nose, throat, and eye irritation, a slight flushing of the face, and a feeling of chest tightness have been reported.

Based on human and animal toxicity data, the relationship of concentration versus time for exposures to acetonitrile are estimated for five levels: odor detection threshold, no observed adverse effect level (NOAEL), onset of reversible/irritation effects level, onset of irreversible effects level, and lethal concentration to 50% of the population (LC_{50}) level. Table 2.1 presents the concentrations or the equations that formulate these levels, which are also depicted in Fig. 2.1. Recommended averaging times for calculating time-weighted averages when measuring exposures are also presented in Table 2.1.

The estimates of health effects provided in this section are intended to be used only in assessing the consequences of postulated accidents in support of the Safety Analysis Report (SAR) program. This information will be used to determine the adequacy of the controls used to manage the risk of the operation being evaluated. The toxicity estimates are *not* intended to be used as acceptable exposure levels for occupational personnel or members of the public. Furthermore, the guidelines in this section are *not* intended for use in developing emergency exposure levels.

Table 2.1. Summary of acetonitrile consequence levels

Endpoint	Level[a]	Recommended averaging times	Comments
Detection threshold	$C = 67$; $t \leq 120$ $C > 67$; $t > 120$	30 min insufficient data	Ether-like odor
No observed adverse effects level	$C = 268$; $t \leq 240$	30 min	
Onset of reversible/irritation effects level	Insufficient data	Insufficient data	Possible nervous system and respiratory system effects
Onset of irreversible effects level	$C = 1600$; $t \leq 60$	10 min	Level based on developmental effects in hamsters
Lethal exposure level (LC_{50})	$C = 47{,}500$; $t \leq 15$ $C \times t = 7.1 \times 10^5$; $t > 15$ to 60 $C \times t = 7.1 \times 10^5$; $t > 60$ to 240	5 min 15 min 30 min	Level based on most sensitive animal species (rabbit)

[a]Concentration (C) = mg/m^3; time (t) = min.

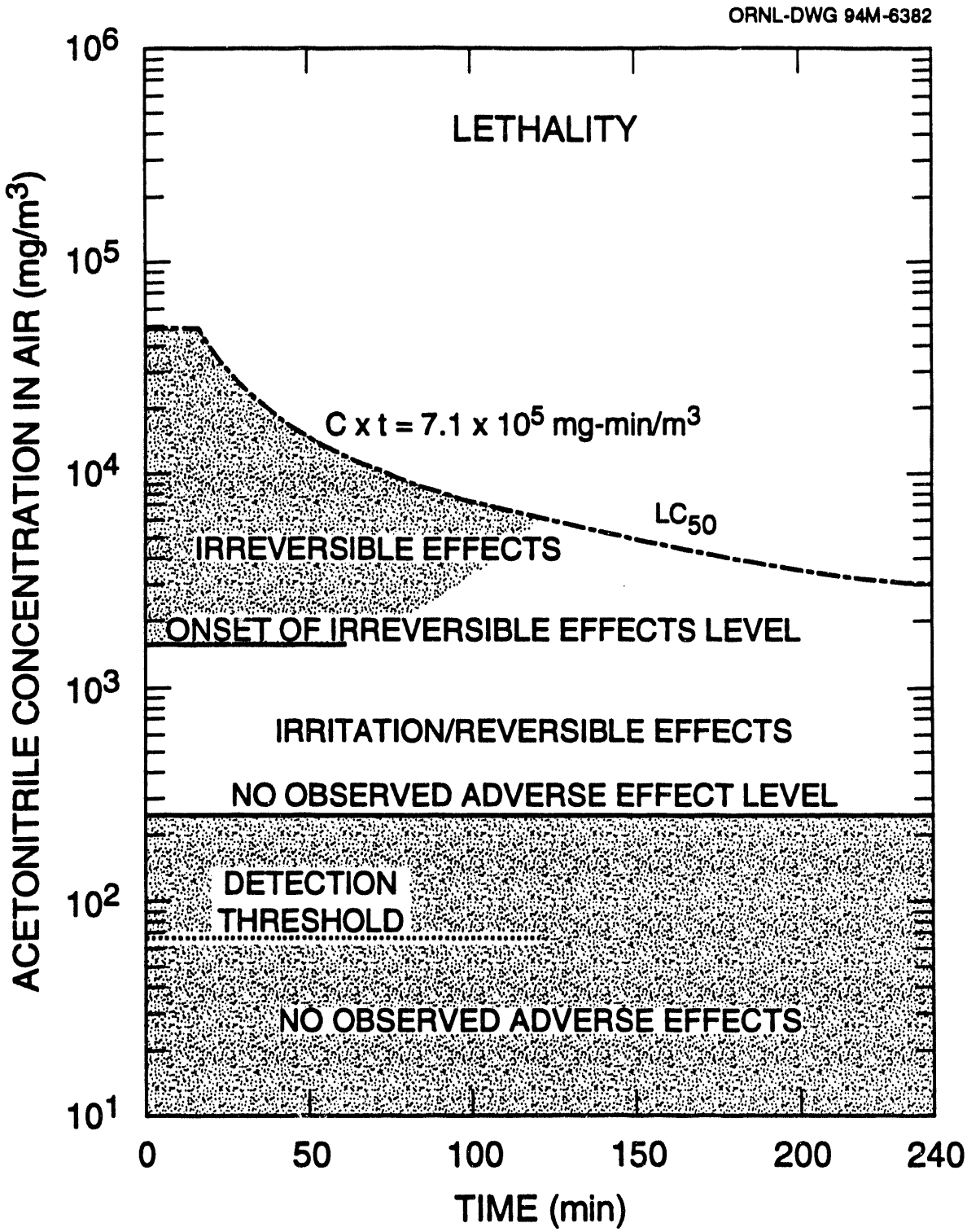

Fig. 2.1. Summary of acute health endpoints for acetonitrile.

2.2 PHYSICOCHEMICAL PROPERTIES

Acetonitrile, or methyl cyanide (CH_3CN), is a colorless liquid with an ether-like odor and burning sweetish taste (Sax and Lewis 1989). It is miscible with water, benzene, methanol, methyl acetate, acetone, ethyl acetate, ether, acetamide solutions, chloroform, carbon tetrachloride, ethylene chloride, and with many unsaturated hydrocarbons (Weast 1989). Contact of acetonitrile with strong oxidizers may cause fires and explosions (Mackison, Stricoff, and Partidge 1981). Some of the physical properties of acetonitrile are presented in Table 2.2.

When acetonitrile is released into the atmosphere, it should exist primarily in the vapor phase and is expected to react with ozone and photochemically generated hydroxyl radicals (indirect photolysis). The estimated half-life for acetonitrile in air is approximately 42 d (based on ozone and hydroxyl reactions) (EPA 1987). It will persist in the troposphere for a long time and may be transported a long distance from its emission source (Atkinson and Carter 1981).

Acetonitrile has the ability to combust to form highly toxic products of decomposition. Hydrogen cyanide (HCN), nitrogen oxides (NO_x), carbon dioxide (CO_2), and carbon monoxide (CO) are the primary combustion products that may be released in a fire involving acetonitrile (Sax 1984; Mackison, Stricoff, and Partridge 1981). A wide variety of trace organics could also be formed. The chemical equations presented below show how the primary combustion products may be formed. The characteristics of the fire will determine the proportions of each product.

$$C_2H_3N + O_2 \rightarrow HCN + CO + H_2O$$
$$4\ C_2H_3N + 9\ O_2 \rightarrow 6\ H_2O + 8\ CO + 4\ NO$$
$$4\ C_2H_3N + 13\ O_2 \rightarrow 6\ H_2O + 8\ CO_2 + 4\ NO$$
$$4\ C_2H_3N + 11\ O_2 \rightarrow 6\ H_2O + 8\ CO + 4\ NO_2$$
$$4\ C_2H_3N + 15\ O_2 \rightarrow 6\ H_2O + 8\ CO_2 + 4\ NO_2$$

In addition, the following reactions may take place after combustion from the heat of the fire:

$$2\ CO + O_2 \rightarrow 2\ CO_2$$
$$2\ NO + O_2 \rightarrow 2\ NO_2$$
$$2\ NO_2 \rightarrow N_2O_4$$

Table 2.2. Physical properties of acetonitrile

Property	Description
Molecular weight	41.05 g/mole
Boiling point	82°C (179°F) (@ 760 torr)
Melting point	–45.7°C (–50°F)
Vapor pressure	73 torr @ 20°C
Specific gravity (vapor)	1.42 (air = 1)
Evaporation rate (compared to butyl acetate)	5.79 (butyl acetate = 1)
Flash point	5.6°C (4°F)

Sources: ACGIH 1986; Clayton and Clayton 1982; NFPA 1986.

2.3 SUMMARY OF EXISTING TOXICITY DATA

This section summarizes the acute toxicity data of acetonitrile and briefly addresses the combustion product HCN. It includes a summary of the mechanism of action of the chemicals in the human body, anticipated human health effects, and applicable animal studies. This report focuses primarily on exposure by inhalation and, where appropriate, skin contact.

2.3.1 Acetonitrile

2.3.1.1 Mechanisms of action

Two studies on the absorption of acetonitrile suggest that the vapor is readily absorbed through the lungs. Absorption of acetonitrile was measured in 16 human subjects who were cigarette smokers. An average of 74% absorption of acetonitrile was measured when the cigarette smoke was held in the mouth for 2 s but was not inhaled. When the smoke was inhaled into the lungs, absorption of acetonitrile increased to 91% (Dalhamn, Edfors, and Rylander 1968a, 1986b). Pozzani et al. (1959) exposed three dogs to acetonitrile vapor for 4 h at 16,000 ppm in air (27,000 mg/m^3).[1] Although actual absorption was not measured, they reported that acetonitrile is absorbed rapidly upon inhalation.

[1]For conversion of ppm of acetonitrile to mg/m^3, 1 ppm = 1.68 mg/m^3. This assumes a barometric pressure of 760 torr and a temperature of 25°C.

Acetonitrile is metabolized by hepatic enzymes to release cyanide, which causes the major acute toxic effects. Acetonitrile possesses little if any toxicity in the absence of normal hepatic function (Willhite and Smith 1981). Acetonitrile exposure by any route (oral, dermal, or inhalation) can produce cyanide-like poisoning from metabolic cyanide released after absorption. Detailed studies have shown that microsomes oxidize acetonitrile to cyanide (Freeman and Hayes 1988; Fiereman and Cederbaum 1989). Acetonitrile was found to metabolize to cyanide very quickly in mice (Ahmed et al. 1992).

Cyanide exerts toxic effects by reacting with iron in cytochrome oxidase, the enzyme that catalyzes the terminal step in mitochondrial respiration. The acute toxicity of cyanide may result from the production of cytotoxic anoxia (severe deficiency of oxygen) through the inhibition of cytochrome oxidase (ATSDR 1989). As a result, the enzyme is unable to catalyze the reactions in which electrons are transferred from reduced cytochrome to oxygen. Cellular oxygen utilization is thus impaired, with a resultant reduction in or cessation of aerobic metabolism (ATSDR 1989). Because utilization of oxygen is blocked, venous blood remains oxygenated and is almost as bright red as arterial blood (Gilman, Goodman, and Gilman 1985). The cyanide ion produces acute anoxia of the central nervous system (CNS) by inactivating the cytochrome oxidase enzyme system necessary for tissue respiration.

Cyanide is primarily detoxified in the body when the cyanide ion is conjugated with sulfur to form the less toxic thiocyanate. Conjugation is catalyzed by rhodanese, a mitochondrial enzyme that is widely distributed in most animal tissues (and particularly in the liver) (ATSDR 1989). The half-life for the conversion of a nonlethal dose of cyanide to thiocyanate in humans is between 20 min and 1 h (NIOSH 1976). Thiocyanate is eventually excreted in the urine (ATSDR 1989). It is possible that existing liver disease might slow the rate of cyanide metabolism because the liver contains the highest activity of rhodanese (EPA 1980). In an evaluation of an accidental acetonitrile exposure (described further in Sect. 2.3.1.2), Amdur (1959) concluded that the direct cause of poisonous effects was due to thiocyanate. In general, acetonitrile metabolites have much longer elimination half-lives than acetonitrile (Ahmed et al. 1992), and the signs of toxicity produced by acetonitrile are primarily those of cyanide and thiocyanate poisoning.

2.3.1.2 Acute human health effects/toxicity data

Grabois (1955) described a case of accidental poisoning in workers exposed to acetonitrile vapor, which was discussed further by Amdur (1959). Sixteen workers in a chemical manufacturing plant were accidentally exposed to acetonitrile vapor while brush-painting the inside walls of a storage tank with corrosion-resistant resinous primer paint. Exposure

concentrations and durations are not known; however, exposure occurred over a 2-d painting job. One worker developed convulsions and fell into a deep coma and died. The other workers had symptoms that included chest pain, a feeling of tightness in the chest and abdomen, palpitations, shortness of breath, nausea, vomiting, abdominal cramps, urinary frequency, headache, difficulty swallowing, lassitude, and fatigue. The onset of symptoms were delayed from 3 to 12 h. Amdur (1959) concluded that the direct cause of the poisonous effects were due to thiocyanate, the detoxification product of cyanide, and not to cyanide, because cyanide would be expected to act more quickly. Six workers, including the one who died, had elevated blood cyanide concentrations, which decreased in the survivors over the following 2 weeks.

Dequidt, Furon, and Haguenoer (1972) and Dequidt et al. (1974) reported the fatal outcome of a photographic laboratory worker's "massive exposure" to acetonitrile vapor. About 4 h after his exposure, he began experiencing gastric distress and nausea. Other symptoms for the next few days included vomiting, hypersalivation, conjunctivitis, very low urine output, and low blood pressure. He experienced cardiac and respiratory arrest and died 6 d after the initial exposure.

In a study by Pozzani et al. (1959), three human subjects were exposed to 40 ppm (67 mg/m^3) of acetonitrile, and two subjects were exposed to 80 ppm (134 mg/m^3) and two were exposed to 160 ppm (268 mg/m^3) for 4 h. At 40 ppm (67 mg/m^3), none of the subjects reported adverse effects, except for one subject who experienced slight chest tightness a few hours after exposure and a "cooling sensation" in the lung the next morning and the rest of the day. No detectable cyanide was found in blood specimens, but one subject showed a slightly elevated urinary thiocyanate level. Also at 40 ppm (67 mg/m^3), all three subjects recognized the odor for the first 2 to 3 h of the 4-h exposure period and then experienced some olfactory fatigue. At 80 ppm (134 mg/m^3), there were no subjective signs of toxicity and no blood cyanide, but urinary thiocyanate excretion fluctuated. At 160 ppm (268 mg/m^3) exposure, one subject reported a slight flushing of the face 2 h after inhalation and a slight feeling of bronchial tightness 5 h later. Blood cyanides and urinary thiocyanates did not change significantly from pre-exposure values.

In a compilation of odor thresholds and irritating concentrations for several chemicals, Ruth (1986) reported an odor threshold of 70 mg/m^3 and an irritation level of 875 mg/m^3 for acetonitrile. Exposure times and the type of irritation were not specified. The odor threshold reported by Ruth was based on human olfactory perception of acetonitrile with no other chemicals present in the air. Ruth's (1986) compilation of data is limited in its usefulness because it does not list references specific to each chemical and does not provide much explanation of the levels presented. The American Conference of Governmental Industrial Hygienists (ACGIH 1986) reported an odor threshold of 40 ppm (67 mg/m^3).

Secondary sources have summarized the acute health effects of acetonitrile as follows. Acute clinical effects from inhalation exposure are observed in various organ systems: in the nervous system—headache, lassitude, and dizziness leading to coma or seizures at high concentrations; in the respiratory system—hyperpnea (respiration rate increase), respiratory depression, and chest tightness; in the cardiovascular system—tachycardia has been noted in poisoning cases; and in the gastrointestinal system—nausea and vomiting. Dermatologic effects occur from skin contact with liquid acetonitrile causing mild erythema of short duration. The liquid is also irritating to skin and eyes, and it may cause burning at these sites (DOT 1990; Sittig 1979). Local effects of vapor exposure, including nose, throat, and eye irritation, a slight flushing of the face, and a feeling of chest tightness have been reported (Sittig 1979).

Tietz (1983) stated that airborne concentrations up to 838 mg/m^3 cause irritation of mucous membranes and concentrations above 838 mg/m^3 cause weakness, nausea, convulsions, and death. However, no exposure time was provided with these estimates. Mackison, Stricoff, and Partidge (1981) report that inhaling 838 mg/m^3 for "brief periods" was reported to cause some irritation of the nose and throat. Individuals with a history of fainting spells or convulsive disorders might have an added risk while working with acetonitrile (Sittig 1985), as they may be hypersensitive to acetonitrile.

2.3.1.3 Animal data

Animal studies of particular interest to this analysis are inhalation studies with single exposures of up to 8 h. The pertinent results from such studies are presented in Table 2.3; these studies evaluated effects from acute exposures of 30 to 480 min. In the studies that addressed acute effects, rats, guinea pigs, rabbits, dogs, and mice were exposed to concentrations ranging from 2828 to 89,000 mg/m^3. When available, concentrations that killed 50% of the exposed populations (LC_{50} levels) are provided in Table 2.3.

A study by Willhite (1983) indicates that acute inhalation exposure to acetonitrile may cause developmental effects. In this study, pregnant hamsters were exposed to 3018, 6372, 8384, or 13,415 mg/m^3 of acetonitrile for 1 h on the eighth day of gestation. Inhalation of acetonitrile was associated with a significant increase in the number of malformed offspring at the two highest concentrations (Table 2.3). One fetus in the 13,415 mg/m^3 exposure group developed extrathoracic ectopia cordis, a rare condition that in humans is exemplified by protrusion of the heart through a sternal defect. Willhite (1983) suggested that in vivo liberation of cyanide from acetonitrile was responsible for the production of the teratogenic effects.

Table 2.3. Animal inhalation data for acetonitrile

Species	Time (min)	Concentration (mg/m^3)	Effects	Reference
Hamster (pregnant)	60[a]	3,018	No malformations in offspring; no signs of maternal intoxication	Willhite 1983
Hamster (pregnant)		6,372	No malformations in offspring; 1 of 6 mothers exhibited dyspnea, tremors, hypersalivation, ataxia and hypothermia and died from exposure	Willhite 1983
Hamster (pregnant)	60[a]	8,384	Skeletal malformations in offspring, ranging from fused ribs to severe axial skeletal disorders; 1 maternal death	Willhite 1983
Hamster (pregnant)	60[a]	13,415	Skeletal malformations in offspring, ranging from fused ribs to severe axial skeletal disorders; 3 of 6 maternal deaths after tremors and coma; 4 of the six mothers exhibited respiratory difficulty, lethargy, ataxia, hypothermia, eye and nose irritation and gasping; 3 of those developed tremors followed by a deep coma and death	Willhite 1983
Mouse	60	4,516	LC_{50}; intense dyspnea, tachypnea, gasping, tremors, convulsions, and corneal opacity; delayed deaths	Willhite 1981
Rabbit (males)	240	2,828	LC_{50}; prostration, usually followed by convulsive seizures, preceded death; often pulmonary hemorrhage or congestion; delayed deaths	Pozzani et al. 1959
Guinea pig (male and female)	240	9,483	LC_{50}; see comment for rabbit	Pozzani et al. 1959

Table 2.3 (cont.)

Species	Time (min)	Concentration (mg/m^3)	Effects	Reference
Dog	240	3,354	No deaths in 2 exposed dogs	Pozzani et al. 1959
Dog	240	13,415	No death in one exposed dog	Pozzani et al. 1959
Dog (male)	240	26,830	All 3 male dogs died	Pozzani et al. 1959
Rat	30	4,695	No deaths among 3 exposed rats	Haguenoer, Dequidt, and Jacquemont 1975
Rat	30	41,922	Three of 3 rats died; difficult breathing, cyanosis	Haguenoer, Dequidt, and Jacquemont 1975
Rat	30	89,000	LC_{50}; see comment for rabbit	Pozzani et al. 1959
Rat	240	33,454	LC_{50}; hemorrhaging in lungs and death	Monsanto n.d. (EPA Docket No. 878210774)
Rat	240	13,415	One of 6 rats died	Smyth and Carpenter 1948
Rat	240	80,000	LC_{50}; salivation, lethargy, increasing weakness, tremors and convulsions, collapse and death	YLI 1978
Rat	240	26,900	LC_{50}; no details provided	Pozzani, Weil, and Carpenter 1959
Rat (male and female)	240	26,830	LC_{50}; see comment for rabbit	Pozzani et al. 1959
Rat (female)	480	20,852	LC_{50}; see comment for rabbit	Pozzani et al. 1959
Rat	480	12,662	LC_{50}; see comment for rabbit.	Pozzani et al. 1959

[a]Exposed on eighth day of gestation, which is during the early primitive streak stage of embryogenesis.

2.3.1.4 Exposure limits/standards

Acetonitrile exposure limits have been established by various agencies. ACGIH recommends threshold limit values (TLVs) for exposure to chemicals in the workplace. The recommended time-weighted average (TWA) TLV for acetonitrile is 40 ppm (67 mg/m^3), and the short-term exposure limit (STEL) is 60 ppm (101 mg/m^3). The TWA TLV is an 8-h exposure level at which average workers can be exposed repeatedly day after day without showing adverse effects. The STEL TLV establishes exposure limits based on 15-min exposure periods. The TLVs for acetonitrile are recommended to protect against organic cyanide poisoning and injury to the respiratory tract (ACGIH 1986). Based on ACGIH recommendations, the Occupational Safety and Health Administration (OSHA) has promulgated permissible exposure limits (PELs) of 40 ppm (67 mg/m^3) TWA and 60 ppm (101 mg/m^3) STEL (29 CFR Pt. 1910). The National Institute for Occupational Safety and Health (NIOSH) recommended a 10-h TWA exposure limit of 20 ppm (34 mg/m^3) (ACGIH 1986). The level that is listed by NIOSH as immediately dangerous to life and health (IDLH) is 4000 ppm (6708 mg/m^3). The IDLH is the maximum concentration from which one could escape within 30 min without experiencing any escape-impairing (e.g., severe eye irritation) or irreversible health effects (DHHS 1990). Although the American Industrial Hygiene Association (AIHA) sets emergency response planning guidelines (ERPGs) for several chemicals, they have not established or drafted any guidelines for acetonitrile.

2.3.2 Hydrogen Cyanide

More human data are available for exposures to HCN than for acetonitrile. An extensive data set of animal exposures is also available for HCN exposure (all routes of exposure). Because the focus of this report is acetonitrile, this section will only briefly summarize human health effects as described in various secondary sources. The purpose of this section is to compare the general effects of acetonitrile and HCN.

2.3.2.1 Human health effects from HCN

Symptoms of HCN poisoning may appear within seconds to minutes after ingesting the liquid or breathing the vapors (ATSDR 1989; Goodman and Gilman 1975). Hydrogen cyanide dissociates in vivo, thereby releasing cyanide ions. Cyanides are absorbed from the skin and mucosal surfaces and are dangerous when inhaled because toxic amounts can be absorbed through bronchial mucosa and alveoli (Haddad and Winchester 1983). People with chronic diseases of kidneys, respiratory tract, skin, or thyroid are at greater risk of developing toxic cyanide effects than are healthy individuals (ILO 1983). CNS effects observed after acute inhalation exposure to HCN include headaches, numbness and paresis, coma, and seizures; in

fatal cases, necrosis of brain tissue and asphyxial convulsions may precede death (ATSDR 1989; Haddad and Winchester 1983; Gosselin, Smith, and Hodge 1984). Cardiac and respiratory effects (e.g., cyanosis, metabolic acidosis, hypoventilation, respiratory tract irritation, pulmonary edema, hyperpnea), which may be secondary to effects on the CNS, have also been reported (ATSDR 1989; Haddad and Winchester 1983; Gosselin, Smith, and Hodge 1984). As cyanide levels in the blood rise, ataxia develops, followed by coma, convulsions, and death (Haddad and Winchester 1983). Cardiovascular changes may include atrial fibrillation, ectopic ventricular beats, tachycardia and hypertension, and hypotension. The most specific pathological finding in acute cases of cyanide poisoning is the bright red color of venous blood due to oxyhemoglobin, which results from the inability of cells to utilize oxygen. Venous blood is about 1 vol % lower in oxygen content than arterial blood (Clayton and Clayton 1982). Other effects (e.g., gastrointestinal) include nausea and vomiting (Haddad and Winchester 1983; Gosselin, Smith, and Hodge 1984). Cyanide is distributed to all organs and tissues via the blood (EPA 1980). The nonlethal short-term effects of cyanide poisoning are reversible with time because cyanide is eliminated from the body (ATSDR 1989; Gosselin, Smith, and Hodge 1984).

The almond odor of the chemical does not alert all people that it is in the air because not all persons can detect the odor of HCN (ATSDR 1989) and the vapors may deaden the sense of smell. HCN is a mild upper respiratory irritant and may cause slight irritation of the nose and throat. There may also be irritation from skin and eye contact with the liquid (Sittig 1985; DOT 1987).

Hydrogen cyanide could be formed during an acetonitrile fire as a product of combustion. Carbon monoxide and HCN, often found in fire environments, act in an additive manner in terms of lethality (ATSDR 1989). Sublethal concentrations of HCN may interact with other toxicants in fire environments and cause death. It has also been speculated by Birky and Clarke (1981) that cyanide could lead to incapacitation, preventing escape, so that the victim could be exposed to high levels of carbon monoxide (ATSDR 1989).

2.3.2.2 Exposure limits/standards

The ACGIH ceiling TLV (the concentration that cannot be exceeded in any time) and the OSHA PEL (8-hr TWA) for hydrogen cyanide are both 11 mg/m^3. The NIOSH 10-min ceiling level is 5 mg/m^3, and the IDLH is 55 mg/m^3.

2.4 ESTIMATES OF HEALTH EFFECTS LEVELS

This section attempts to estimate exposure limits for five consequences. This analysis addresses short-term exposures of acetonitrile (i.e., from a few minutes to a few hours).

2.4.1 Detection Threshold

The only study that has measured human odor perception was conducted by Pozzani et al. (1959) (see Sect. 2.3.1.2). Based on this study, the odor detection threshold is believed to be 67 mg/m^3. Olfactory fatigue is expected to occur in 2 to 3 h after an exposure to this concentration. The odor thresholds listed by ACGIH (1986) and Ruth (1986), of 67 mg/m^3 (40 ppm) and 70 mg/m^3, respectively, are consistent with the Pozzani et al. study. The odor detection threshold is depicted on Fig. 2.1.

Because the odor is detected below the NOAEL (see following section) and because olfactory fatigue does not occur rapidly, acetonitrile is treated as material with adequate warning properties (Mackison, Stricoff, and Partridge 1981). However, the National Fire Protection Agency (NFPA 1986) states that "it has insufficient warning properties to prevent people from working in atmospheres which may cause death." This latter statement may be attributed to olfactory fatigue effects.

2.4.2 No Observed Adverse Effects Level (NOAEL)

Pozzani et al. (1959) found no adverse effects in humans exposed to 67 to 268 mg/m^3 for 4 h (Sect. 2.3.1.2). Other human studies detailing concentrations of acute exposures and associated effects are not available. Furthermore, animal studies focused more on lethality than on levels causing nonlethal effects. Based on Pozzani et al. (1959), a NOAEL of 268 mg/m^3 is found at exposures of 4 h. Because additional data with exposures of shorter duration are not available, we conservatively assumed that 268 mg/m^3 is the NOAEL for shorter exposure durations. Therefore, the NOAEL is leveled at the concentration predicted for 480 min (Fig. 2.1); i.e., 268 mg/m^3.

2.4.3 Reversible/Irritation Health Effects Level

Since exposure to acetonitrile may cause both local irritation and systemic effects in humans, the onset of each type of effect may differ. The only reference to irritating or reversible effects are reports of concentrations with no exposure times (Sect. 2.3.1.2). Ruth (1986) reported an

"irritating" level of 875 mg/m^3; Tietz (1983) reported irritation to mucous membranes at concentrations up to 838 mg/m^3; and Mackison, Stricoff, and Partidge (1981) reported irritation of the nose and throat from "brief periods" of exposure at 838 mg/m^3. None of these data are sufficient to estimate the onset of irritation/reversible effects. Therefore, no level is provided in Fig. 2.1. All that can be concluded is that at some concentration above the NOAEL, irritation and irreversible effects will be expected to occur and that exposure to 838 and 875 mg/m^3 for any exposure period would probably be irritating.

2.4.4 Irreversible Health Effects Level

Willhite (1983) reported that teratogenesis (an irreversible effect) can occur from acute exposure of the mother to acetonitrile (see Sect. 2.3.1.2). He found that a 1-h exposure to 8384 mg/m^3 can result in malformations in offspring. The observation that the inhaled dose is affecting the fetus indicates that the chemical is being systemically absorbed.

A dose absorbed by an animal from an inhaled concentration can be presented in terms of the mass of the chemical (milligrams) per body weight of the animal (kilograms). Converting an inhaled concentration to an absorbed dose allows for extrapolation to other species using body weight as a common denominator. Assuming all the acetonitrile that is inhaled into the lungs is absorbed into the body, the absorbed dose is calculated using Eq. 2.1. The absorbed dose is than used to calculate the human equivalent concentration using Eq. 2.2.

$$AbsD = \frac{Y \times V_{Ta} \times f_a \times t}{BW_a} \tag{2.1}$$

$$HEC = \frac{AbsD \times BW_h}{V_{Th} \times f_h \times t} , \tag{2.2}$$

where

$AbsD$ = the absorbed dose of acetonitrile (mg/kg),
Y = concentration of acetonitrile in air (animal exposure) (mg/m^3),
$V_{Ta,h}$ = tidal volume of an animal species or human (m^3),
$f_{a,h}$ = breathing frequency (breaths/min)
t = time of exposure (min),
$BW_{a,h}$ = body weight of an animal species or human (kg),
HEC = human equivalent concentration in air (mg/m^3).

Employing these equations, the 1-h 8384 mg/m^3 exposure for a pregnant hamster is converted to an HEC of 15,967 mg/m^3 through use of the following values:

Y = 8384 mg/m^3 (Willhite 1983),
$(V_{Ta} \times f_a) = IR_a$ (inhalation rate) = 6×10^{-5} m^3/min (Altman and Dittmer 1964),
t = 60 min (Willhite 1983),
BW_a = 0.092 kg (Altman and Dittmer 1964),
BW_h = 73 kg (ICRP 1994),
$(V_{Th} \times f_h) = IR_h$ (inhalation rate) = 0.025 m^3/min (light work conditions) (ICRP 1994).

The HEC assumes an inhalation rate during light work conditions because for many applications an individual is expected to be active (e.g., attempting to exit) in the event of a short-term release. A lower inhalation rate may be appropriate for individuals, such as office workers, who are engaged in sedentary activity.

Because it is not known exactly how the metabolism of acetonitrile and associated responses in humans compare to those in hamsters or even how hamsters compare to other mammals, an uncertainty factor of 10 is applied to the HEC, as suggested by the EPA (EPA 1989). This results in a 60-min HEC for irreversible effects of 1597 mg/m^3. Lacking additional data, this modified 60-min HEC was derived as the estimated onset-of-irreversible-effects level for exposure durations from 0 to 60 min. It would be reasonable to expect that higher concentrations could be tolerated for shorter times but, lacking other data we used the constant value of approximately 1600 mg/m^3. There are no available data that would support an extrapolation to times longer than 60 min. The following relationship represents the onset-of-irreversible-effects-level (Fig. 2.1):

$$C = 1600 \text{ mg/m}^3;\ t \leq 60 \text{ min}$$

Other irreversible effects such as respiratory effects may occur also; however, quantitative data were not available to evaluate them.

2.4.5 Lethal Exposure Level (LC_{50})

While anecdotal human evidence of death from inhalation of acetonitrile exists (Sect. 2.3.1.2), adequate human data are not available for determining an airborne concentration that is lethal to 50% of the exposed population (i.e., an LC_{50}). The goal of this analysis is to develop a concentration-time relationship for a human LC_{50} from short-term exposures.

In the absence of sufficient human data, this analysis is based on animal to human extrapolations. Because acetonitrile is absorbed into the body upon inhalation to cause systemic effects (e.g., CNS effects such as convulsions and coma), animal LC_{50} data will be converted to human-equivalent LC_{50} values based on the absorbed animal dose. Although respiratory effects may also occur, it is assumed that death would occur from systemic effects. Assuming all the acetonitrile that is inhaled into the lungs is absorbed into the body, the human equivalent LC_{50} is calculated using Eqs. 2.1 and 2.2 in the previous section. Table 2.4 lists the animal LC_{50} levels (presented earlier in Table 2.3), the associated absorbed doses, and the calculated human equivalent LC_{50} levels.

To help understand the exposure-response relationship, the product of concentration and time ($C \times t$), which represents the cumulative exposure, is calculated for each LC_{50} value. Table 2.5 lists the $C \times t$ values for each estimated human equivalent LC_{50}. According to Haber's law, $C \times t$ = a constant (k) for a specific effect (e.g., death) (Klaasen, Amdur, and Doull 1986). Haber's law has been challenged by ten Berge, Zwart, and Appelman (1986), who found it to be unreliable for predicting mortality response in some chemicals. They state that the concentration-time relationship for lethality for some volatile industrial chemicals is $C^n \times t$ = a constant, where n is a species-specific factor derived empirically from acute inhalation toxicity experiments. This n was derived by fitting LC_{50} data to the given equation. While ten Berge et al. (1986) did not derive an n for acetonitrile, they did do so for HCN systemic effects. They calculated an n of 2.7 (95% confidence limits 1.8 and 3.7) for HCN. Because both HCN and acetonitrile may result in cyanide-like effects, we applied the n value of 2.7 to acetonitrile to further evaluate the concentration-time relationships. However, this relationship was not found to be valid for acetonitrile and is not addressed further.

The k values (i.e., $C \times t$) in Table 2.5 represent the slope of the LC_{50} curves for each time-specific animal study. Although the true relationship of $C \times t$ is not known, by assuming that k is constant at different times (i.e., Haber's law), a curve representing concentration (LC_{50}) versus time can be drawn. In essence, this is extrapolating from a concentration at a given time to other exposure times. Since each different k results in a different curve, the range of LC_{50} values is determined by taking the most sensitive and most resistant species and extrapolating to different times using the k value. For example, the most sensitive species is the rabbit (240 min) (Pozzani et al. 1959) because it has the lowest k value. The highest k value (most resistant) is the second rat-240 study (YLI 1978) listed in Table 2.5. Fig. 2.2 shows the upper and lower bounds of predicted LC_{50} values from the most resistant and most sensitive species. The following equations represent those curves:

Upper bound (from rat-240 study): $C \times t = 2.07 \times 10^7$ mg-min/m^3,
Lower bound (from rabbit-240 study): $C \times t = 7.12 \times 10^5$ mg-min/m^3.

Table 2.4. Animal LC_{50}'s, absorbed doses, and calculated human equivalent LC_{50}

Species	Animal LC_{50} (mg/m^3)[a]	Time (min)	IR (m^3/min)[b]	BW (kg)	Absorbed dose (mg/kg)	Human equivalent LC_{50} (mg/m^3)[c]
Mouse	4,516	60	2.45×10^{-5}	0.02	331	16,120
Rabbit	2,828	240	1.07×10^{-3}	5	244	2,966
Guinea pig	9,483	240	1.62×10^{-4}	0.466	791	9,626
Rat	89,000	30	7.40×10^{-5}	0.2	986	95,969
Rat	33,454	240	7.40×10^{-5}	0.2	2,969	36,124
Rat	80,000	240	7.40×10^{-5}	0.2	7,100	86,385
Rat	26,900	240	7.40×10^{-5}	0.2	2,397	29,047
Rat	26,830	240	7.40×10^{-5}	0.2	2,381	28,972
Rat	20,852	480	7.40×10^{-5}	0.2	3,701	22,516
Rat	12,662	480	7.40×10^{-5}	0.2	2,248	13,673

[a]References for animal LC_{50}'s are provided in Table 2.3.

[b]IR = inhalation rate = tidal volume (V_T) × breathing frequency (f) (Altman and Dittmer 1964).

[c]Assume an average human body weight of 73 kg and an inhalation rate during light work conditions of about 0.025 m^3/min (ICRP 1994). Light work conditions are considered reasonable because an individual is expected to be active (e.g., attempting to exit) in the event of a short-term release.

Because there is such a large range of predicted LC_{50} values, and because it is not known which species' sensitivity more closely resembles that of humans, a conservative approach is to use the most sensitive species data to represent human LC_{50} values. Therefore, we have chosen the lower bound curve as the estimated LC_{50} curve (Fig. 2.1). Note that what occurs at very short exposure times is not known. As depicted in Fig. 2.1, the LC_{50} is assumed to be constant at exposure times less than 15 min.

Although this extrapolation assumes death occurs from systemic effects, death may in some instances occur from respiratory effects. As such, there may be a different exposure-response relationship associated with such effects. Note also that the estimated levels developed in this analysis for acetonitrile incorporate both interpolations and extrapolations. Many uncertainties are inherent in such predictive methods. For example, animal-to-human extrapolations were made assuming the mass of the chemical per unit body weight has the same effect in laboratory animals as in humans. In addition to uncertainties incurred in this analysis, the data

Table 2.5. Comparison of concentration and time relationships for acetonitrile lethality data

Animal study[a]	HEC (LC_{50})[b] (mg/m^3)	$C \times t$ ($mg\text{-}min/m^3$)
Mouse—60 min	16,120	9.67×10^5
Rabbit—240 min	2,966	7.12×10^5
Guinea pig—240 min	9,626	2.31×10^6
Rat—30 min	95,969	2.88×10^6
Rat—240 min	36,124	8.67×10^6
Rat—240 min	86,385	2.07×10^7
Rat—240 min	29,047	6.97×10^6
Rat—240 min	28,972	6.95×10^6
Rat—480 min	22,516	1.08×10^7
Rat—480 min	13,673	6.56×10^6

[a]References are provided in Table 2.2, and studies are listed in the same order as in Table 2.4.

[b]From Table 2.4.

themselves have their own associated uncertainties. Consequently, it should be recognized that the recommended levels provide best estimates of effects of exposure to acetonitrile as confined by many unavoidable uncertainties.

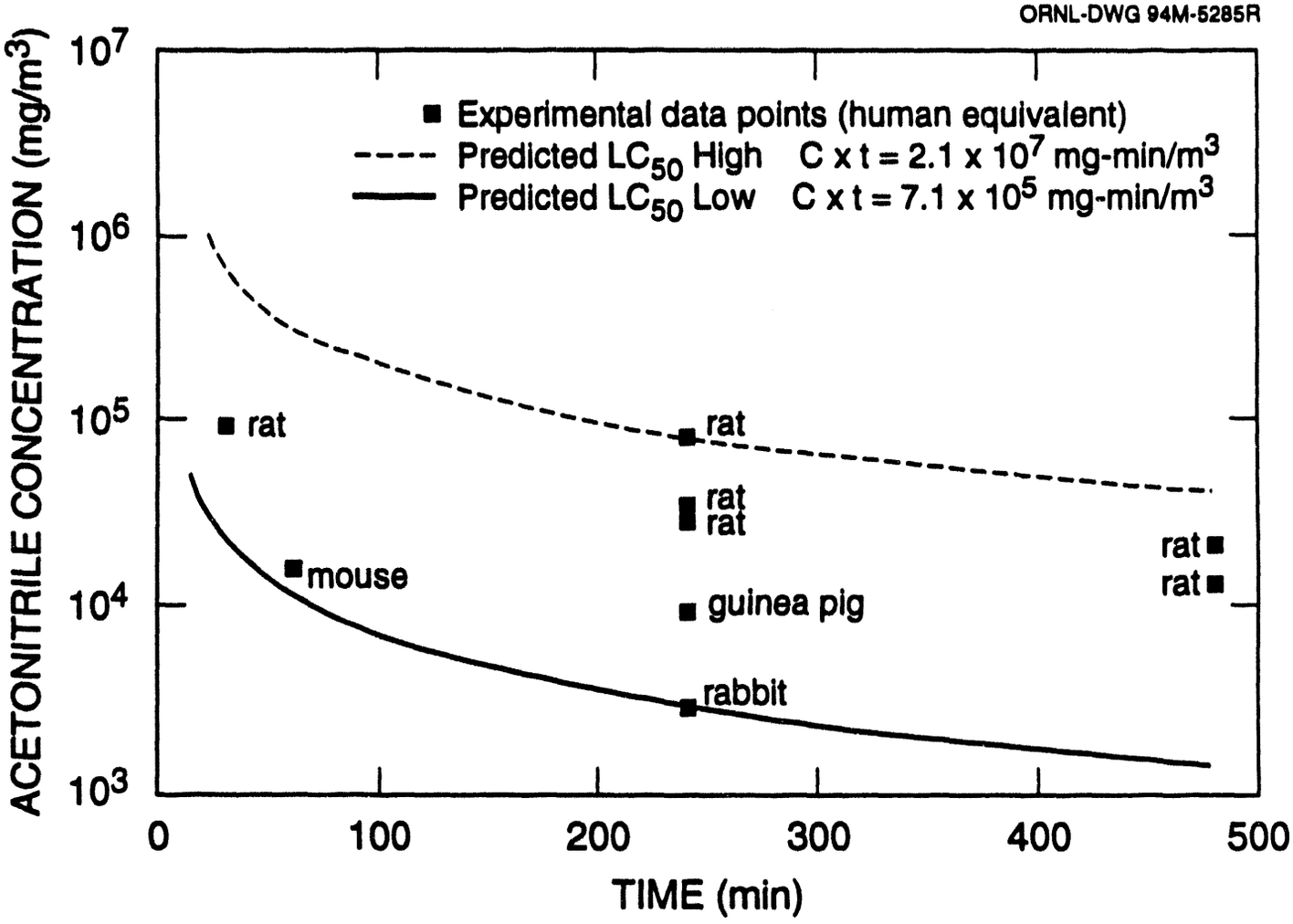

Fig. 2.2. Human equivalent LC_{50} data for acetonitrile.

2.5 REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) 1989. *Toxicological Profile for Cyanide*, ATSDR/TP-88/12, Department of Health and Human Services (DHHS), December.

Ahmed, A. E. et al. 1992. "Studies of the Mechanism of Acetonitrile Toxicity. I. Whole Body Autoradiographic Distribution and Macromolecular Interaction of 2-14C-Acetonitrile in Mice," *Pharm. Toxicol.*, **70**, 322–330.

Altman, P. L., and D. S. Dittmer, eds. 1964. *Biology Data Book*, Pub. Federation of American Societies for Experimental Biology, Washington, D.C.

Amdur, M. L. 1959. "Accidental Group Exposure to Acetonitrile–A Clinical Study," *J. Occup. Med.* **1**, 627–33.

American Conference of Governmental Industrial Hygienists (ACGIH) 1986. *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th ed., Cincinnati, Ohio.

Atkinson, R., and W. P. L. Carter 1984. "Kinetics and Mechanics of Gas-Phase Reactions of Ozone with Organic Compounds Under Atmospheric Conditions," *Chem. Rev.* **84**, 437–70.

Birky, N. M., and F. B. Clark 1981. "Inhalation of Toxic Products from Fires." *Bull. New York Acad. Med.* **57**, 997–1013.

Clayton G. D., and F. E. Clayton, eds. 1982. *Patty's Industrial Hygiene and Toxicology*, vols. 2A, 2B, and 2C, *Toxicology*, 3rd ed., John Wiley and Sons, New York, p. 4868.

Dalhamn, T., M. L. Edfors, and R. Rylander 1968a. "Mouth Absorption of Various Compounds in Cigarette Smoke." *Arch. Environ. Health*, **16**(6), 831–35.

Dalhamn, T., M. L. Edfors, and R. Rylander 1968b. "Retention of Cigarette Smoke Components in Human Beings." *Arch. Environ. Health*, **17**, 746–48.

Department of Health, Education, and Welfare (DHEW) 1978. *NIOSH Criteria for a Recommended Standard Occupational Exposure to Nitriles*, PB81-225534, DHEW, Public Health Service, Center for Disease Control, and National Institute for Occupational Safety and Health, September.

Department of Health and Human Services (DHHS) 1990. *National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards*, DHHS (NIOSH) Publication 90-117, U.S. Government Printing Office, Washington, D.C., p. 126.

Department of Transportation (DOT) 1987. *Emergency Response Guidebook 1987*, DOT P 5800.4, U.S. Government Printing Office, Washington, D.C.

Department of Transportation (DOT) 1990. *Emergency Response Guidebook* 1990, DOT P 5800.5, U.S. Government Printing Office, Washington, D.C.

Dequidt, J., D. Furon, and J. M. Haguenoer 1972. "Fatal Intoxication by Acetonitrile." *Bull. Soc. Pharm. Lille*, **4**, 143–48.

Dequidt, J., D. Furon, F. Wattel, H. M. Haguenoer, P. Scherpereel, B. Gosselein, and A. Ginestet 1984. "Intoxication with Acetonitrile with a Report of a Fatal Case," *Eur. J. Toxicol.*, **7**, 91–97.

Dudley, H. C., T. R. Sweeney, and J. W. Miller 1942. "Toxicology of Acrylonitrile (Vinyl Cyanide). II. Studies of Effects of Daily Inhalation," *J. of Indus. Hyg. and Tox.* **24**, 255–58.

Environmental Protection Agency (EPA) 1980. *Ambient Water Quality Criteria Document: Cyanides*, EPA 440/5-80-037, Washington, D.C.

Environmental Protection Agency (EPA) 1983. *Acute Toxicological Properties and Industrial Handling Hazards of N,N-Dimethylaminoacetonitrile*, FYI-OTS-0483-0238, Office of Toxic Substances, Dow Chemical Co.

Environmental Protection Agency (EPA) 1987. *Health Effects Assessment for Acetonitrile PB 88-179502*, Cincinnati, June.

Environmental Protection Agency (EPA) 1989. *Interim Methods for Development of Inhalation Reference Doses*, Office of Health and Environmental Assessment, EPA/600/8-88/066F, Washington, D.C., August.

Fiereman, D. E., and A. I. Cederbaum 1989. "Role of Cytochrome P-450 IIE1 and Catalase in the Oxidation of Acetonitrile to Cyanide," *Chem. Res. Toxicol.*, **2**(6), 359–66.

Freeman, J. J. and E. P. Hayes 1988. "Microsomal Metabolism of Acetonitrile to Cyanide" *Biochem. Pharma.*, **37**(6), 1153–59.

Gilman A. G., L. S. Goodman, and A. Gilman eds. 1985. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed., Macmillan, New York, p. 1642.

Goodman and Gilman eds. 1975. *The Pharmacological Basis of Therapeutics*. 5th ed, Macmillan, New York, p. 904.

Gosselin, R. E., R. P. Smith, and H. C. Hodge 1984. *Clinical Toxicology of Commercial Products*, 5th ed., Williams and Wilkins, Baltimore.

Grabois, B. 1955. "Fatal Exposure to Methyl Cyanide." *New York Department Labor Div. Ind. Hyg. Mon. Rev.* **34**, 1,7,8.

Haddad, L. M., and J. F. Winchester 1983. *Clinical Management of Poisoning and Drug Overdosage*, W. B. Saunders Co., Philadelphia, Pa., p. 745.

Haguenoer, J. M., J. Dequidt, and M. C. Jacquemont 1975. "Experimental Acetonitrile Intoxications. II. Acute Intoxications by the Pulmonary Route," *Eur. J. Toxicol.* **8**, 102–6.

International Commission on Radiation Protection (ICRP) 1994. *Human Respiratory Tract Model for Radiological Protection*, ICRP Publication 66, *Annals of the ICRP* **24**(1–4), in press.

International Labour Office (ILO) 1983. *Encyclopaedia of Occupational Health and Safety*, vols. 1 and 2, International Labour Office, Geneva, Switzerland, p. 576.

Klaasen, C. D., M. O. Amdur, and J. Doull, eds. 1986. *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 3rd ed., Macmillian, New York, p. 815.

Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr., eds. 1981. *NIOSH/OSHA—Occupational Health Guidelines for Chemical Hazards*, DHHS (NIOSH) Publication No. 81–123 (3 vols.), U.S. Government Printing Office, Washington, D.C., January.

Monsanto Environmental Health Lab n.d. "A Study of Acute Inhalation Toxicity (4-Hour LC_{50}) of Acetonitrile in Rats," Study No. 780007, EPA/OTS Docket No. 878210774.

National Fire Protection Association (NFPA) 1986. *Fire Protection Guide on Hazardous Materials*, 9th ed., Batterymarch Park, Quincy, Mass.

National Institute of Occupational Safety and Health (NIOSH) 1976. *Criteria Document: Hydrogen Cyanide and Cyanide Salts*, DHEW Pub. NIOSH 77-108.

National Research Council (NRC) 1981. *Drinking Water and Health*, vol. 4, National Academy Press, Washington D.C.

Pozzani, U. C., C. S. Weil, and C. P. Carpenter 1959. "The Toxicology Basis of Threshold Limit Values. 5. The Experimental Inhalation of Vapor Mixtures by Rats, with Notes upon the Relationship Between Single Dose Inhalation and Single Dose Oral Data," *Am. Ind. Hyg. Assoc. J.* **20**, 364–69.

Pozzani, U. C., C. P. Carpenter, P. E. Palm, C. S. Weil, and J. H. Noir, III. 1959. "An Investigation of the Mammalian Toxicity of Acetonitrile." *J. of Occup. Med.* **1**, 634–642.

Ruth, J. H. 1986. "Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review," *Am. Ind. Hyg. Assoc. J.* **47**, A-142–151.

Sax, N. I. 1984. *Dangerous Properties of Industrial Materials*, 6th ed., Van Nostrand Reinhold, New York.

Sax, N. I., and R. J. Lewis, Sr. 1989. *Dangerous Properties of Industrial Materials*, 7th ed., vol. 2, Van Nostrand Reinhold, New York.

Sittig, M. 1979. *Hazardous and Toxic Effects of Industrial Chemicals*, Noyes Data Corp., Park Ridge, N.J.

Sittig, M. 1985. *Handbook of Toxic and Hazardous and Toxic Chemicals and Carcinogens*, 2nd ed., Noyes Data Corp., Park Ridge, N.J., p. 508.

Smyth, H. F., and C. P. Carpenter 1948. "Further Experience with the Range Finding Test in the Industrial Toxicology Laboratory," *J. Ind. Hyg. Toxicol.* **30**, 63–68.

ten Berge, W. F., A. Zwart, and L. M. Appelman 1986. "Concentration-Time Mortality Response Relationship of Irritant and Systemically Acting Vapours and Gases," *J. Hazard. Materials*, **13**, 301–9.

Tietz, N. W., ed. 1983. *Clinical Guide to Laboratory Tests*, W. B. Saunders Co., Philadelphia, Pa., p. 5.

Verschueren, K. 1983. *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., Van Nostrand Reinhold, New York.

Weast, R. C., ed. 1989. *Handbook of Chemistry and Physics*, 69th ed., CRC Press Inc., Boca Raton, Fla., C-52.

Willhite, C. C. 1981. "Inhalation Toxicology of Acute Exposure to Aliphatic Nitriles," *Clin. Toxicol.*, **18**(8), 991–1003.

Willhite, C. C., and R. P. Smith 1981. "The Role of Cyanide Liberation in the Acute Toxicity of Aliphatic Nitriles," *Toxicol. Appl. Pharmacol.* **59**(3), 589–602.

Willhite, C. C. 1983. "Developmental Toxicology of Acetonitrile in the Syrian Golden Hamster," *Teratology* **37**(3), 313–25.

World Health Organization (WHO) 1970. *Technical Report Series*, in RTECS (Registry of Toxic Effects of Chemical Substances) database 1993.

Younger Laboratories Incorporated (YLI) 1978. *Toxicological Investigation of Acetonitrile*, Monsanto Project Number Y-78–130, EPA/OTS Docket No. 878210773.

3

HYDROGEN CHLORIDE

3. HYDROGEN CHLORIDE

3.1 SUMMARY

Hydrogen chloride (HCl) is a colorless gas with a pungent, penetrating odor. Due to its highly hygroscopic nature, the anhydrous gas forms aerosols of microdroplets of hydrochloric acid under normal atmospheric conditions. Hydrogen chloride is corrosive to biological tissues and is a primary irritant. The primary target organ for toxic effects from HCl vapor or aerosols is the upper respiratory tract, although eyes and skin may also be affected. The symptoms of exposure include nose, throat, and eye irritation; coughing and sneezing; chest pain; hoarseness; and bronchoconstriction. Delayed or chronic effects from HCl exposure seem quite rare in humans. Experimental animal studies and evidence from a few human studies suggest that HCl is not a carcinogen.

Concentration-time relationships for exposures to hydrogen chloride are predicted for five health endpoints, as shown in Table 3.1 and plotted in Fig. 3.1. There is a wide range of values for odor detection of HCl in humans. Since irritation is a more sensitive indicator of HCl detection than odor, we have selected irritation as the endpoint for the detection threshold. Detection threshold levels chosen were 6 mg/m^3 for ≤10 min, 3 mg/m^3 for >10 min to 120 min, and 1 mg/m^3 for >2 to 4 h. The no observed adverse effect level (NOAEL) chosen was the same set of HC1 concentrations as was used for detection thresholds. These levels are to be considered ceilings, and the adverse effect considered is irritation. The irritation/ reversible effects threshold chosen was the same set of values used for the NOAEL. Concentrations of HCl above these levels might be expected to initiate irritation. These levels are based on human volunteer exposures and the expert judgment of committees of toxicologists. An irreversible effects level for HCl for humans could not be defined. Primate studies indicate that even very-high-level exposures (>1500 mg/m^3 for 15 min) do not produce irreversible effects in baboons. The estimated human lethality levels [lethal concentrations to 50% of an average human population (LC_{50})] for HCl were based on calculations from rodent acute lethality studies. The lethal HCl concentrations for time periods up to 120 min were calculated from the equation $C \times t = 92{,}000$ mg-min/m^3.

The estimates of health effects provided in this section are intended to be used only in assessing the consequences of postulated accidents in support of the Safety Analysis Report (SAR) program. This information will be used to determine the adequacy of the controls used to manage the risk of the operation being evaluated. The toxicity estimates are *not* intended to be used as acceptable exposure levels for occupational personnel or members of the public. Furthermore, the guidelines in this section are *not* intended for use in developing emergency exposure levels.

Table 3.1. Summary of effect levels for hydrogen chloride

Endpoint	HCl concentration and time[a]	Averaging time (min)	Comments
Detection threshold	C = 6; t ≤ 10 C = 3; t > 10 to 120 C = 1; t > 120 to 240	5 10 30	Detection is based on sensing irritation (nose and throat), not upon odor. Initiation of irritation might occur above these levels.
No observed adverse effects level	C = 6; t ≤ 10 C = 3; t > 10 to 120 C = 1; t > 120 to 240	0 0 0	HCl levels at or below these values should have no adverse effect. Suggested as ceiling levels, since HCl concentrations above these levels might initiate irritation.
Onset of irritation/reversible effects	C > 6; t ≤ 10 C > 3; t > 10 to 120 C > 1; t > 120 to 240	5 10 30	HCl concentrations above the NOAEL threshold might be expected to initiate irritation.
Onset of irreversible/serious effects	No value could be established		
Lethal exposure level (LC_{50})	C = 18,500; t ≤ 5 m C × t = 92,000; t > 5 to 60 C × t = 92,000; t > 60 to 120	5 10 30	Data supporting Haber's law did not extend beyond 1 h. We extended the exposure time to 2 h using Haber's law but do not recommend extension > 2 h because of the uncertainty about the nature of the dose-response relationship. There is similar uncertainty regarding very short exposure times (<5 min). The values used for human LC_{50}'s were derived by direct extrapolation from rodent data exclusively.

[a]Concentration (C) = mg/m^3; time (t) = min.

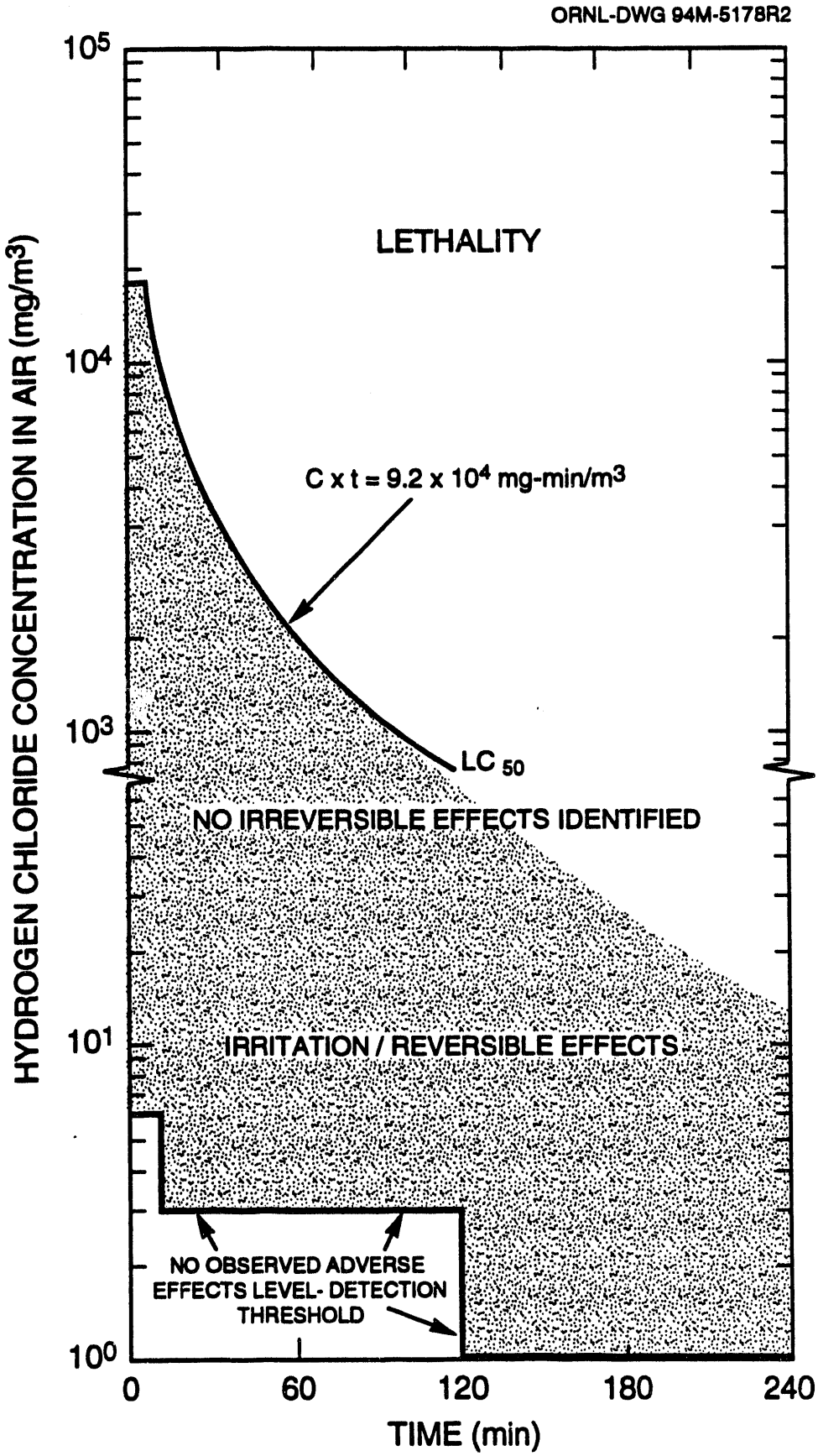

Fig. 3.1. Summary of acute health endpoints for hydrogen chloride.

3.2 PHYSICOCHEMICAL PROPERTIES OF HYDROGEN CHLORIDE

3.2.1 Background

Hydrogen chloride (HCl) is a colorless gas which, upon dissolution in water, forms the common acid, hydrochloric acid. Physical properties are described in Table 3.2. HCl has a pungent, irritating odor. In this report, the toxicology of only the commonly expected gaseous form (aerosols of hydrochloric acid) will be considered. It must be noted that HCl gas is very hygroscopic; when the gas is released into the air, dense white fumes form from the condensation of HCl and water vapor in the air (AIHA 1989; Henderson and Haggard 1943). Anhydrous HCl gas exposure is a greater biological hazard than exposure to the hydrochloric acid microdroplets because of tissue dessication as well as tissue corrosion (Henderson and Haggard 1943; NAS 1976). Unusual conditions could give rise to accidental exposure to anhydrous HCl gas, but as the document on chlorine (Cl_2) and HCl prepared by the National Academy of Sciences (NAS)/National Research Council (NRC) points out, even in industrial settings, the anhydrous gas will quickly form the aerosol if released (NAS 1976). This same document further concludes that "it must be assumed that published reports deal with hydrochloric acid aerosol unless they specifically state otherwise." The studies of Darmer, Kinkead, and DiPasquale (1974) indicate that the gas and aerosol states of HCl have very similar toxicities for rodents (in some cases, LC_{50} values for one state lie within the 95% confidence limits of the LC_{50} value for the other state) in their experimental system. The background document for the Emergency Response Planning Guidelines (ERPG) values for HCl (AIHA 1989) does not distinguish between the aerosol and gas forms in terms of the various ERPG levels. We will follow the lead of the NAS (1976) document in this report and assume explicitly that aerosols of HCl are being discussed in terms of exposure.

Hydrogen chloride can generally be defined toxicologically as a corrosive irritant. The common toxic reactions from HCl vapor exposure are irritation of the eyes, nose, and throat; coughing; bronchoconstriction; and edema of conducting airways or alveoli (Kamrin 1992). The evidence for pulmonary edema comes exclusively from rodent studies, however, and primate (baboon) experiments indicate that even a high level of HCl exposure (10,000 ppm, or 15,000 mg/m^3) does not produce pulmonary edema in primates (Kaplan et al. 1988). Although irritation of the eyes is one of the symptoms of HCl exposure, there is general agreement that the upper respiratory tract is the primary target for HCl and that irritation of this area is the most sensitive indicator of exposure (WHO 1982; Darmer, Kinkead, and DiPasquale 1974; Kamrin 1992). Also, very little quantitive information is available regarding ocular toxicity. Accordingly, in this document, the focus has been placed on the respiratory tract as the site for toxic effects, and all toxicity levels have been evaluated with regard to this site. Very few

Table 3.2. Physical properties of hydrogen chloride

Property	Description
State	Gas at normal conditions of temperature and pressure
Color	Colorless
Molecular weight	36.46 g/mole
Boiling point (1 atm)	-84.9°C
Freezing point (1 atm)	-114.8°C
Density (vapor)	1.268 (air = 1.000) or 1.639 g/L@ 0°C
Density (liquid)	1.194 @ -26°C
Vapor pressure	4.0 atm @ 17.8°C
Solubility in water	823 g/L @ 0°C
Solubility in other solvents	Very soluble in ethanol; soluble in benzene and ether

Sources: HSDB 1993; Lewis 1992; WHO 1982; Windholz et al. 1983.

human studies assessing the chronic effects of HCl exposure in people have been reported. The consensus of the information available suggests that only local effects on the membranes of the eyes and upper respiratory tract are produced, with no chronic or systemic effects (NAS 1976; WHO 1982; HSDB 1993). Animal carcinogenesis studies provide no indication HCl is a carcinogen (Sellakumar et al. 1985). Teratogenic or mutagenic effects have not been reported in human exposures to HCl (WHO 1982). In this analysis, attention will be focused on acute toxic effects exclusively.

3.2.2 Chemical Properties/Combustion

Hydrogen chloride is a colorless (in pure form) gas at normal conditions of temperature and pressure. The gas is extremely soluble in water (823 g/L at 0°C) and forms the strong aqueous acid, hydrochloric acid (concentrated solutions are 35–38% HCl by weight). The aqueous solution is colorless or slightly yellow. Hydrogen chloride is generally characterized as corrosive. Most metals are attacked by aqueous solutions of the gas, with release of flammable hydrogen gas. Aqueous solutions will also attack some forms of plastics, rubber, and various coatings. Contact of HCl (gas or liquid) with alkali or active metals may develop enough heat to cause fire in combustible materials in the adjacent area. A variety of materials (chemicals)

may produce hazardous chemical reactions with HCl; these include calcium carbide, cesium carbide, lithium silicide, magnesium boride, uranium phosphide, calcium phosphide, and sodium (HSDB 1993). Hydrogen chloride gas is described as having a pungent, irritating odor.

Hydrogen chloride is considered to be noncombustible. Reaction with metals, as indicated above, may, however, generate hydrogen gas, which is highly flammable in air. Also, heat associated with fires may cause pressurized containers of HCl gas to explode and release the gas. Furthermore, many of the hazardous reactions of various chemicals with HCl produce chemical fires, which may ignite combustible materials. The above information on chemical properties and fire hazards was taken from HSDB (1993), NFPA (1986), and NFPA (1971).

3.3 SUMMARY OF EXISTING HUMAN TOXICITY DATA

The following is a brief summary of toxic effects in humans from either short- or long-term exposure to HCl. The World Health Organization (WHO) Environmental Health Criteria document on Cl_2 and HCl (1982) provides valuable information that we have used for the following discussion. Flury and Zernik in the 1930s reported that eyes, skin, nose, mouth, pharynx, larynx, and trachea were all primary targets for HCl gas. Respiratory symptomology associated with short-term exposure can include sneezing, laryngitis, chest pain, hoarseness, and a feeling of suffocation. Conjunctival irritation, epidermal inflammation, and superficial corneal damage may also occur, but the upper respiratory tract seems most sensitive to the toxic action of HCl. Skin exposure to HCl gas escaping from leaks in apparatus has resulted in severe burns (Clayton and Clayton 1981). Flury and Zernik also noted that long-term HCl exposures produced brown spots on teeth and erosion of the crowns of teeth. Other studies (Ten Bruggen Cate as cited in WHO 1982) have also shown this erosional effect on teeth; however, many of these exposures were to combinations of acids, with HCl being only one component. The NAS report on Cl_2 and HCl (NAS 1976) indicates that laryngeal spasm, pulmonary edema, and death can occur from exposures to high concentrations of HCl, but the more usual effect (at lower HCl concentrations) is only a mild transitory upper respiratory tract irritation. Because of the irritant nature of HCl, people voluntarily escape an HCl-containing atmosphere if they are able to do so. The evidence with respect to HCl toxicity in humans suggests that it predominantly produces local adverse effects on the eyes and respiratory tract, with no known chronic or acute systemic effects (WHO 1982).

More recent reports of human HCl exposures are infrequent in the literature. Rosenthal et al. (1978) reported on an explosion in a factory that released HCl, phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride, and oxalic acid. Eleven individuals received exposures during the 0.5- to 2-min interval required for escape. The major symptoms

experienced were hoarseness, wheezing, coughing, and shortness of breath. Fine crepitations and scattered rhonchi were heard in the lungs. In 9 of the 11 patients, there was evidence of effects on the respiratory system. The authors suggest the underlying pathology was interstitial and alveolar edema, although it must have been mild, as X rays of the lungs were normal. In eight patients, the pulmonary abnormalities resolved completely in a few days. In one patient, resolution took 4 weeks, while in another, normal pulmonary function returned in 2½ months. In the final case, the pulmonary abnormalities (dyspnea, crepitations, rhonchi) persisted at least 2 years (final period of testing after the accident). This one individual certainly appears to have received permanent damage. It is not clear, however, that this was due to HCl, because of the variety of chemicals released. The authors point out that free chlorine may also have been produced.

Finnegan and Hobson (1989) reported on the case of a woman exposed to a vapor cloud of HCl and a small amount of PCl_3 for 15 min. No estimate of concentration was given, but the vapor caused the paint on a boat to blister. The woman was hospitalized for 3 days and then released, but subsequently developed a prolonged hypoxemia and asthma. The authors indicate that single exposures of humans to high concentrations of pulmonary irritants may cause persistent asthma, which has been referred to as reactive airways dysfunction syndrome. However, this patient showed no evidence of irreversible airways obstruction, and the authors concluded that the underlying cause of her hypoxemia could not be determined. That this is not a frequent response to HCl exposure is indicated by the authors' comment that of the 47 cases of inhalation of HCl fumes recorded at Guy's Hospital poison center, none developed hypoxemia and all recovered within one week.

Existing toxicity data on HCl lead to the following conclusions:

- Local effects on the upper respiratory tract and eyes seem to dominate acute HCl vapor poisoning symptomology; skin burns can also occur.
- Evidence from accidental HCl human exposures suggests that no permanent adverse effects are produced in most cases, although damage is concentration dependent, and high concentrations can produce lethality.
- Individuals who are perhaps more sensitive or have preexisting conditions may develop persistent lung-function abnormalities.

3.4 ESTIMATES OF HEALTH EFFECTS LEVELS

3.4.1 Detection Threshold

For a variety of chemicals, warning of their presence in air can be provided, often quite sensitively, by the sense of smell. Chemicals that produce damage at concentrations at which they are not detected by odor or by some other physiological sensation pose a particularly insidious danger. The odor of hydrogen chloride has been described as irritating and pungent. The description of the odor as *irritating*, in and of itself, suggests irritation may be an acceptable physiological detection sign, and the confusion of numerous lower limits for odor detection leads us to choose irritation as the detection sign of choice. The review by Ruth (1986) gave a range of odor detection from 7.0 mg/m^3 (low) to 49.0 mg/m^3 (high). However, this same publication listed the 49 mg/m^3 (30 ppm) value as an irritating concentration. Other general toxicology sources (Lewis 1992) have also indicated that irritation was produced by short exposures to HCl in the 45 to 60 mg/m^3 range. Clayton and Clayton (1981) indicated that HCl concentrations ≥ 5 ppm (7.5 mg/m^3) were *immediately* (no specific time given) irritating to the nose and throat. The Emergency Response Planning Guideline (ERPG) (AIHA 1989) lists results of various studies that indicated 0.4 mg/m^3 of HCl could be detected by the most sensitive volunteer, while 14.9 mg/m^3 (10 ppm) was said to be detectable by all exposed volunteers. The 14.9 mg/m^3 HCl concentration was also noted as irritating (AIHA 1989). The Environmental Health Criteria document on Cl_2 and HCl (WHO 1982) provided a summary table of odor perception threshold levels. Low values were in the range of 0.1 to 0.2 mg/m^3, while the high end of the range was 14.5 to 28.3 mg/m^3 and above. In another study, trained industrial hygienists reported their subjective perception of the presence of HCl and correlated this with actual air concentration measurements (WHO 1982). No detectable sensation was noted at 0.09 to 2.68 mg/m^3, minimal reaction was at 0.10 to 3.23 mg/m^3, and obvious perception was at 2.83 to 12.8 mg/m^3. These individuals were trained industrial hygienists, and therefore their odor perception might be more acute than a representative population sample. The NAS/NRC document on Cl_2 and HCl noted that Heyroth felt most people could detect HCl in the range of 1.5 to 7.5 mg/m^3, while 7.5 to 15.0 mg/m^3 was characterized as being disagreeable (NAS 1976). However, Heyroth also indicated that others (unspecified) have stated that HCl cannot be detected at up to 52 mg/m^3 either by smell or taste. Leonardos et al. (referenced in NAS 1976) found the odor threshold in humans to be 15 mg/m^3. In Sect. 3.4.3, we conclude that the irritation threshold is in the range of 6 mg/m^3 for 10-min exposures and 3 mg/m^3 for 10- to 60-min exposures. If the odor detection threshold is 15 mg/m^3, as Leonardos et al. state, this may leave the impression that HCl is an insidious hazard, since it produces damage (irritation) at lower concentrations than it can be detected. Such is not the case, however, since irritation (of nose and throat) is commonly accepted as a clearly *detectable* sign of the presence of HCl. We therefore conclude that odor detection is

not an appropriately sensitive indicator of HCl presence, and instead suggest irritation as the appropriate detectable sign. There is considerable variation in the toxicology literature regarding HCl irritation thresholds for humans, but reasonable levels seem to be 6 to 7.5 mg/m^3. We suggest that 6 mg/m^3 be taken as a detection threshold for HCl for 10-min exposure and 3 mg/m^3 for >10- to 120-min exposures (see Sect. 3.4.3).

To conclude:

- A wide range of odor detection thresholds are reported for HCl; a mid-range value might be 10 mg/m^3.
- Odor detection is not as sensitive an endpoint as irritation for HCl, and we suggest the detection threshold be defined as that for irritation.
- A reasonable irritation threshold might be 6 mg/m^3 for ≤10-min exposures, 3 mg/m^3 for >10- to 120-min exposures, and 1 mg/m^3 for >2- to 4-h exposures.

3.4.2 No Observed Adverse Effects Level (NOAEL)

The irritation/reversible effects level portion of this report (Sect. 3.4.3) indicates that human respiratory irritation may be expected in the range between 7.5 and 15.0 mg/m^3 of HCl. Since irritation is an adverse effect (even though health consequences may be negligible), the no observed adverse effects level (NOAEL) would be expected to be below at least 7.5 mg/m^3 (5 ppm). The threshold limit value (TLV) for HCl is 7.5 mg/m^3 (5 ppm), ceiling limit (ACGIH 1986). Note that this is a ceiling limit and is interpreted as being low enough to prevent toxic injury, but may still be irritating (AIHA 1989). The OSHA permissible exposure level (PEL) is also established as 7.5 mg/m^3, ceiling value (AIHA 1989). Exposures of rats to 15 mg/m^3 HCl for 6 h/d, 5 d/week for a lifetime leads to laryngeal hyperplasia (Sellakumar et al. 1985). These long-term exposures probably have no relevance to exposures of one or a few hours, however. On the basis of relative toxicity of HCl and H_2SO_4 in animals, Kamrin (1992) estimated a NOAEL for HCl to be 0.3 to 3 mg/m^3 (0.2 to 2 ppm). Barrow et al. (1977), on the basis of results of respiratory rate decreases seen in mice, suggested a TLV of 4.5 to 46 mg/m^3 (3 to 31 ppm) for humans, with the lower limit predicted to produce very slight or no irritating sensation.

These estimated human limits based on animal data [i.e., 3 mg/m^3 (Kamrin) and 4.5 mg/m^3 (Barrow et al.)] are fairly consistent with human data suggesting a possible threshold for irritation in the neighborhood of 7.5 mg/m^3 of HCl (see Sect. 3.4.4 for a more extensive assessment of this threshold). The NAS/NRC Committee on Toxicology (see NAS 1976; AIHA 1989) has set the short-term public limits (STPLs) for HCl as follows:

Exposure duration	*Concentration*
10 min	6 mg/m^3 (4 ppm)
30 min	3 mg/m^3 (2 ppm)
60 min	3 mg/m^3

Note that these are values for the general population and are considered to "represent time-weighted averages not considered to present any health hazard" (AIHA 1989). Further, "excursions above these levels are likely to produce objectionable odors and/or irritation" (AIHA 1989). Examination of the STPLs in light of the available data suggest to us that they are reasonable estimates for a NOAEL. These STPLs also provide valuable guidance regarding exposure time. STPLs are stated as time-weighted averages, implying that short excursions above these levels can occur without presenting a health hazard. However, as noted above, such excursions may produce objectionable odors and/or irritation. Although this is perhaps an ultraconservative approach, we suggest that these STPLs be taken as ceilings for NOAEL, at or below which no adverse effects are expected to be experienced.

A simple example may serve to illustrate our reasoning. If the time-weighted average concept is applied to the 10-min STPL of 6 mg/m^3, then a 1-min exposure to 60 mg/m^3, followed by 9 min of no exposure should be an acceptable NOAEL. Yet human volunteer data indicates HCl levels above 15 mg/m^3 are *immediately* irritating (AIHA 1989). It seems, therefore, that the time-weighted averaging concept may not adequately apply (in terms of no observed adverse effects) to "spikes" of high concentrations of HCl over short time intervals. Consequently, we recommend using the STPLs as ceiling NOAEL thresholds over the time intervals given.

It is unclear how the NOAEL might vary with exposure times of 2 to 4 h. NAS/NRC does not provide guidance for these exposure time intervals with regard to STPLs. However, guidance is provided with regard to 5 h/d, 3 to 4 d/month, the recommended STPL being 1 mg/m^3 (0.7 ppm) of HCl. The general principle followed here by NAS/NRC is to reduce the acceptable HCl concentration as the exposure time lengthens. Although we have no specific guidance from the toxicological literature or from various expert committees promulgating guidelines for time intervals of 2 to 4 h, we consider that the STPL of 3 mg/m^3 for 1 h is low enough that it could reasonably serve as a NOAEL for 2-h exposures as well. For exposures of >2 to 4 h, to be very conservative with regard to avoiding any irritation effects, we recommend decreasing the NOAEL to 1 mg/m^3 of HCl.

In conclusion, the following points can be made:

- Human exposure data are sparse regarding establishment of a NOAEL for HCL, but suggest that levels of ≥7.5 mg/m^3 are irritating.
- On the basis of animal data, various authors have suggested NOAEL levels of 0.3 to 3 mg/m^3 or TLV levels of ≥4.5 mg/m^3.
- The current TLV for HCl is 7.5 mg/m^3 (5 ppm), ceiling level.
- NAS/NRC suggests short-term public limits (STPLs) of 6 mg/m^3 for 10-min exposures, and 3 mg/m^3 for 30- or 60-min exposures.
- We suggest adoption of these values as reasonable ceiling levels for NOAELs.
- For times of >1 h, although specific information was not available, we have estimated a NOAEL of 3 mg/m^3 for 1 to 2 h, and 1 mg/m^3 of HCl for >2 to 4 h.

3.4.3 Irritation/Reversible Effects Level

Since HCl is identified as an acutely irritating gas, it is appropriate to define threshold levels that will induce irritation in humans; this irritation would probably be experienced at HCl concentrations lower than those that would cause other reversible effects. We identify irritation of the respiratory tract (including the nasopharyngeal area) as the relevant toxicological endpoint here. Although eye irritation is produced by HCl exposure, not enough dose-effect information exists to make this a usable endpoint. In addition, toxicological reports on human exposures to HCl generally indicate that effects on the upper respiratory tract predominate in terms of symptomology associated with exposure (WHO 1982).

A wide variety of values indicated as producing human irritation can be found in the literature. Thus, Henderson and Haggard (1943) note that 52 mg/m^3 (35 ppm) causes throat irritation after short (undefined) exposures. The WHO document on Cl_2 and HCl (1982) indicates that 52 mg/m^3, while below the eye irritation level, can induce sneezing, laryngitis, chest pain, hoarseness, and feelings of suffocation. Other studies with human volunteers showed that HCl concentrations of much less than 52 mg/m^3 produced irritation, however. Henderson and Haggard (1943) reported that 15 to 75 mg/m^3 (10 to 50 ppm) of HCl was the maximum concentration tolerable for a few hours. Stahl stated that no damage occurred with exposure to 7.0 mg/m^3 of HCl, but irritation of the mucous membrane could occur at 15 mg/m^3 (WHO 1982). Furthermore, irritation was said to increase above the 15 mg/m^3 level. The context associated with Stahl's assessment was the occupational environment. Thus, time of exposure might be inferred to be many hours (8-h day/40-h work week?). Kamrin (1992) refers to very old reports (late 1800s) which indicated that exposures to HCl concentrations above 15 mg/m^3 produced work *impairment* in humans. A large amount of data summarizing human responses

to various concentrations of HCl is provided in the NAS document on Cl_2 and HCl (NAS 1976). Unfortunately, most of these data do not indicate exposure duration. Hydrogen chloride concentrations of 15 mg/m^3 are listed as producing irritation (no exposure time given). Other citations in both the documentation of TLVs (ACGIH 1986) and the ERPG HCl document (AIHA 1989) report that HCl was immediately irritating when inhaled at concentrations ≥7.5 mg/m^3 (5 ppm). Summarizing the above information, there seems to be a general consensus that HCl concentrations in the range of 7.5 to 15 mg/m^3 cause some degree of irritation. The question remains regarding the threshold at which irritation might commence.

The ACGIH TLV (ceiling limit) for HCl is 5 ppm (7.5 mg/m^3). However, the documentation for this TLV (ACGIH 1986) notes that this concentration may be *on the borderline of severe irritation* (emphasis ours). This conclusion was based on statements from Elkins (referenced in ACGIH 1986) and Patty (also ACGIH 1986) that concentrations of HCl ≥ 5 ppm were immediately irritating (Elkins) and that concentrations > 5 ppm were disagreeable (Patty). If 5 ppm borders on severe irritation, the irritation threshold should be somewhat lower. NAS/NRC has set STPLs (TWA) of 4 ppm (6.0 mg/m^3) for 10-min exposures and 2 ppm (3.0 mg/m^3) for 30- or 60-min exposures (NAS 1976; AIHA 1989). AIHA comments that "excursions above these levels are likely to produce objectionable odors and/or irritation" (AIHA 1989). The nature of "excursions" is undefined. We believe these levels are conservative, reasonable, and consistent with the toxicology literature, and accordingly have accepted them as reasonable limits for NOAEL. Therefore, HCl concentrations *above* these levels might be expected to begin to produce irritation, perhaps particularly in sensitive individuals.

The STPLs we have cited from NAS/NRC cover the range of 0 to 60 min; for longer exposures, the STPL is reduced to 0.7 ppm (~1 mg/m^3) for 5 h/d, 3 to 4 d/month. There is no guidance concerning an exposure time of 2 to 4 h. Although it is unclear how the irritation threshold might vary with time of exposure over the range of several hours, we will make the following suggestions. For up to 2 h of exposure, we suggest an irritation threshold of >2 ppm. For 3 or 4 h of exposure, a very conservative approach would be to reduce the irritation threshold concentration to >0.7 ppm, since this is consistent with the NAS/NRC assessment of longer-duration exposures to HCl. All of the above irritation levels are to be considered time-weighted averages (consistent with STPL guidance); see Table 3.1 for averaging times.

The following conclusions can be drawn:

- There is general agreement in the toxicology literature that HCl concentrations of 7.5 mg/m^3 (5 ppm) to 15 mg/m^3 (10 ppm) are irritating.

- According to the ACGIH documentation, levels of 7.5 mg/m^3 may be on the borderline of severe irritation.
- The short-term public limits (STPLs) for HCl are 6.0 mg/m^3 for a 10-min exposure and 3 mg/m^3 for 30- or 60-min exposures.
- We believe levels of HCl greater than the STPLs may reasonably define *thresholds* for irritation at exposure times of 10, 30, and 60 min, particularly for sensitive members of the population.
- How irritation thresholds may vary with duration of exposure over times >1 h to 4 h is not clear.
- We suggest that the >3 mg/m^3 irritation threshold might be extended to 2 h, while for times >2 to 4 h, the irritation threshold might be reduced to >1 mg/m^3 of HCl.

3.4.4 Irreversible/Serious Effects Level

Human exposure experience from neither accidental nor occupational exposures (see Sect. 3.3 above) was available to suggest a level of HCl that might produce irreversible effects. Therefore, if some estimate is to be made, it must be based on animal exposure experiments. Toxicological data indicate that animal exposures to even very high concentrations of HCl (up to almost lethal doses) may not produce grossly obvious irreversible damage, although histopathological damage can be detected (see discussion below). In this section, we will review the evidence for pathological damage to the respiratory tract, as demonstrated by histological examination of tissues. It must be recognized, however, that such damage, even if initially severe, may be well-repaired. Although animal data indicate HCl can produce serious damage to the respiratory tract, we have concluded that there are insufficient data to define a human threshold for irreversible effects.

Darmer et al. (1974) found pathological damage to the respiratory tract and lungs of rats and mice in autopsies at 7 d postexposure, with the minimal HCl concentrations used (for a 30-min exposure period) being 3096 mg/m^3 for rats, 611 mg/m^3 for mice, and corresponding 5-min exposures of 44,700 mg/m^3 for rats and 4,768 mg/m^3 for mice. Stavert et al. (1991) found major tissue disruption in the trachea, including tissue necrosis and accumulation of exudates, when mouth-breathing (by means of tracheal tubes) rats were examined 24 h after exposure to 1937 mg/m^3 of HCl for 30 min. Buckley et al. (1984) found histopathological changes in respiratory tissues in mice exposed for 6 h/d for 5 d to 460 mg/m^3 of HCl. These exposure conditions are much longer than would be anticipated for accidental scenarios of interest to this present report. The above studies provide evidence that 2000 to 4000 mg/m^3 exposures to HCl for 30 min produce significant damage in respiratory tissues of rats, while in mice the HCl concentrations producing damage may be in the range of 500 to 600 mg/m^3. Burleigh-Flayer, Wong, and Alarie (1985) exposed guinea pigs for 30 min to concentrations of HCl

varying between 477 and 2056 mg/m^3. Histological evidence of injury to the airways and alveolar region was seen in animals exposed to 1550 mg/m^3 HCl, persisting for 15 d following exposure (maximal duration when histopathology was performed). Thus, serious respiratory injury was produced in guinea pigs by HCl concentrations of ~1500 mg/m^3 for 30-min exposures.

The Environmental Health Criteria document on Cl_2 and HCl (WHO 1982) summarizes a number of animal studies. Early (1930s) work indicated that animal exposures (cat, rabbit, guinea pig) to ≤300 mg/m^3 HCl for up to 6 h produced slight or no after-effects. Machle et al. (1942) carried out a number of exposures of guinea pigs and rabbits to HCl. Many of the experiments were for 6 h/d for 5 d, and these seem of little relevance for our purposes. Exposures to 5500 mg/m^3 for 5 min did not cause any deaths in rabbits or guinea pigs, but serious respiratory damage was noted, including necrosis of the epithelium of the trachea, bronchi, and alveoli, accompanied by pulmonary edema, emphysema, and atelectasis. Lucia et al. (as reviewed in WHO 1982) examined mice exposed for 10 min to HCl at various concentrations. Minimal superficial ulcerations were seen in the respiratory epithelium at its junction with the squamous epithelium of the external nares at HCl concentrations of 25 mg/m^3. At concentrations of 195 to 417 mg/m^3, mucosal ulceration of this epithelium was observed, while at concentrations of 734 mg/m^3, the squamous epithelium of the external nares was also affected. It should be noted, however, that the mice used in these studies may be much more sensitive than humans to effects of HCl (see discussion in Kaplan et al. 1988).

Kaplan et al. (1988) carried out HCl exposures [745 mg/m^3 (500 ppm), 7450 mg/m^3 (5000 ppm) or 14,900 mg/m^3 (10,000 ppm) for 15 min] on baboons, and argue persuasively that these primates provide a much better surrogate for human exposures than rodents. These researchers did not do histopathology on any of the animals but did carry out extensive pulmonary function testing at 3 d and 3 months postexposure. The respiratory response (breathing rate, blood gases, etc.) was also analyzed during the exposure. Exposures to 745 mg/m^3 HCl did not affect respiratory response, and none of the three concentrations employed produced significant alterations in pulmonary function (as observed at 3 d and 3 months postexposure). The two higher concentrations of HCl produced hypoxemia and changes in breathing frequency and minute volume. Chest X rays of the animals 1 h following exposure did not reveal evidence of pulmonary edema. It should be noted that these exposures were for 15 min, and results may not necessarily extrapolate to time periods of one to a few hours. The observation that no roentgenological evidence of pulmonary edema was seen in the baboon, even at exposures of 14,900 mg/m^3 for 15 min, is significant, and suggests that even a relatively high concentration of HCl, for a short exposure, may not induce "serious" pulmonary damage.

Human studies indicate that concentrations of HCl > 100 ppm (150 mg/m^3) for an exposure > 1 h produce an environment which is "intolerable" (Henderson and Haggard 1943). This descriptive terminology suggests severe irritation, not necessarily an irreversible effect.

In conclusion, the following points may be made:

- Animal toxicology studies on rodents suggest that levels of several hundred milligrams per cubic meter of HCl produce histological damage in mice when exposures are in the range of 30 min, while upwards of 2000 mg/m^3 of HCl over the same time interval is necessary for histological damage in the rat.
- Similar ranges to those of the rat were found for guinea pigs for 30-min exposures.
- Exposures of baboons to 745 mg/m^3 of HCl for 15 min did not produce obvious serious effects, and even exposures of 7450 and 14,900 mg/m^3 for 15 min did not produce evidence of respiratory functional damage or X-ray evidence of pulmonary edema.
- Primate studies appear to be the most definitive. Extrapolation regarding exposure times greater than 15 min is uncertain.
- The primate study data suggest that humans may be not seriously affected by exposures to several hundred milligrams per cubic meter of HCl for ~1 h duration. Reports of human exposure trials, however, suggest that > 150 mg/m^3 HCl might induce severe (intolerable) discomfort.
- We are unable to define a realistic irreversible effect level for humans. There were no human data to evaluate, primate studies showed no permanent respiratory damage, and rodent studies did not provide evidence for permanent (irreversible) respiratory problems.

3.4.5 Lethal Exposure Level (LC_{50})

Human exposure incidents have yielded very sparse information in terms of concentrations of HCl that might cause human lethality. Both the *Registry of Toxic Effects of Chemical Substances* (RTECS) (Sweet 1993) and *Sax's Dangerous Properties of Industrial Materials* (Lewis 1992) list two values for lowest lethal concentration (LC_{LO}) (by inhalation) for HCl for humans—1300 ppm (1937 mg/m^3) for 30 min and 3000 ppm (4470 mg/m^3) for 5 min. The lowest lethal concentration is simply the lowest concentration that has been reported to cause lethality; there are many variables associated with these values which decrease enormously their usefulness as predictors of human lethality. (E.g., was the HCl concentration measured or estimated? Was the exposure time estimated? What was the antecedent health of the exposed individual?) Therefore, these values may serve as little more than benchmarks to suggest order-of-magnitude levels which might produce lethality. In addition, both sources cited above list an LD_{LO} of 81 mg/kg for humans, by an unreported route of administration (details apparently lacking in the original literature citation).

Because of the sparseness of human data, we have chosen to use animal data, and by extrapolation to estimate lethal HCl concentrations to humans. This process implicitly assumes that the experimental animals used in the tests and humans share the same sensitivity to the lethal toxicity of HCl. This assumption is unlikely to be true (see discussion regarding baboon study, below).

Lethal animal exposures to HCl have unanimously shown that damage to the tissues of the respiratory tract (necrosis of the trachea and bronchi, atelectasis, emphysema, edema, and damage to pulmonary blood vessels) is the major pathology associated with such exposures (NAS 1976). The ERPG for HCl (AIHA 1989) also confirms this assessment, noting that HCl is mainly a strong irritant to the respiratory tract, and serious systemic effects are unlikely with repeated or prolonged exposure. All of the above is consistent with the categorization of HCl toxicologically as a primary contact irritant. The tissues at primary risk are those of the respiratory tract, which bear the brunt of the exposure. Therefore, the concentration of HCl gas in the air impinging on the respiratory tissue is the primary determinant in the extent of damage done, and not the absorbed dose. Thus, probably the most scientifically defensible extrapolation would take into account differences in anatomy, physiology, and surface area of the respiratory tract of humans and experimental animals.

All of the factors of importance in such an extrapolation are not known. We have chosen to use the following formula (EPA 1989) as an initial attempt to come to grips with respiratory differences in species:

$$\text{Regional gas dose (RGD)} = \frac{YV_t f \times t}{S} , \qquad (3.1)$$

where

Y = exposure concentration (mg/m^3),
V_t = tidal volume (m^3/breath),
f = respiratory rate (breaths/min),
S = regional surface area (cm^2) for respiratory tract area affected,
t = time of exposure (min).

The numerator of the above equation simply allows one to calculate the milligrams of HCl inhaled per minute by any given species. This dose of HCl then does a certain amount of damage to the respiratory tract, dependent on the actual milligram dose inhaled. One may then calculate a milligram per square centimeter per minute dose to specific respiratory tissues, based upon the respiratory tract surface areas of the animals involved. Multiplying by time of exposure yields the milligram per square centimeter dose to the respiratory tract. Although subsections of the total respiratory tract may be at more risk than others from HCl toxicity,

animal data suggest that damage occurs throughout the respiratory tract, and therefore we have chosen to use the *total* surface area of the respiratory tract for the value of S. Table 3.3 shows the relevant animal LC_{50} data and the various calculated parameters, based on the total respiratory tract surface area for the rat and mouse

As noted in Sect. 3.2, Darmer, Kinkead, and DiPasquale (1974) provide data on lethality for both HCl gas and HCl aerosols. They find that both the aerosol and the gas have very similar LC_{50}'s. For this reason, and because the other lethality studies do not specify gas or aerosol, we have included only the HCl gas data from the Darmer study in Table 3.3.

There was reasonable agreement among the various animal experiments that determined LC_{50}'s. The calculated total RGD differed by only about threefold from lowest to highest (i.e., 3.6×10^{-3} mg/cm^2 to 9.6×10^{-3} mg/cm^2). The 30-min exposure times provided both the highest and lowest RGD values. There was no obvious relationship between the calculated RGD and time of exposure—that is, the RGD was not consistently higher or lower as a function of a certain exposure time. The expected lethal doses based on the rat and mouse data may be estimated for humans by using the total surface area of the human respiratory tract (640,758 cm^2) (Jarabek et al. 1989). Multiplying the total RGD (mg/cm^2) from each of the animal studies by the human respiratory tract total surface area (in cm^2) gives the values shown in Table 3.4. Because no one of these values can be selected as more "correct" than any others, we have chosen to use the most sensitive animal test (i.e., Hartzell, Grand, and Switzer 1987) as the basis for estimating a lethal dose to humans. This provides a measure of conservatism, and the results appear to be consistent with primate data.

Using the value from the Hartzell, Grand, and Switzer 30-min exposure study (e.g., 2307 mg = human lethal dose, Table 3.4), an estimated lethal concentration for humans may be calculated. This so-called human equivalent concentration (HEC) can be calculated from the following equation:

$$HEC = \frac{RGD_a \times S_h}{V_{th} \cdot f_h \cdot t} \tag{3.2}$$

where

RGD_a = regional gas dose (for the animal experiment),
S_h = human respiratory tract surface area (640,758 cm^2) (Jarabek et al. 1989),
V_{th} = human tidal volume (m^3/min),
f_h = human respiratory rate (breaths/min),
$V_{th} \cdot f_h$ = human minute volume = 0.025 m^3/breath (light activity assumed) (ICRP 1994),
t = time of human exposure.

Note that the numerator of Eq. 3.2 is the human lethal dose (mg) of Table 3.4. The human minute volume of 0.025 m^3/min is for light work conditions (ICRP 1994); other conditions could be assumed, leading to different minute volumes.

Note also that body weight does not enter into this calculation, except indirectly as related to body size, which may affect respiratory tract surface area. Using the calculated human lethal dose from the animal study with the smallest RGD (Hartzell, Grand, Switzer 1987), the total dose deposited in the human respiratory tract would be 2307 mg (Table 3.4), and assuming a 60-min exposure, 1.5 m^3 of air would be inspired. Thus, the calculated 1-h human LC_{50} would be 1540 mg/m^3 (1025 ppm) (i.e., 2307 mg ÷ 1.5 m^3). This is in reasonable agreement with the human LC_{LO} values reported in RTECS (1300 ppm/30 min and 3000 ppm/5 min). None of the details surrounding the incidents leading to these LC_{LO} values are known, however. For extrapolation to other times, the Haber relationship $C \times t = k$ (constant) was used, for the following reasons. First, examination of the animal data revealed that the $C \times t = k$ relationship was reasonable for the small number of data points available. Second, ten Berge, Zwart, and Appelman (1986) recommend this relationship for HCl, based on the study of Darmer, Kinkead, and DiPasquale. The corresponding lethal concentrations for humans for exposures of 30, 15, and 5 min, respectively, would therefore be 3100 mg/m^3 (2100 ppm), 6200 mg/m^3 (4100 ppm), and 18,500 mg/m^3 (12,300 ppm). (If $C \times t = k$, for 60-min exposures C = 1540 mg/m^3, and therefore k = 92,000 mg-min/m^3. For other times C is calculated directly using this k value.) Figure 3.2 shows the human lethality curve for HCl using this equation. An envelope of uncertainty is also shown on the figure, employing the highest and lowest levels from the 95% confidence limits of the animal data [i.e., 1827 mg (Hartzell, Grand, and Switzer 1987) and 7048 mg (Darmer, Kinkead, and DiPasquale 1974), which converts into calculated lethal doses for humans of 1220 mg/m^3 and 4700 mg/m^3 for 60-min exposures]. These upper- and lower-bound curves were drawn using the same $C \times t = k$ relationship (but using a different k, calculated from the data: k = 73,000 mg-min/m^3 for the lower-bound curve, and k = 280,000 mg-min/m^3 for the upper-bound curve).

In using the LC_{50} data for accident calculations, it would be appropriate to incorporate the analytical form of Haber's law. However, not all accident situations or calculational methods allow for analytic solutions. During the first 5 min we have no lethality data and therefore recommend an LC_{50} value from 1 to 5 min that is the same as the 5-min value. During the remainder of the first hour, because of the strong concentration dependence, we recommend short averaging times (i.e., 5 min). Beyond 1 h, the slope decreases, and the averaging time may be extended to 10 min. We do not recommend the use of Haber's law beyond 2 h, since the longest time in our data was 1 h.

Table 3.3. LC_{50} concentrations of HCl for various species/times of exposure and calculated regional gas dose (RGD) to respiratory tissues based on this data

Animal	LC_{50} (95% confidence limit) (ppm)	Exposure time (min)	Inhaled dose per unit time (mg/min)	Total inhaled dose[a] (mg)	Total RGD received during exposure[b] (mg/cm^2)	Reference
Rat	40,989 (34,803–48,272)	5	4.5	22.5	6.5×10^{-3}	Higgins et al. 1972
Rat	4701 (4129–5352)	30	0.52	15.6	4.5×10^{-3}	Darmer et al. 1974
Rat	3817 (2980–4890)	30	0.42	12.6	3.6×10^{-3}	Hartzell et al. 1987
Rat	3124 (2829–3450)	60	0.35	21.0	6.0×10^{-3}	Wohlslagel et al. 1976
Mouse	13,745 (10,333–18,283)	5	0.49	2.5	8.4×10^{-3}	Higgins et al. 1972
Mouse	2644 (2264–3086)	30	0.095	2.8	9.6×10^{-3}	Darmer et al. 1974
Mouse	1108 (874–1404)	60	0.040	2.4	8.1×10^{-3}	Wohlslagel et al. 1976

Note: The relevant animal physiological data were as follows: *minute volume of inspired air* ($V_t \times f$), rat = 74 cm^3/min, mouse = 24 cm^3/min; *total respiratory tract surface area*, rat = 3473 cm^2, mouse = 298 cm^2. (Animal data from Altman and Dittmer 1964; Jarabek et al. 1989; EPA 1989.)

[a]Exposure time (col. 3) × inhaled dose per unit time (col. 4).

[b]RGD = Regional Gas Dose [Eq. 3.1] × time of exposure; i.e., total inhaled dose (col. 4) ÷ respiratory tract surface area (rat or mouse). For HCl, ppm concentration can be converted to mg/m^3 by the equation 1 ppm = 1.49 mg/m^3.

Table 3.4. Calculated human lethal dose based on animal lethality studies

Animal study	Human lethal dose[a] (mg)
Rat — 5 min	4165
Rat — 30 min (Darmer et al.)	2883
Rat — 30 min (Hartzell et al.)	2307
Rat — 60 min	3845
Mouse — 5 min	5382
Mouse — 30 min	6151
Mouse — 60 min	5190

[a]Based upon respiratory tract total surface area for humans of 640,758 cm^2.

Whenever human health endpoints are estimated by extrapolation or calculations from animal data, there are obvious concerns about how valid such estimates might be. In the case of the HCl lethality estimates calculated above, this question cannot be answered from examination of human data, since such data are lacking. For HCl, which is a primary irritant with its main target organ being the respiratory tract, the most important factors governing degree of damage (and subsequent toxicological response) may be concentration of the gas and time of exposure. Using available animal data, Table 3.5 presents various physiological responses as a function of total exposure (i.e., $C \times t$). Although our estimated $C \times t$ (92,000 mg-min/m^3) for human lethality from exposure to HCl lies in the range of $C \times t$ doses producing lethality in other species, this does not increase our confidence in this estimate for the following reasons. First, there is a very broad range of $C \times t$ producing lethality in various species (from 24,000 to 450,000 mg-min/m^3). Second, the human lethality estimate we derived was based on animal data (rat and mouse) and therefore, perforce, must lie within the ranges expressed in Table 3.5.

The baboon data gathered by Kaplan et al. is of relevance, however, because of greater physiological similarities between nonhuman primates and man, and because of the significant differences in respiratory physiology and anatomy between man and rodents (see Kaplan et al. 1988 for a discussion of these differences). Kaplan et al. (1988) exposed anesthesized baboons for 15 min to 500, 5000, or 10,000 ppm (745, 7450, or 14,900 mg/m^3) of HCl in a head-only

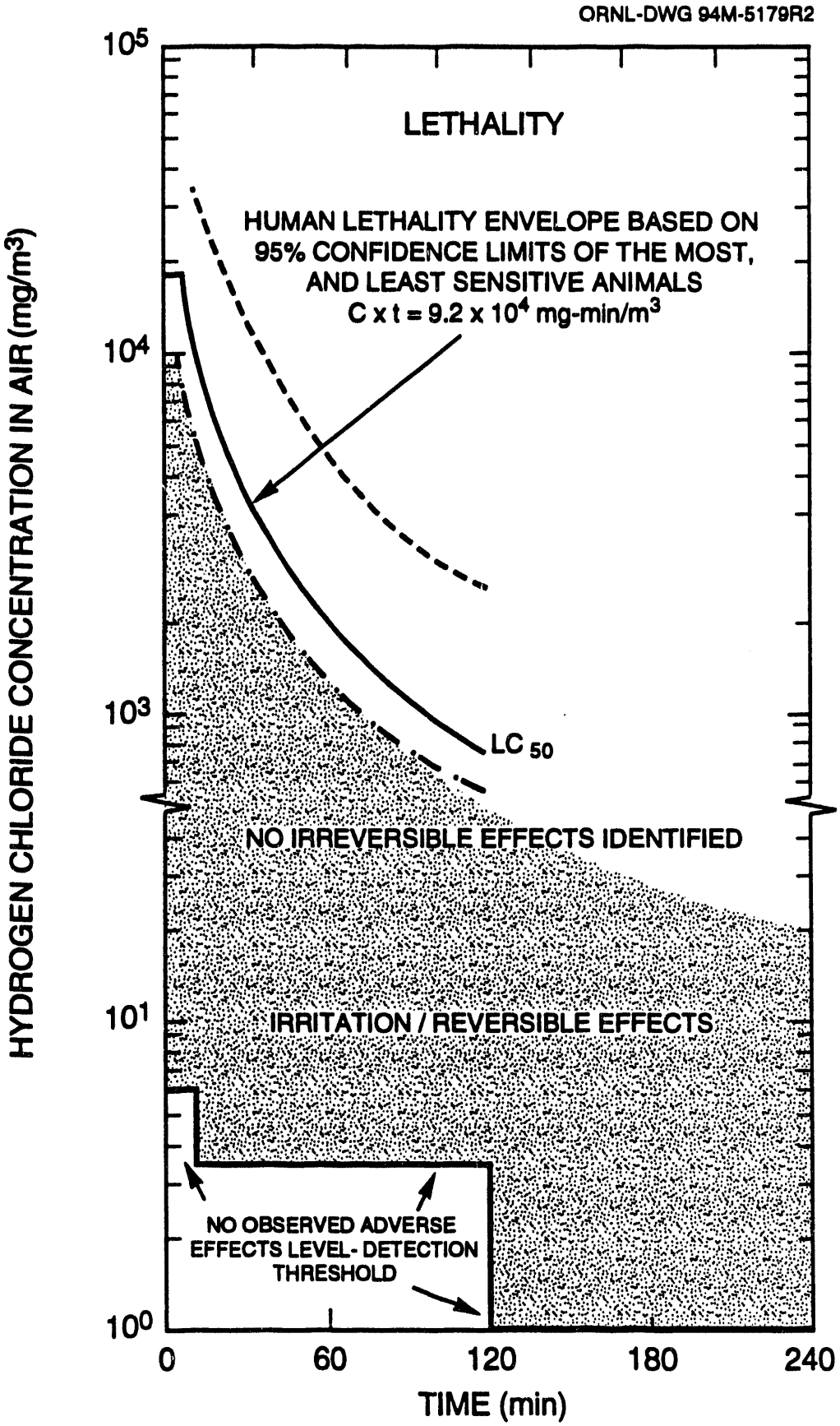

Fig. 3.2. Detailed summary of acute endpoints for hydrogen chloride.

mode. Although severe effects on respiratory response and arterial blood gases were clearly evident at the two higher doses, no results reported in the paper indicated that the baboons were lethally affected. Other studies by this same group, summarized in Kaplan et al. (1988), found that one baboon survived a 5-min exposure to 30,000 ppm (44,700 mg/m^3) and another animal survived a 10-min exposure to 15,000 ppm (22,350 mg/m^3). The concentrations from the baboon experiments provide a modicum of confidence that the calculated human values may at least be in the correct range. (For baboons, HCl concentrations of 44,700 mg/m^3 for 5 min, 22,350 mg/m^3 for 10 min, and 14,900 mg/m^3 for 15 min were not lethal. The estimated lethality value for humans calculated above was 18,500 mg/m^3 for 5 min, 9200 mg/m^3 for 10 min, and 6200 mg/m^3 for 15 min.)

The rodent LC_{50} data on which human lethality estimates were based extend to only 60 min of exposure time. Any extrapolation to longer exposure times involves an additional level of uncertainty, in addition to the species-to-species uncertainty. We have used Haber's law ($C \times t = k$) to estimate human lethality over the time period 0 to 60 min. Although the sparse rodent lethality data available support, in a general way, the Haber relationship, we have no experimental data for HCl that might suggest a time span for which the Haber relationship might be valid. We make the suggestion that the Haber relationship might be extended to exposure times of 2 h, but do not have any assurance that exposure times of >2 h may be valid using Haber's law. To err, if at all, on the side of conservatism, we do not recommend extending the extrapolation to times > 2 h.

We have a similar lack of confidence in using the $C \times t = k$ relationship for very short times of exposure (i.e., 1–2 min). As can be seen from the slope of the curve in Fig. 3.2, the hyperbolic nature of the equation results in very high C values (>50,000 mg/m^3) for 1- to 2-min exposures. As was pointed out previously, HCl is a primary irritant, and the absolute concentration of such substances in air, rather than total dose, is of most importance in assessing their toxic effect. It may very well be that concentrations of HCl of ≥50,000 mg/m^3 will produce so much respiratory damage that they will be lethal, even if inhaled in one breath. Because of total lack of animal data regarding these very short times, we feel it is unwise to simply extend the Haber relationship upward in an asymtotic manner, and we recommend that the concentration calculated for the 5-min exposure (18,500 mg/m^3) also be used for the time interval 0 to 5 min. Assuming that the lethal concentration for 5 min is also the lethal concentration for <5 min is very conservative, but has the virtue that it does not increase HCl concentrations estimated to cause lethality to unrealistic (and untested) levels.

Table 3.5. Physiological effects vs total exposure (gas concentration × time) produced by HCl in animals

Effect	$C \times t$ (mg-min/m^3)	Species	Reference
Lethal to 50%	100,000–310,000	Rats, mice	Darmer et al. 1974 Higgins et al. 1972 Wohlslagel et al. 1976 Hartzell et al. 1987
Lethal (level unspecified)	450,000	Rabbits, guinea pigs	Lehmann in NAS 1976
Lethal to 100%	195,000–360,000	Rabbits, guinea pigs	Machle et al. 1942
Lowest dose causing death	128,000–238,000	Rats	Darmer et al. 1974
Lowest dose causing death	24,000–53,000	Mice	Darmer et al. 1974
Respiratory distress, cloudy cornea	150,000	Rabbits, guinea pigs	Lehmann in NAS 1976 Machle et al. 1942
Running nose, salivation, irritation	< 76,000	Cats, rabbits	Lehmann in NAS 1976
No deaths	28,000	Rabbits, guinea pigs	Machle et al. 1942

The following conclusions may be drawn:

- Human data are lacking from which to estimate lethal doses of HCl, with the exception of two LC_{LO} values (see Sect. 3.4.5).
- Animal exposure data (rodent, exclusively) were available for the time period 0–60 min and were used to calculate a lethal dose of HCl (based on total respiratory surface area) for the various species and times of exposure.
- The lowest lethal regional gas dose from the animal studies (3.6×10^{-3} mg/cm^2) (mg) was used to calculate a lethal human exposure level—i.e., 1540 mg/m^3 for a 60-min exposure.
- Lethal concentrations at other exposure times were calculated by the equation $C \times t = k$, where $k = 92{,}000$ mg/m^3.
- Use of the $C \times t = k$ relationship for time periods > 2 h is discouraged.
- For very short time periods (0–5 min), due to uncertainty regarding the HCl concentration that might be expected to more or less instantaneously cause lethal respiratory damage, we have chosen an ultraconservative approach, and suggest that the 5-min LC_{50} HCl concentration (18,500 mg/m^3) be used for these times.
- Baboon data provide some supporting evidence that the estimated human lethality values may be reasonable (at least in the same order of magnitude). Human LC_{LO} data also support, in general, the human lethality estimates.

3.5 REFERENCES

Altman, P. L., and D. S. Dittmer, eds. 1964. *Biology Data Book*, Pub. Federation of American Societies for Experimental Biology, Washington, D.C., p. 220.

American Conference of Governmental Industrial Hygienists (ACGIH) 1986. "Hydrogen Chloride," p. 313 in *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th ed., ACGIH, Cinncinnati, Ohio.

American Industrial Hygiene Association (AIHA) 1989. *Emergency Response Planning Guideline: Hydrogen Chloride*, AIHA Emergency Response Planning Guideline Committee, Akron, Ohio, March 28.

Barrow, C. S., Y. Alarie, J. C. Warrick, and M. F. Stock 1977. "Comparison of the Sensory Response in Mice to Chlorine and Hydrogen Chloride," *Arch. Environ. Health* **32**, 68–76.

Buckley, L. A., X. Z. Jiang, R. A. James, K. T. Morgan, and C. S. Barrow 1984. "Respiratory Tract Lesions Induced by Sensory Irritants at the RD50 Concentration," *Toxicol. Appl. Pharmacol.* **74**, 417–29.

Burleigh-Flayer, H., K. L. Wong, and Y. Alarie 1985. "Evaluation of the Pulomonary Effects of HCl Using CO_2 Challenges in Guinea Pigs," *Fund. Appl. Toxicol.* **5**, 978–85.

Clayton, G. D., and F. E. Clayton, eds. 1981. *Patty's Industrial Hygiene and Toxicology*, 3rd ed., John Wiley and Sons, New York, pp. 2937–3070.

Darmer, K. I., E. R. Kinkead, and L. C. DiPasquale 1974. "Acute Toxicity in Rats and Mice Exposed to Hydrogen Chloride Gas and Aerosols," *Amer. Ind. Hyg. Assoc. J.* **35**, 623–31.

Finnegan, M. J., and M. E. Hobson 1989. "Prolonged Hypoxaemia Following Inhalation of Hydrogen Chloride Vapour," *Thorax* **44**, 238–39.

Hartzell, G. E., A. F. Grand, and W. G. Switzer 1987. "Modeling of Toxicological Effects of Fire Gases. VI. Further Studies on the Toxicity of Smoke Containing Hydrogen Chloride," *J. Fire Sciences* **5**, 368–91.

Hazardous Substances Data Bank (HSDB) (on-line database) 1993. Bethesda, Md.: National Library of Medicine: 1985–1993 (revision date 1993, Apr. 30), *Hydrochloric Acid.*

Henderson, Y., and H. W. Haggard 1943. *Noxious Gases*, Reinhold Pub. Co., New York, p. 126.

Higgins, E. A., V. Fiorca, A. A. Thomas, and H. V. Davis 1972. "Acute Toxicity of Brief Exposures to HF, HCl, NO_2, and HCN with and without CO," *Fire Technol.* **8**, 120–30.

International Commission on Radiological Protection (ICRP) 1994. *Human Respiratory Tract Model for Radiological Protection*, ICRP Publication 66, *Annals of the ICRP* **24**(1-4), in press.

Jarabek, A. M., M. G. Menache, J. H. Overton, Jr., M. L. Dourson, and J. F. Miller 1989. "Inhalation Reference Dose (RfD_i): An Application of Interspecies Dosimetry Modeling for Risk Assessment of Insoluble Particles," *Health Physics* **57**, supplement 1, 179–83.

Kamrin, M. A. 1992. "Workshop on the Health Effects of HCl in Ambient Air," *Regul. Toxicol. Pharmacol.* **15**, 73–82.

Kaplan, H. L., A. Anzueto, W. G. Switzer, and R. K. Hinderer 1988. "Effects of Hydrogen Chloride on Respiratory Response and Pulmonary Function in the Baboon," *J. Toxicol. Environ. Health* **23**, 473–93.

Lewis, R. J., Sr. 1992. *Sax's Dangerous Properties of Industrial Materials*, 8th ed., Van Nostrand Reinhold, New York, vol. 3, p. 1892.

Machle, W., K. V. Kitzmiller, E. W. Scott, and J. F. Treon 1942. "The Effect of the Inhalation of Hydrogen Chloride," *J. Ind. Hyg. and Toxicol.* **24**, 222–25.

National Academy of Sciences (NAS)/National Research Council 1976. *Medical and Biologic Effects of Environmental Pollutants: Chlorine and Hydrogen Chloride*. National Academy of Sciences, Washington, D.C., pp. 125–44.

National Fire Protection Association (NFPA) 1971. *Manual of Hazardous Chemical Reactions, 1971*, Batterymarch Park, Quincy, Mass.

National Fire Protection Association (NFPA) 1986. *Fire Protection Guide on Hazardous Materials*, 9th ed., NFPA No. SPP-1E, Batterymarch Park, Quincy, Mass., pp. 49–53.

Rosenthal, T., G. L. Baum, U. Frand, and M. Molho 1978. "Poisoning Caused by Inhalation of Hydrogen Chloride, Phosphorus Oxychloride, Phosphorus Pentachloride, Oxalyl Chloride and Oxalic Acid," *Chest* **73**, 623–26.

Ruth, J. H. 1986. "Odor Thresholds and Irritation Levels of Several Chemical Substances: A Review," *Am. Ind. Hyg. Assoc. J.* **47**, A-142–A-151.

Sellakumar, A. R., C. A. Synder, J. J. Solomon, and R. E. Albert 1985. "Carcinogenicity of Formaldehyde and Hydrogen Chloride in Rats" *Toxicol. Appl. Pharmacol.* **81**, 401–6.

Stavert, D. M., D. C. Archuleta, M. J. Behr, and B. E. Lehnert 1991. "Relative Acute Toxicities of Hydrogen Fluoride, Hydrogen Chloride, and Hydrogen Bromide in Nose- and Pseudo-Mouth-Breathing Rats," *Fund. Appl. Toxicol* **16**, 636–55.

Sweet, D. V., ed. 1993. *Registry of Toxic Effects of Chemical Substances* (RTECS), National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, RTECS Accession MW402500.

ten Berge, W. F., A. Zwart, and L. M. Appelman 1986. "Concentration-Time Mortality Response Relationship of Irritant and Systemically Acting Vapours and Gases," *J. Hazard. Materials* **13**, 301–9.

U.S. Environmental Protection Agency (EPA) 1989. *Interim Methods for Development of Inhalation Reference Doses*, EPA/600/8-88/066F, Office of Health and Environmental Assessment, Washington, D.C.

Windholz, M., S. Budvari, R. F. Blumetti, and E. S. Otterbein, eds. 1983. *The Merck Index*, 10th ed., Merck & Co., Rahway, N.J., no. 4701.

Wohlslagel, J., L. C. Dipasquale, and E. H. Vernot 1976. "Toxicity of Solid Rocket Motor Exhaust: Effects of HCl, HF, and Alumina on Rodents," *J. Combustion Toxicol.* **3**, 61–70.

World Health Organization (WHO) 1982. *Environmental Health Criteria 21*, "Chlorine and Hydrogen Chloride," WHO, Geneva, Switzerland.

4

FLUORINE

4. FLUORINE

4.1 SUMMARY

Fluorine (F_2) is a pale yellow gas with a choking, irritating odor. It is the most reactive nonmetal element and will react vigorously with most oxidizable substances at room temperature, frequently with ignition. Fluorine reacts violently with water to form hydrogen fluoride and ozone (OSHA 1989).

Fluorine is not flammable but it is a strong oxidizer. Fluorine ignites bromine, iodine, sulfur, crystallized silicon, alkaline metals, and a number of organic substances (i.e., benzene and ethyl alcohol). It explodes on contact with hydrogen and attacks chlorides, bromides and iodides (ILO 1983). Gaseous diffusion plant operations use F_2 to convert UF_4 to UF_6. It is also used as an oxidizer in rocket fuel systems and in the manufacture of various fluorides and fluorocarbons (ILO 1983).

Fluorine is a severe irritant of the eyes, mucous membranes, skin, and lungs. In humans, the inhalation of high concentrations causes laryngeal spasm and bronchospasm, followed by the delayed (1 to 2 d) onset of pulmonary edema. Symptoms progress for 1 to 2 d and then regress slowly over a period of 10 to 30 d. Death usually results from respiratory damage and pulmonary edema. At sublethal levels, severe local irritation and laryngeal spasm will preclude voluntary exposure to high concentrations. A blast of fluorine gas on the shaved skin of a rabbit caused a second-degree burn. Lower concentrations cause severe burns of insidious onset, resulting in ulceration, similar to effects produced by hydrogen fluoride.

Table 4.1 provides a summary of the available acute inhalation toxicity data for the five endpoints of concern. These data are presented graphically in Fig. 4.1.

The estimates of health effects provided in this section are intended to be used only in assessing the consequences of postulated accidents in support of the Safety Analysis Report (SAR) program. This information will be used to determine the adequacy of the controls used to manage the risk of the operation being evaluated. The toxicity estimates are *not* intended to be used as acceptable exposure levels for occupational personnel or members of the public. Furthermore, the guidelines in this section are *not* intended for use in developing emergency exposure levels.

Table 4.1. Summary of effect levels for fluorine

Endpoint	F_2 concentrations and time[a]	Averaging time (min)	Effects/comments
Detection odor threshold	C = 0.2; t > 0		Choking, irritating odor
No observed adverse effects level (NOAEL)	C = 3.1; t ≤ 15	5	
	C = 1.6; t > 15 to ≤120	15	
Irritation/reversible effects	C = 80; t ≤ 3	3	Irritation of eyes, nose, and respiratory system
	C = 37; t > 3 to ≤5	2	
	C = 16; t > 5 to ≤15	5	
	C = 12; t > 15 to ≤120	15	
Irreversible effects	C = 40; t ≤ 30	15	Respiratory damage
	C = 16; t > 30 to ≤120	15	
Lethal effects	C = 516; t ≤ 5	5	LC_{50}; respiratory damage, pulmonary edema, hemorrhaging
	C = 516 − 24.3 × t; t > 5 to ≤15	5	
	C = 273 − 3.5 × t; t > 15 to ≤ 60	15	

[a]Concentration (C) = mg/m^3; time (t) = min.

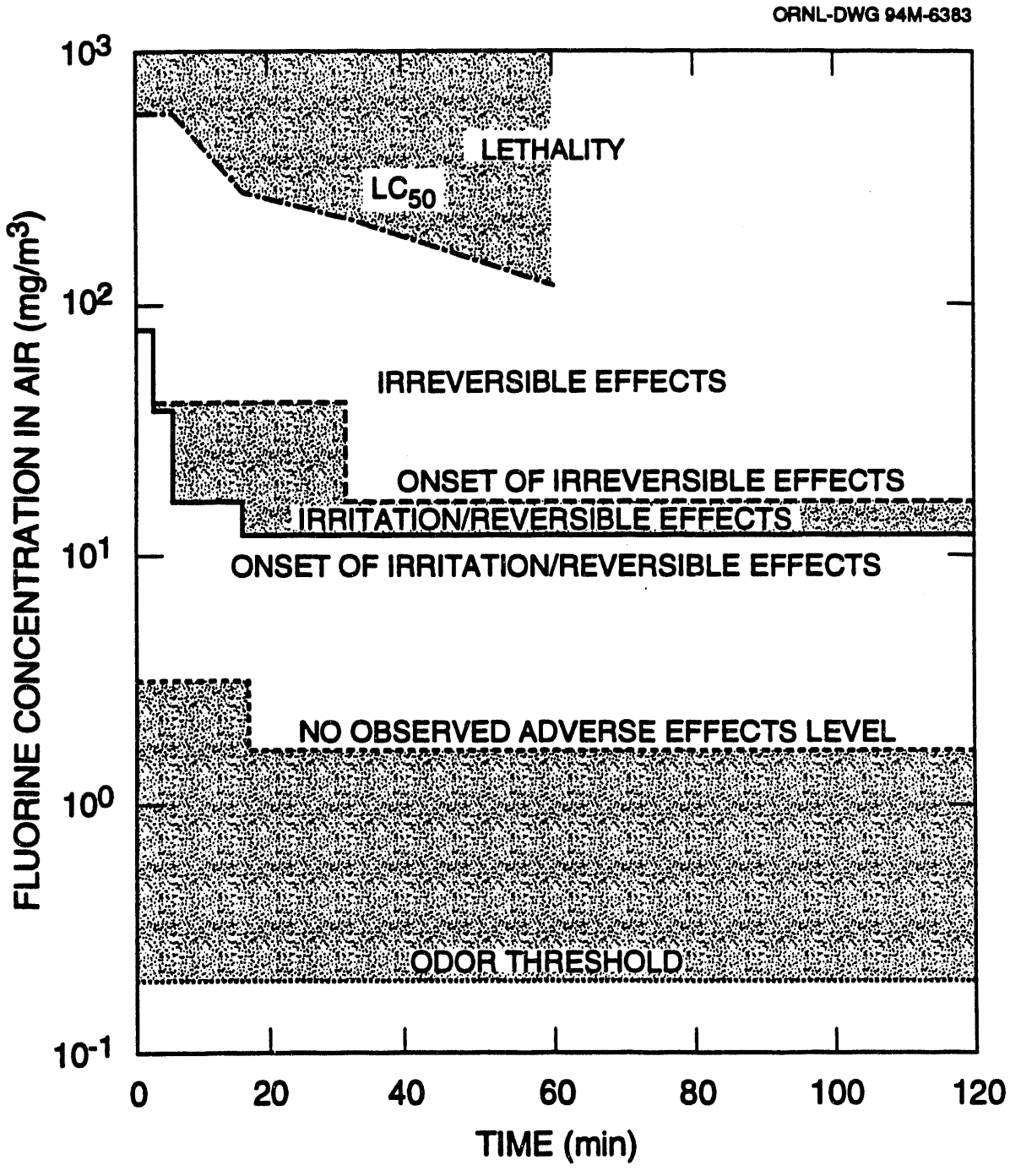

Fig. 4.1. Summary of acute endpoints for fluorine.

4.2 PHYSICOCHEMICAL PROPERTIES OF FLUORINE

4.2.1 Background

This analysis was prepared to give toxicity information about fluorine (F_2) specifically regarding the human health effects that may result from an acute inhalation exposure. Harmful health effects from a substance such as F_2 are determined by many factors. These factors determine what effects will occur and what the type and severity of those health effects will be, and include the dose, duration, route or pathway by which exposure occurs (breathing, eating, drinking, or skin contact), other chemicals to which the individual is exposed, and individual characteristics such as age, gender, nutritional status, family traits, lifestyle, and state of health.

Fluorine and its compounds are primarily obtained directly or indirectly from calcium fluoride (fluorspar) and phosphate rock (fluorapatite) or chemicals derived from them. Elemental F_2 is most commonly produced by electrolysis of a hydrogen fluoride/potassium fluoride solution. Gaseous diffusion plant operations use F_2 to convert UF_4 to UF_6. It is also used as an oxidizer in rocket fuel systems and in the manufacture of various fluorides and fluorocarbons (ILO 1983).

4.2.2 Physical Properties

Fluorine is the most electronegative of all the elements and, in pure concentrated form, reacts violently with a wide range of substances. Fluorine has a molecular weight of 38, a boiling point of −188°C, a specific gravity of 1.31 at 21°C, and a vapor density of 1.695 g/L (air = 1). A summary of the physical properties of fluorine is given in Table 4.2.

Fluorine is a pale yellow gas with a choking, irritating odor. It is the most reactive nonmetal and reacts vigorously with most oxidizable substances at room temperature, frequently with ignition. Fluorine is a halogen but, unlike chlorine, bromine and iodine, will form only fluorides, not fluorates and perfluorates. Fluorine reacts violently with water to form hydrogen fluoride and ozone (OSHA 1989). It reacts with nitric acid to form fluorine nitrate, an explosive gas.

Although F_2 is not flammable, it is a strong oxidizer and reacts with most oxidizable materials at room temperature (NFPA 1986). Fluorine ignites bromine, iodine, sulfur, crystallized silicon, alkaline metals, and a number of organic substances (i.e., benzene and ethyl alcohol). It explodes on contact with hydrogen and attacks chlorides, bromides, and iodides (ILO 1983). Combustion and decomposition products include hydrogen fluoride and oxygen difluoride

Table 4.2. Physical properties of fluorine

Property	Description
State	Gas at normal conditions of temperature and pressure
Color	Pale yellow
Molecular weight	38.0 g/mole
Boiling point (1 atm)	−188.14°C
Melting point (1 atm)	−219°C
Density (vapor)	1.695 (air = 1.000)
Vapor pressure	71 atm @ 20°C
Solubility in water	Reaction

Sources: ACGIH 1993; APCI 1993.

(APCI 1990). Elevated temperatures may cause cylinders containing F_2 to burst. Fluorine reacts with nearly all materials, including metal containers and piping if the passivating film is broken. Absolute cleanliness is required in conveying systems to prevent localized reactions and subsequent fire hazards. Special lubricant-free valves are used to prevent reactions with lubricants.

4.3 EXISTING HUMAN HEALTH TOXICITY DATA

Fluorine is a severe irritant of the eyes, mucous membranes, skin, and lungs. After an acute inhalation exposure, F_2 is severely irritating and corrosive to the mucous membrane of the nose, throat, and respiratory tract, causing cough, choking, difficulty in breathing, and pneumonitis (APCI 1990). Fluorine may be converted to hydrofluoric acid in the lungs and other moist tissues. Inhalation of high concentrations results in delayed (1 to 2 d) pulmonary edema and hemorrhaging. Symptoms progress for 1 to 2 d and then regress slowly over a period of 10 to 30 d (Dreisback 1983). When death occurs, it is usually the result of respiratory damage and pulmonary edema. Fluorine is highly irritating and corrosive to the skin and eyes, causing chemical burns, lesions, scarring, and possible loss of vision. The target system for inhalation exposures is the respiratory system. Chronic health effects of ingestion include mottled enamel of teeth, osteosclerosis, and calcification of ligaments (APCI 1990).

Fluorine is not listed as a carcinogen or potential carcinogen by the International Agency for Research on Cancer (IARC). Based on limited data, it is not a developmental toxicant (Smith 1935). The Agency for Toxic Substances and Disease Registry (ATSDR), in its *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine (F)*, states that no studies were located regarding developmental and reproductive effects in humans or animals after inhalation or oral exposures to fluoride (ATSDR 1991). Persons with impaired pulmonary function may be at an increased risk from exposure to F_2.

4.3.1 Summary of Acute Health Effects: Human Fluorine Studies

Keplinger and Suissa (1968) conducted a study in which five human volunteers were exposed to F_2. These tests were designed to test for irritation only. A face mask was connected to an inhalation chamber so that a known concentration of F_2 in the air could be pulled through the mask. The concentration of F_2 in the air leaving the mask also was measured analytically. The human volunteer placed his face into the mask, which covered the eyes and nose, but not the mouth. The subject could withdraw quickly from the mask and could inhale uncontaminated air through his mouth at any time. These data indicate that irritation to the eye was the most sensitive index of a subjective effect. A concentration of 10 ppm (16 mg/m^3) was not irritating to the eyes, nose, or respiratory tract after a 15-min exposure. Concentrations on the order of 23 ppm (37 mg/m^3) were slightly irritating to the eyes, while concentrations as high as 25 ppm (40 mg/m^3) could be inhaled intermittantly for 5 min without respiratory discomfort. A concentration of 50 ppm (80 mg/m^3) was irritating to the eyes and nose after 3 min of exposure. Concentrations of 67 ppm (107 mg/m^3) to 100 ppm (160 mg/m^3) were very irritating to the eyes, nose, and skin, and respiratory difficulty was experienced after a few seconds. The volunteers concluded that a concentration of 100 ppm (160 mg/m^3) was extremely uncomfortable and that they would evacuate an area immediately if such concentrations were present. When exposure to F_2 was repeated at weekly intervals, the volunteers did not notice as much irritation as experienced from the first exposure. A few repeated, intermittent exposures at a concentration of 10 ppm (16 mg/m^3) were made. Exposure for 3 to 5 min every 15 min over a 2- or 3-h period caused slight irritation to the eyes and skin but no other subjective effects (Keplinger and Suissa 1968).

Outdoor spill tests conducted by the U.S. Air Force and reported by Rickey (1959) reported that a single, short-term exposure of two human volunteers at 25 ppm (40 mg/m^3) caused sore throats and minor chest pain. A concentration of 50 ppm (80 mg/m^3) made breathing impossible without respiratory protective equipment (Keplinger and Suissa 1968). Belles (1965) reported that nine male volunteers all tolerated repeated short-term inhalation exposures up to 10 ppm (16 mg/m^3) without "intolerable discomfort." The majority of subjects found that 15 ppm (24 mg/m^3) to 25 ppm (40 mg/m^3) caused some nasal and eye irritation after just two

or three breaths. Skin exposure tests indicated that reaction with body hair and dermal irritation may be expected between 100 ppm (160 mg/m^3) and 200 ppm (320 mg/m^3) (Ricca 1970). Direct exposure of the skin to pure F_2 and interhalogen fluorides can cause severe burns in 0.2 s and thermal flash burns (comparable to those produced by an oxyacetylene flame) in 0.6 s (Braker, Mossman, and Seigel 1977).

Ricca (1970) established short-term occupational exposure limits known as emergency exposure limits (EELs) in his review of the acute toxicity of elemental F_2. The EELs apply to situations which require the quantitative assessment of the risk to personnel who may be exposed briefly to very high concentrations of airborne toxicants. EELs are designed to limit occupational exposures, but not necessarily without some discomfort or rapidly reversible irritation or subtle changes in members of a healthy adult population. EELs are used essentially as disaster control guidelines for unplanned hazardous situations. It is assumed that functional impairment which will prevent self-rescue will not be tolerated, and the population is controlled so that no individual is present who is predisposed to potentiation or hypersensitivity response. Very mild reversible pathological symptoms are acceptable for EEL exposures. Ricca's EELs for F_2 are 39 mg/m^3 for 5 min, 23 mg/m^3 for 15 min, 18 mg/m^3 for 30 min, and, 15 mg/m^3 for 60 min. Ricca contends that above the no-effect level, pathological symptoms are more dependent on concentration than on exposure time.

4.3.2 Summary of Chronic Health Effects: Human Fluorine Studies

Lyon (1962) conducted a 7-year study of 61 workers exposed to F_2. The average F_2 values in the air were compiled for the years 1952 through 1959. It should be pointed out that reliable techniques for differentiating between F_2 and hydrogen fluoride in air were not available. In this study, F_2 was considered to be present if during sampling (1) the characteristic odor of F_2 was detected or (2) the characteristic odor of hydrogen fluoride was not detected in circumstances where the contaminant was likely to be F_2. A total of 2535 randomly collected urine samples were obtained from the 61 exposed employees during the years 1952 through 1959. This study revealed an average daily F_2 urine concentration of 1.1 mg/L. Yearly average exposures to F_2 in air ranged from 0.3 to 1.4 ppm (0.5 to 2.2 mg/m^3). Exact exposures to the individuals cannot be established, but the group included (1) individuals who normally spent 50 to 60% of their daily work time for periods of 7 to 9 months in the area, and (2) individuals who spent as little as 10% of their daily work time in the area but who did this almost continuously. Criteria used for this study were illness clinic visits (all causes), respiratory complaints, and absences as a result of respiratory complaints. The study showed that the exposed group had a better health record than the 2000 to 3000 employees used as controls. From their medical records, Lyon found no impairment to the health of people working in F_2 concentrations up to a yearly average of 1.4 ppm. Although this study was

conducted over a 7-year period, the National Institute for Occupational Safety and Health (NIOSH) and others were critical of the findings because the study, in their opinion, was a compilation of data on workers who may have had some short-term exposures to F_2 rather than a study of workers constantly exposed to the chemical.

4.3.3 Summary of Acute Health Effects: Animal Fluorine Studies

Keplinger and Suissa (1968) exposed mice, rats, and guinea pigs to F_2 for 5, 15, 30, and 60 min. Fluorine at 10,000 ppm (16,000 mg/m^3) caused 100% mortality in all animals following an exposure of 60 min. Three hours of exposure at 200 ppm (320 mg/m^3) caused mortalities of 100% in mice, 96% in rats, and 85% in guinea pigs. Fluorine caused severe, corrosive damage to the respiratory tract, as shown by edema, emphysema, and hemorrhage. The lethal concentration to 50% of the population (LC_{50}) for these animals ranged from 150 ppm (233 mg/m^3) for mice (exposure time of 60 min) to 700 ppm (1,088 mg/m^3) for rats (exposure time of 5 min). LC_{50}'s for all three species at the different exposures were similar, suggesting comparable species sensitivity and perhaps a common cause of death. Signs of intoxication at lethal concentrations included irritation of the eyes and nose (as shown by conjunctivitis), pawing at the nose, increased secretions, and sneezing. Dyspnea, loss of body weight, general weakness, and death were observed. Very few signs of intoxication were observed immediately after exposure. Frequently, the animals looked quite well (with some irritation of the eyes and nose). Dyspnea and lethargy were not observed until several hours after exposure. At lethal concentrations, there was little or no visible damage to the liver or kidneys. Death was attributed to respiratory failure. With the exception of very high concentrations [≥5000 ppm (≥8000 mg/m^3)], death occurred approximately 12 to 18 h after exposure. A few deaths were recorded about 24 h after exposure. In general, if an animal lived for 48 h, it survived. At sublethal concentrations the target organs affected were the lungs, the liver, and the kidneys. Effects in the lung were observed immediately after exposure. Effects in the kidney and the liver were observed on the 7th to 14th day following exposure. Pathology in the lung or kidney occurred from exposure to almost the same concentration. Exposure to higher concentrations was necessary before effects were observed in the liver. Exposure to concentrations at or below 100 ppm (160 mg/m^3) for 5 min, 70 ppm (112 mg/m^3) for 15 min, 55 ppm (88 mg/m^3) for 30 min, or 45 ppm (72 mg/m^3) for 60 min caused no apparent effects in the animals (Keplinger and Suissa 1968).

A blast of F_2 gas on the shaved skin of a rabbit caused a second-degree burn; lower concentrations caused severe burns of insidious onset, resulting in ulceration, similar to that produced by hydrogen fluoride (ILO 1983).

4.4 ESTIMATES OF HUMAN HEALTH EFFECTS

4.4.1 Odor Threshold

John Amoore and Earl Hautala (1983), in their discussion on odor as an aid to chemical safety, determined the odor threshold for F_2 (in air) to be approximately 0.14 ppm (0.2 mg/m^3) (Amoore and Hautala 1983). In the *Occupational Health Guideline for Fluorine*, the Occupational Safety and Health Administration (OSHA) states that F_2 can be detected by odor in concentrations of only a few parts per million (OSHA 1978). Belles and coworkers reported a series of tests measuring the exposure of nine male volunteers. The subjects' odor thresholds were found to be between 0.10 and 0.20 ppm, or 0.2 to 0.3 mg/m^3 (Ricca 1970). Variation in the odor threshold may be due to several factors, including (1) individual differences in odor perception, (2) a variety of sample presentations, (3) an inconsistency of the purity of F_2, and (4) data interpretation.

On the basis of the studies, the following conclusion can be drawn:

- The odor detection threshold for F_2 is approximately 0.14 ppm (0.2 mg/m^3).

4.4.2 No Observed Adverse Effects Level (NOAEL)

Keplinger and Suissa (1968) found that 10 ppm (16 mg/m^3) was not irritating to humans for as long as 15 min. Exposure for 3 to 5 min every 15 min over a 2- or 3-h period caused slight irritation to the eyes and skin (Keplinger and Suissa 1968). Lyon (1962) found that 61 workers' yearly average exposures to F_2 ranged from 0.3 to 1.4 ppm (0.5 to 2.2 mg/m^3). The exposed group had a better health record than about 2000 to 3000 employees used as controls (Lyon 1962).

The American Conference of Governmental Industrial Hygienists (ACGIH) has developed threshold limit values (TLVs) as guidelines to assist in the control of health hazards. Threshold limit values (TLVs) refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. Threshold limit values (TLVs) are based on the best available information from industrial experience, from experimental human and animal studies, and, when possible, from a combination of the three. The basis on which the values are established may differ from substance to substance; protection against impairment of health may be a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may form the basis for others (ACGIH 1993–1994). The ACGIH threshold limit value-time weighted average (TLV-TWA) is for a normal 8-h workday and a

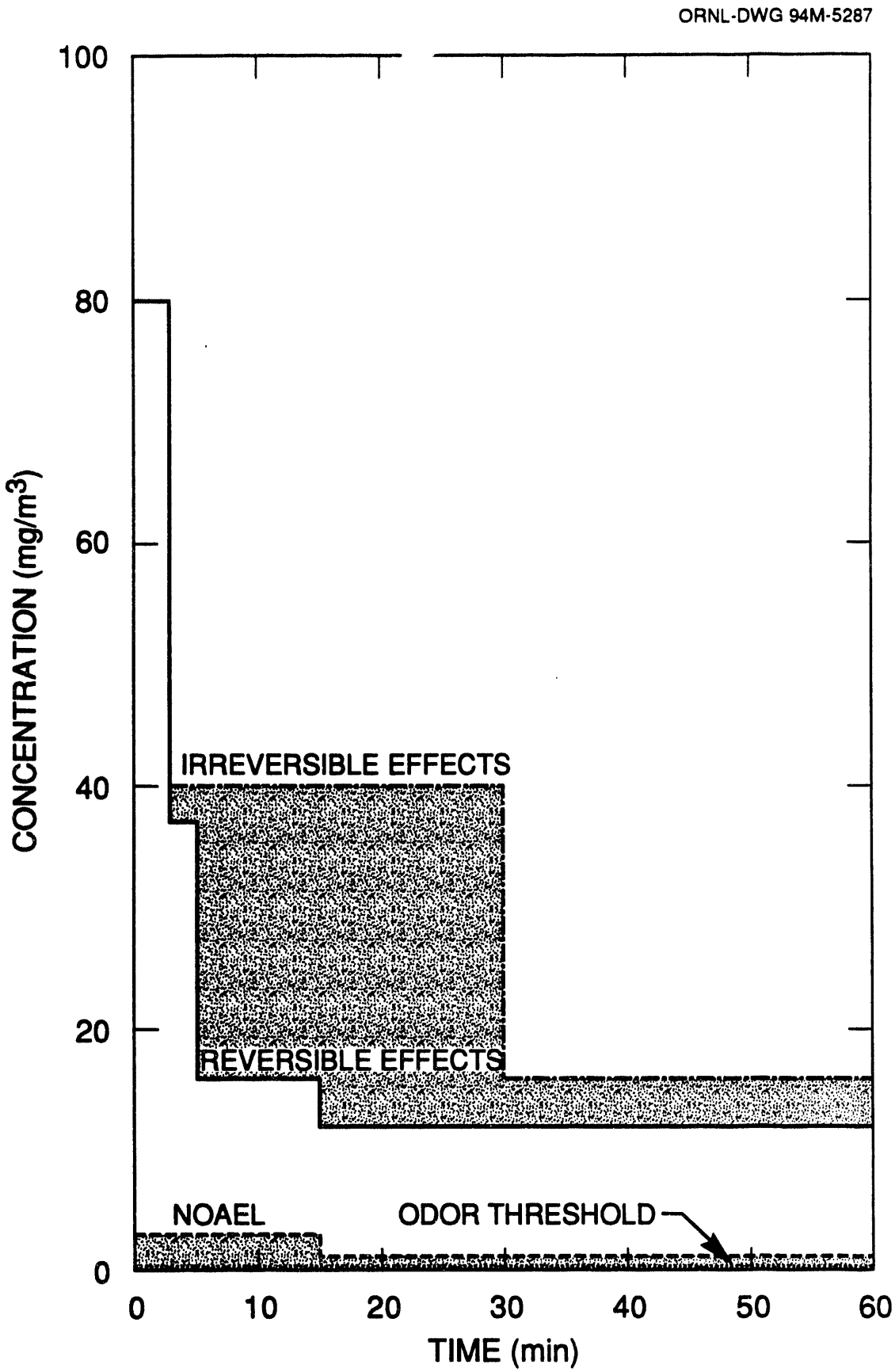

Fig. 4.2. Summary of reversible and irreversible effects of fluorine.

40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The threshold limit value–short-term exposure limit (TLV-STEL) is the concentration to which workers can be exposed continuously for a short period of time (15 min TWA) without suffering from (1) irritation, (2) chronic or irreversible tissue damage, or (3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue, or materially reduce work efficiency, and provided that the daily TLV-TWA is not exceeded (ACGIH 1993–1994).

Based on early animal studies conducted by Stokinger (1949), ACGIH concluded that the TLV-TWA should be set at 0.1 ppm (0.2 mg/m^3). However, ACGIH believed that the lack of significant medical findings in workers exposed to F_2 in excess of 0.1 ppm for 7 years (Lyon 1962) provided a basis on which to recommend and adopt a TLV-TWA of 1 ppm (1.6 mg/m^3).

Keplinger and Suissa's (1968) study of F_2 showed that a few intermittent exposures of 10 ppm (16 mg/m^3), repeated at 3- to 5-min intervals every 15 min for 2 to 3 h, caused only slight irritation to the eyes and skin. On the basis of this study, ACGIH recommends a TLV-STEL of 2 ppm (3.1 mg/m^3).

OSHA and NIOSH agree on 0.1 ppm or 0.2 mg/m^3 as a TWA (8-h workday, 40-h workweek) low enough to avoid adverse health effects. OSHA and NIOSH believed the Lyon study was not a study conducted on 61 workers constantly exposed to F_2, but instead, a compilation of data on workers who may have had some short-term exposure to F_2; thus, their TWA value is 10 times lower than that of ACGIH.

Based on the information reviewed, the following conclusions can be drawn:

- The NOAEL for F_2 for ≤15 min is 2 ppm, or 3.1 mg/m^3.
- The NOAEL for F_2 for >15 min is 1 ppm, or 1.6 mg/m^3.

The Emergency Response Planning Guidelines (ERPGs) were established by the American Industrial Hygiene Association (AIHA) for emergency response purposes. There are no ERPGs for F_2; however, the Subcommittee on Consequence Assessment and Protective Actions (SCAPA) of the Emergency Management Advisory Committee (EMAC) developed preliminary alternative guideline limits for chemicals without ERPGs (EMAC 1993). The preliminary alternative ERPG-1 guideline defines the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing effects other than mild transient adverse health effects or perceiving a clearly defined objectionable odor. The preliminary alternative ERPG-1 for F_2 is 2 ppm, or 3.1 mg/m^3; this is the same as the ACGIH STEL. Since the ERPG-1 definition emphasizes experiencing mild, transient health

effects, it is appropriate to assume mild irritation could be experienced; therefore, the NOAEL should be lower. The ERPG-1 of 2 ppm (3.1 mg/m^3) is the same as the NOAEL for exposures ≤15 min, and very close to the NOAEL recommended for exposures ≥15 to ≤60 min (1.6 mg/m^3).

4.4.3 Irritation/Reversible Effects Level

Keplinger and Suissa (1968) conducted a study in which five human volunteers were exposed to F_2. These tests were designed to test for irritation only. A concentration of 50 ppm (80 mg/m^3) was irritating after 3 min of exposure to the eyes and nose. After about 5 min of exposure, concentrations on the order of 23 ppm (37 mg/m^3) were slightly irritating to the eyes, while concentrations as high as 25 ppm (40 mg/m^3) could be inhaled without respiratory discomfort. A concentration of 10 ppm (16 mg/m^3) was not particularly irritating to the eyes, nose, or respiratory tract after a 15-min exposure.

The ERPG-2 specifies the airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action (see Sect. 4.5 for a more detailed explanation of ERPGs). The preliminary alternative ERPG-2 equivalent concentration-limit guideline is 7.5 ppm, or 12 mg/m^3. Because there is human toxicity information regarding irritation/reversible effects on the exact concentration levels for exposures up to 15 min, those levels were used for this analysis. However, since there was no acute toxicity information on irritation/reversible effects for the concentration levels of >15 to ≤60 min, the preliminary alternative ERPG-2 was adopted.

Based on the information reviewed, the following conclusions can be drawn.

- The irritation/reversible effects level for F_2 is as follows:

≤3 min	C = 80 mg/m^3
>3 to ≤5 min	C = 37 mg/m^3
>5 to ≤15 min	C = 16 mg/m^3
>15 to ≤60 min	C = 12 mg/m^3

- Dermal irritation may be expected at approximately 107 mg/m^3.
- Irritation to the eye appears to be the most sensitive index of subjective effects.

For comparison, the conclusions of this report and Ricca's (1970) EELs for F_2 are as follows.

	This Report		*Ricca's EELs*
>3 to ≤5 min	C = 37 mg/m^3	5 min	C = 39 mg/m^3
>5 to ≤15 min	C = 16 mg/m^3	15 min	C = 23 mg/m^3
>15 to ≤60 min	C = 12 mg/m^3	60 min	C = 15 mg/m^3

Ricca's EELs were established under the assumption that very mild reversible pathological symptoms were acceptable. Ricca established short-term occupational exposure limits that apply to situations requiring a quantitative assessment of the risk to personnel who may be exposed briefly to very high concentrations of airborne toxicants. EELs are designed to limit occupational exposures, but not necessarily without some discomfort, rapidly reversible irritation, or subtle changes in members of a healthy adult population. EELs are used essentially as disaster control guidelines for unplanned hazardous situations. Ricca's EELs are very close to the levels found in this report and help to build confidence in this report's conclusion on irritation/reversible levels.

4.4.4 Irreversible Effects Level

No human studies documenting specif[illegible] exposure levels and time of exposure were found for acute, irreversible health effect[illegible]r, there are two established levels that can be used to determine the onset of possible i[illegible]e effects levels. For F_2, NIOSH recommends an immediately dangerous to life or health (IDLH) level of 25 ppm, or 40 mg/m^3. NIOSH defines the IDLH level as encompassing "conditions that pose an immediate threat to life or health or conditions that pose an immediate threat of severe exposure to contaminants, such as radioactive materials, which are likely to have adverse cumulative or delayed effects on health." Two factors are considered when establishing IDLH concentrations. First, the worker must be able to escape without losing his/her life or suffering permanent (irreversible) health damage within 30 min. OSHA considers 30 min as the maximum permissible exposure time for escape. Second, the worker must be able to escape without severe eye or respiratory irritation or other reactions that could inhibit escape. Since the criteria used in establishing IDLH specifies suffering no irreversible (or life-threatening) health effects, it seems reasonable to assume exposure to F_2 for 30 min or less at 25 ppm (40 mg/m^3) would prevent irreversible effects. Therefore, exposures above 25 ppm (40 mg/m^3) would indicate the onset of possible development of irreversible health effects.

Using the same approach, the AIHA ERPG-3 specifies the airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing or developing life-threatening health effects. The preliminary ERPG-3 equivalent concentration-

limit guideline is 10 ppm, or 16 mg/m^3. The definition stresses exposure up to 1 h without experiencing or developing life-threatening health effects. Although life-threatening health effects would not be experienced, it is reasonable that irreversible health effects could be experienced. Lacking additional human or animal data from which to draw conclusions, the guidelines developed for IDLH and ERPG are adopted.

- The irreversible effects level for F_2 is as follows:

≤30 min	C = 40 mg/m^3
30 to ≤60 min	C = 16 mg/m^3

4.4.5 Human Lethal Exposure Level

This section estimates the exposure level for lethality in humans (see Fig. 4.3). Rarely can quantitative information on the inhalation exposure levels that cause death in humans be found. An evaluation of the available human exposure information makes it clear that it would be very difficult to define a concentration and time of exposure which would lead to a human fatality.

4.4.5.1 Methodology

In the absence of sufficient human data, animal toxicity data were used and extrapolated for human equivalent data. Toxicological studies have determined LC_{50}'s for a few species at exposure times ranging from 5 to 60 min.

Lethal animal exposures have shown that damage to the tissues of the respiratory tract (edema, emphysema, and hemorrhage) is the major pathology associated with such exposures (Keplinger and Suissa 1968). ACGIH, OSHA, NIOSH, and others acknowledge that F_2 is a severe irritant of the eyes, mucous membranes, skin, and lungs. Serious systemic effects are unlikely from an acute exposure. In general, if an animal lived for 48 h, it survived. The primary tissues at risk are those of the respiratory tract, which sustain the impact of the exposure. Therefore, the concentration of F_2 gas in air impinging on the respiratory tissue, and not the absorbed dose, is the primary determinant in the extent of damage done. Accordingly, the most scientifically defensible extrapolation would take into account differences in anatomy, physiology and size of the respiratory tract of humans and experimental animals.

Animal LC_{50} data are first converted to human-equivalent LC_{50} levels. The dose to the respiratory tract, expressed in terms of the mass of the chemical (milligrams) per

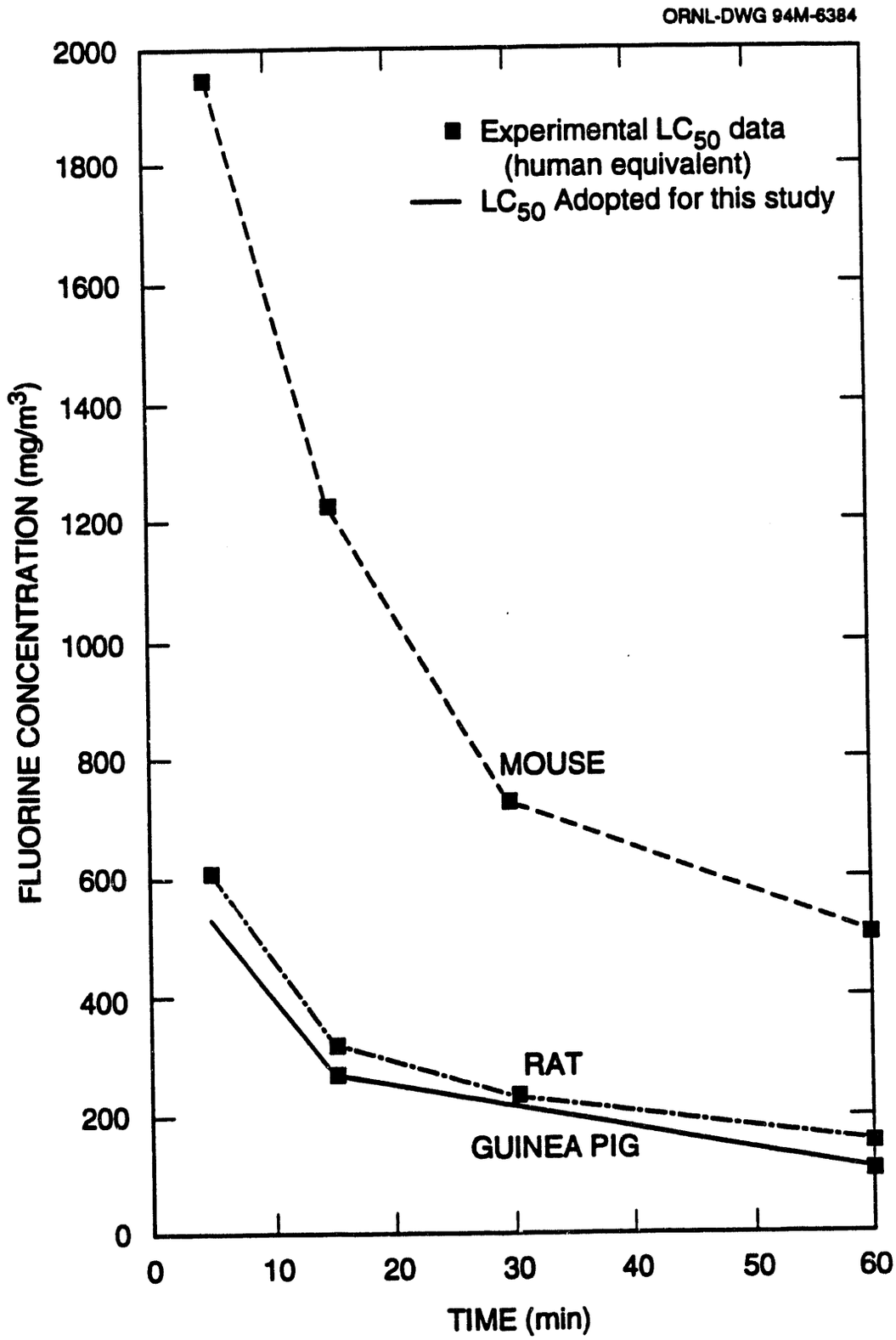

Fig. 4.3. Estimated human lethality (LC_{50}) for fluorine.

surface area of the lung (square centimeters) of the animal is called the regional gas dose (RGD) (EPA 1989). The RGD allows for extrapolation to other species using lung surface area as a common denominator. The formula is as follows:

$$RGD = \frac{YV_t f \times t}{S} , \tag{4.1}$$

where

Y = exposure concentration (mg/m^3),
V_t = tidal volume (m^3/breath),
f = respiratory rate (breaths/min),
S = regional surface area (cm^2) for respiratory tract area affected,
t = exposure time.

The RGD can then be used to estimate the human-equivalent concentration (HEC) LC_{50} based on the average inhalation rate and respiratory tract total surface area of a human:

$$\text{HEC} = \frac{RGD \times S}{V_t \cdot f \cdot t} , \tag{4.2}$$

where

RGD = mass of chemical per total surface area of the respiratory tract (mg/cm^2),
V_t = tidal volume (m^3/breath),
f = respiratory rate (breaths/min),
S = regional surface area (cm^2) for respiratory tract area affected,
t = exposure time.

After using the above extrapolation techniques, the concentrations for specific times were calculated to determine the HEC LC_{50}. Figure 4.3 shows the estimated LC_{50} for 5, 15, 30, and 60 min. Figure 4.3 also confirms that the guinea pig is the most sensitive of the three animals exposed to F_2. Therefore, the guinea pig values were used to evaluate the HEC LC_{50}. This choice is made because we do not have other information that suggests which animal model may most closely resemble a human subject. Animal LC_{50} values were found in the study conducted by Keplinger and Suissa (1968) and are listed in Table 4.3 with the regional gas

Table 4.3. Regional gas doses for animals exposed to fluorine

Exposure time and species	Concentration (mg/m^3)	Regional gas doses (mg/cm^2)	Estimated human LC_{50} (mg/m^3)
5 min			
Mouse	932	3.8×10^{-4}	1948
Rat	1088	1.2×10^{-4}	615
15 min			
Mouse	583	7.2×10^{-4}	1230
Rat	606	1.9×10^{-4}	325
Guinea pig		1.6×10^{-4}	273
30 min			
Mouse	350	8.6×10^{-4}	735
Rat	420	2.7×10^{-4}	231
60 min			
Mouse	233	1.2×10^{-3}	513
Rat	287	3.7×10^{-4}	158
Guinea pig	264	2.7×10^{-4}	115

Note: Values are based on the following inhalation rates and respiratory tract surface areas: *mouse*, 24.45 ml/min, 298 cm^2; *rat*, 74 ml/min, 3473 cm^3; *guinea pig*, 162 ml/min, 9384 cm^2; *human*, 25,000 ml/min, 640,758 cm^2.

Sources: Inhalation rates for the mouse, rat, and guinea pig are from Altman and Dittmer 1964; the human inhalation rate, from ICRP 1994. The guinea pig and mouse respiratory tract surface areas are from EPA 1989; the human and rat respiratory tract surface areas, from Jarabek et al. 1989.

dose and the calculated human LC_{50} levels. There were no guinea pig data for the 5-min exposure. However, by using the ratio of the guinea pig concentration to the rat concentration at 15 min, the 5-min rat concentration was scaled to estimate the 5-min guinea pig concentration.

$$GP_5 = R_5 \times \frac{GP_{15}}{R_{15}} \quad , \tag{4.3}$$

where

GP_5/R_5 = Guinea pig or rat concentration at 5 min exposure, and
GP_{15}/R_{15} = Guinea pig or rat concentration at 15 min exposure.

The estimated human LC_{50} is as follows:

- 516 mg/m^3 for 5 min,
- 273 mg/m^3 for 15 min, and
- 115 mg/m^3 for 60 min.

4.4.5.2 Discussion of lethal exposure levels

When the LC_{50}'s for all three species (order of sensitivity is guinea pig, rat, mouse) at the different exposure times were compared, they were similar, suggesting comparable species sensitivity and perhaps a common cause.

Signs of intoxication at the lethal concentrations included irritation of the eyes and nose (as shown by conjunctivitis), pawing at the nose, increased secretions, and sneezing. Dyspnea, loss of body weight, general weakness, and death were observed. Few signs of intoxication were observed immediately after exposure. Frequently the animals looked quite well (with some irritation of the eyes and nose). Dyspnea and lethargy were not observed until several hours after exposure. At lethal concentrations there was little or no visible damage to the liver or kidney. Death was attributed to respiratory failure. With the exception of very high concentrations [≥5000 ppm (≥8000 mg/m^3)], death occurred approximately 12 to 18 h after exposure. A few deaths were recorded about 24 h after exposure. In general, if an animal lived for 48 h, it survived.

4.5 REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) 1991. *Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine (F)*, U.S. Department of Health and Human Services.

Air Products and Chemicals, Inc. (APCI) 1990. Material Safety Data Sheet, Fluorine, Allentown, Pa.

Alexeeff, G. V., M. J. Lipsett, and K. W. Kizer 1989. "Problems Associated with the Use of Immediately Dangerous to Life and Health (IDLH) Values for Estimating the Hazard of Accidental Chemical Releases," *Am. Indus. Hyg. Assoc. J.* **50**(11), 598–605.

Altman, P., and D. S. Dittmer, eds. 1964. *Biology Data Book*, Committee on Biological Handbooks, Federation of American Societies for Experimental Biology, Washington, D.C.

American Conference of Governmental Industrial Hygienists (ACGIH) 1993–94. *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, Ohio.

Amoore, J. E., and E. Hautala 1983. "Odor as an Aid to Chemical Safety: Odor Thresholds Compared with Threshold Limit Values and Volatilities for 214 Industrial Chemicals in Air and Water Dilution," *J. of App. Toxico.* 3(6), 272–90.

Belles, F., ed. 1965. *Fluorine Handbook*, National Aerospace and Space Administration, Lewis Research Center, Cleveland, as cited in Ricca 1970.

Braker, W., A. L. Mossman, and D. Siegel 1977. *Effects of Exposure to Toxic Gases: First Aid and Medical Treatment*, 2nd ed., Matheson, Lyndhurst, N.J.

Dreisbach, R. H. 1983. *Handbook of Poisoning: Prevention Diagnosis and Treatment*, 11th ed., Lange Medical Publications, Los Altos, Calif.

Emergency Management Advisory Committee (EMAC) 1993. Subcommittee on Consequence Assessment and Protective Actions of the Emergency Management Advisory Committee, *Alternative Guideline Limits for Chemicals Without ERPGs*, SRT-RAM-930170, Westinghouse Savannah River Company, Aiken, S.C., October.

International Commission on Radiological Protection (ICRP) 1994. *Human Respiratory Tract Model for Radiological Protection*, ICRP Publication 66, *Annals of the ICRP* **24**(1–4), in press.

International Labour Office (ILO) 1983. *Encyclopaedia of Occupational Health and Safety*, 3rd rev. ed., vol. 1 (A–K).

Jarabek, A. M., M. G. Menache, J. H. Overton, Jr., M. L. Dourson, and F. J. Miller 1989. "Inhalation Reference Dose (RfD_i): An Application of Interspecies Dosimetry Modeling for Risk Assessment of Insoluble Particles," *Health Physics* **57**, supplement 1, 177–83.

Keplinger, M. L., and L. W. Suissa 1968. "Toxicity of Fluorine Short-Term Inhalation," *Am. Indust. Hyg. Assoc. J.*, **29**(1) 10–18.

Lyon, J. S. 1962. "Observations on Personnel Working with Fluorine at a Gaseous Diffusion Plant," *J. of Occup. Med.* **4**, 199.

National Fire Protection Association (NFPA) 1986. *Fire Protection Guide on Hazardous Materials*, 9th ed., Batterymarch Park, Quincy, Mass.

Occupational Safety and Health Administration (OSHA) 1978. *Occupational Health Guideline for Fluorine*, U.S. Department of Labor.

Occupational Safety and Health Administration (OSHA) 1989. *Industrial Exposure and Control Technologies for OSHA-Regulated Hazardous Substances*, U.S. Department of Labor.

Ricca, P. M. 1970. "A Survey of the Acute Toxicity of Elemental Fluorine," *Am. Indust. Hyg Assoc. J.* **31**(1), 22–29.

Rickey, R. P. 1959. *Decontamination of Large Liquid Fluorine Spills*, U.S. Air Force Flight Training Command, TR-59-21, as cited in Ricca 1970.

Smith, M. C., and H. V. Smith 1935. "Occurrence of Mottled Enamel on the Temporary Teeth," *J. of Am. Dental Assoc.* **22**, 814–17.

U.S. Environmental Protection Agency (EPA) 1989. *Interim Methods for Development of Inhalation Reference Doses*, EPA/600/8-88/066F, Office of Health and Environmental Assessment, Washington, D.C.

5

POLYCHLORINATED BIPHENYLS AND THEIR COMBUSTION PRODUCTS

5. POLYCHLORINATED BIPHENYLS AND THEIR COMBUSTION PRODUCTS

5.1 SUMMARY

Polychlorinated biphenyls (PCBs) are complex mixtures of oily chlorinated hydrocarbons that were widely used from the 1930s to 1977 as insulators in capacitors and electrical transformers, as lubricants, and in other applications. Because of their fat-solubility and biological stability, they have become ubiquitous environmental contaminants, accumulating in ecosystems and the human food chain. Human populations, particularly in industrialized societies, carry measurable body burdens of PCBs, particularly of the more highly chlorinated and toxic congeners. Commercial PCB mixtures may be contaminated with polychlorinated dibenzofurans (PCDFs) during production. Heating of PCB-containing fluids above 200°C will produce more highly chlorinated PCBs, polychlorinated quaterphenyls, and the more toxic, highly chlorinated PCDFs. Pyrolysis, or incomplete combustion, will result in the formation of small but toxicologically significant amounts of PCDFs and, often, polychlorinated dibenzodioxins (PCDDs). Human populations also carry body burdens of these extremely toxic contaminants. Section 5.2 provides a discussion of the physicochemical properties of PCBs, including the concentration of PCBs and their combustion products in soot samples and surface contamination from a number of PCB fire and pressurized release incidents (see Table 5.2). The present analysis does not take into account the existing body burden of PCBs, PCDFs, and PCDDs, as current data on the local population are not at hand; the air levels calculated corresponding to various toxicological endpoints assume no previous exposure and therefore may not be protective.

The body burdens and concentration-time products are presented in Table 5.1 for PCBs, PCBs in pyrolysis (oil) or combustion product (soot) mixtures, and for 2,3,7,8-tetrachlorinated dibenzo-*p*-dioxin (2,3,7,8-TCDD), PCDD, and tetrachlorinated dibenzofuran (TCDF)/PCDF. These concentration-time products were calculated using the International Commission on Radiological Protection (ICRP) reference adult human ventilation rate of 25 L/min for light activity (1994). The effects of these chemicals are cumulative; there are no restrictions on averaging time. Thus, air levels can be calculated for any exposure duration (in minutes) directly from the concentration-time product. The endpoints listed for the general population and female workers are based on human data for developmental neurotoxicity from environmental PCB exposure. The air levels of PCBs estimated to result in absorbed doses corresponding to systemic toxicity, no observed adverse effect level (NOAEL), reversible effects, and LD_{50} endpoints for exposure durations of 1 to 120 min are shown in Fig. 5.1. The air levels of PCBs estimated to result in absorbed dose accumulation corresponding to NOAEL and irreversible effects levels based on developmental neurotoxicity endpoints for exposures of 1 to 120 min are shown in Fig. 5.2. Air levels of 2,3,7,8-TCDD that are estimated to result in absorbed dose accumulation corresponding to NOAEL, reversible effects, irreversible effects, and LD_{50} endpoints are illustrated for exposure durations of 1 to 120 min in Fig. 5.3. Air

levels that are estimated to result in absorbed dose accumulations corresponding to these endpoints are illustrated in Fig. 5.4 for PCDDs and in Fig. 5.5 for TCDFs/PCDFs. The PCB air levels corresponding to the $LD_{1.2}$ absorbed dose for PCBs/PCDFs based on Yu-Cheng oil poisoning and to NOAEL, irreversible effects, and LD_{50} absorbed doses for Binghamton soot are shown in Figs. 5.6 and 5.7 for exposure times of 1 to 120 min. It should be noted that there is significant uncertainty associated with these estimates that cannot be quantified.

The estimates of health effects provided in this section are intended to be used only in assessing the consequences of postulated accidents in support of the Safety Analysis Report (SAR) program. This information will be used to determine the adequacy of the controls used to manage the risk of the operation being evaluated. The toxicity estimates are *not* intended to be used as acceptable exposure levels for occupational personnel or members of the public. Furthermore, the guidelines in this section are *not* intended for use in developing emergency exposure levels.

Table 5.1. Summary of PCB and PCB combustion product effects levels

Substance	Endpoint	Absorbed dose (mg)	Concentration-time[a] (mg-min/m^3)	Comments
	Quantitative measures: systemic effects (male workers)			
PCBs	Detection threshold			None identified
	No observed adverse effect	150	5,800	Based on rat liver weight and cholesterol study; oral
	Irritation/reversible effects	290	12,000	Based on rat liver weight and cholesterol study; oral
	Irreversible effects			No animal value available
	Lethality (LCt_{50}/LD_{50})	74,000	3.0×10^6	Based on rat data; oral
	Quantitative measures: developmental neurotoxicity (general public, female workers)			
	Detection threshold			None identified
	No observed adverse effect	1.5	60	Based on human oral data; pertinent to general population and female workers
	Irritation/reversible effects			No reversible effects on memory observed
	Irreversible effects	1.9	75	Based on human data; in utero effects on visual recognition memory in infants and short term memory in same children at age 4
	Lethality (LCt_{50}/LD_{50})			None identified

Table 5.1 (cont.)

Substance	Endpoint	Absorbed dose (mg)	Concentration-time[a] (mg-min/m^3)	Comments
	Quantitative measures: systemic effects			
PCB_{oil}	Detection threshold			None identified
	No observed adverse effect			None identified
	Irritation/reversible effects			None identified
	Irreversible effects			No threshold identified
	Onset of lethality ($LCt_{1.2}/LD_{1.2}$)[b]	1,500	58,000	Based on human data. Yu-Cheng incident; estimates based only on PCB content of mixture
	Lethality (LCt_{50}/LD_{50})			None identified
	Quantitative measures: systemic effects			
PCB_{soot}	Detection threshold			None identified
	No observed adverse effect	0.48	19	Based on female guinea pig data, Binghamton soot suspension, adjusted for PCB content = 0.5% and for toxicity as if given in oil; oral
	Irritation/reversible effects			None identified
	Irreversible effects	4.8	190	Based on female guinea pig data as in NOAEL
	Lethality (LCt_{50}/LD_{50})	20	790	Based on female guinea pig data as in NOAEL

Table 5.1 (cont.)

Substance	Endpoint	Absorbed dose (mg)	Concentration-time[a] (mg-min/m³)	Comments
		Quantitative measures		
2,3,7,8-TCDD	Detection threshold			None identified
	No observed adverse effect	0.000073	0.0029	Based on oral rat data
	Irritation/reversible effects	0.00015	0.0058	Based on oral rat data
	Irreversible effects	0.0038	0.15	Based on oral rat data
	Lethality (LCt_{50}/LD_{50})	1.8	73	Based on oral and IP rat data
PCDD	Detection threshold			None identified
	No observed adverse effect	0.00029	0.012	Based on potency relative to 2,3,7,8-TCDD
	Irritation/reversible effects	0.00058	0.023	Based on potency relative to 2,3,7,8-TCDD
	Irreversible effects	0.015	0.61	Based on potency relative to 2,3,7,8-TCDD
	Lethality (LCt_{50}/LD_{50})	7.3	290	Based on potency relative to 2,3,7,8-TCDD
TCDF/PCDF	Detection threshold			None identified
	No observed adverse effect	0.0015	0.058	Based on potency relative to 2,3,7,8-TCDD
	Irritation/reversible effects	0.0029	0.12	Based on potency relative to 2,3,7,8-TCDD
	Irreversible effects	0.077	3.1	Based on potency relative to 2,3,7,8-TCDD
	Lethality (LCt_{50}/LD_{50})	36	1,460	Based on potency relative to 2,3,7,8-TCDD

[a]No limitations on averaging time.
[b]Absorbed dose and $LCt_{1.2}$ based on 1.2% mortality and severe health effects, many persisting >20 years.

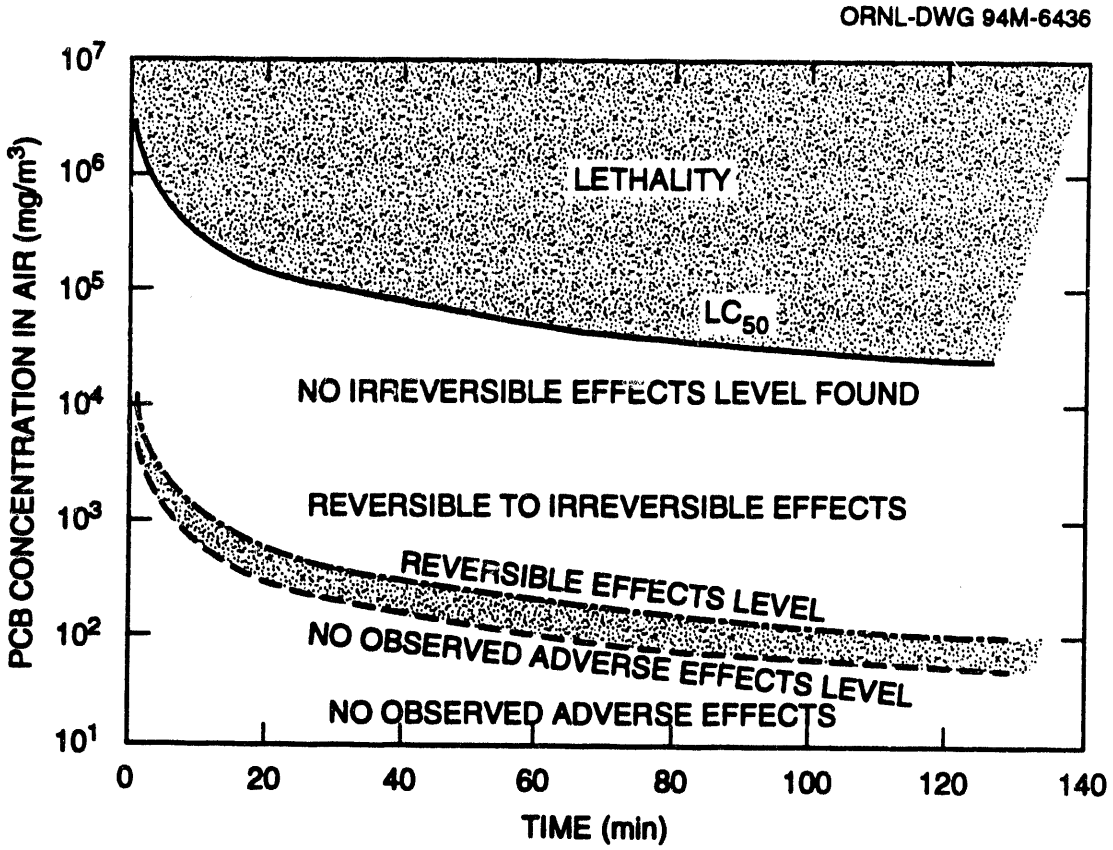

Fig. 5.1. Air levels of PCBs that are estimated to result in accumulation of absorbed doses corresponding to systemic toxicity NOAEL, reversible effects, and LD_{50} levels for exposures of 1 to 120 min.

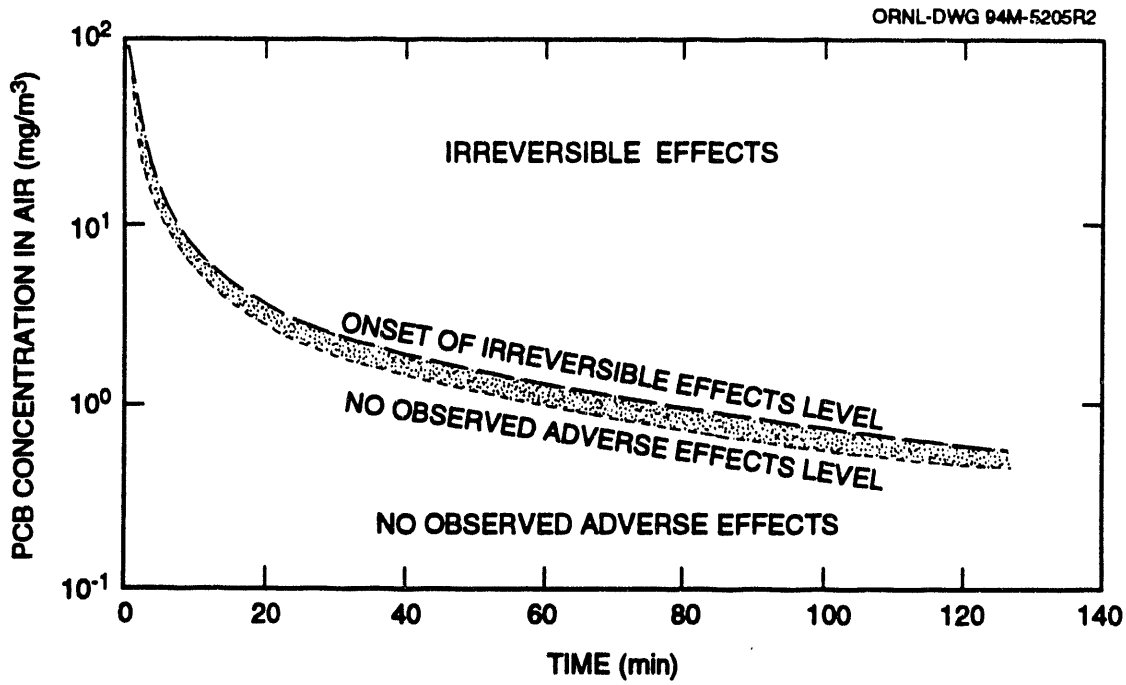

Fig. 5.2. Air levels of PCBs that are estimated to result in accumulation of absorbed doses corresponding to NOAEL and irreversible effects levels based on developmental neurotoxicity endpoints for exposures of 1 to 120 min.

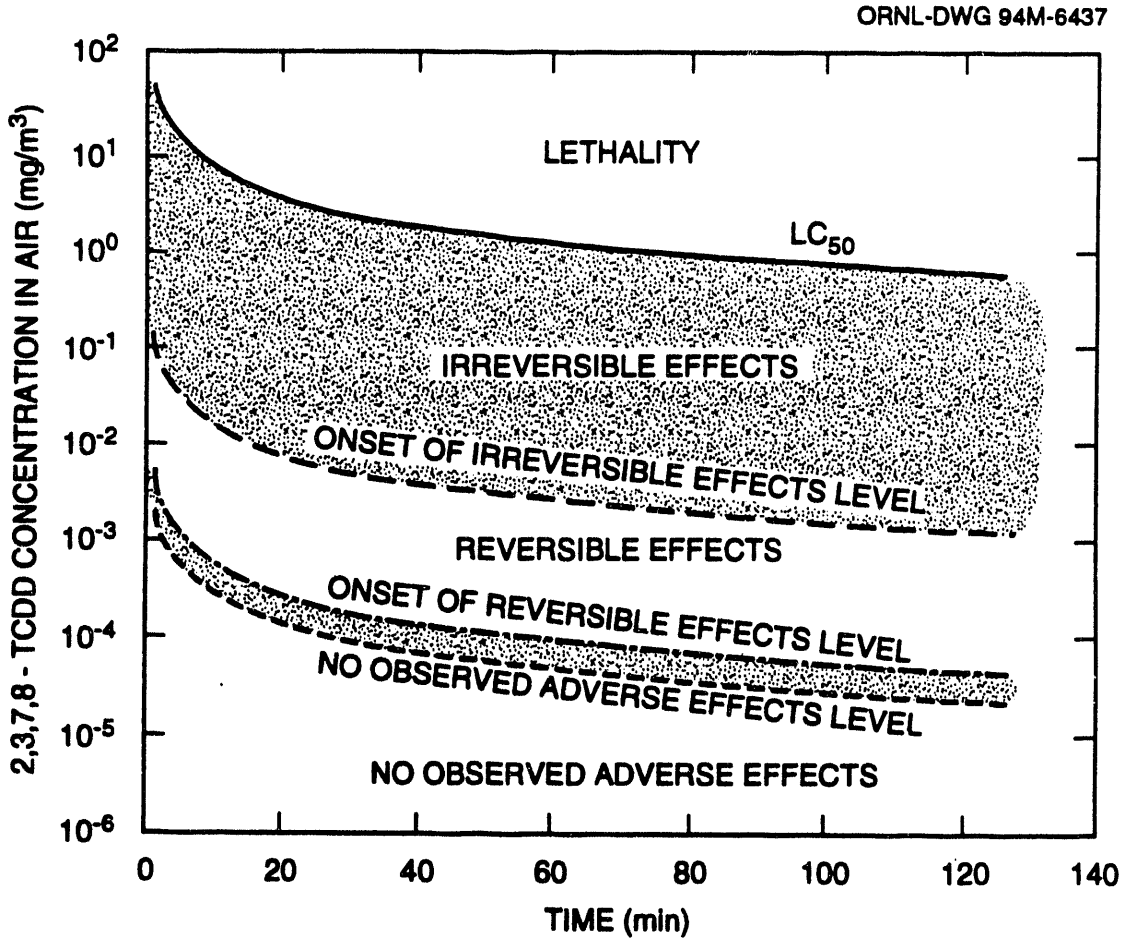

Fig. 5.3. Air levels of 2,3,7,8-TCDD that are estimated to result in accumulation of absorbed doses corresponding to NOAEL, reversible effects, irreversible effects, and LD_{50} levels for exposures of 1 to 120 min.

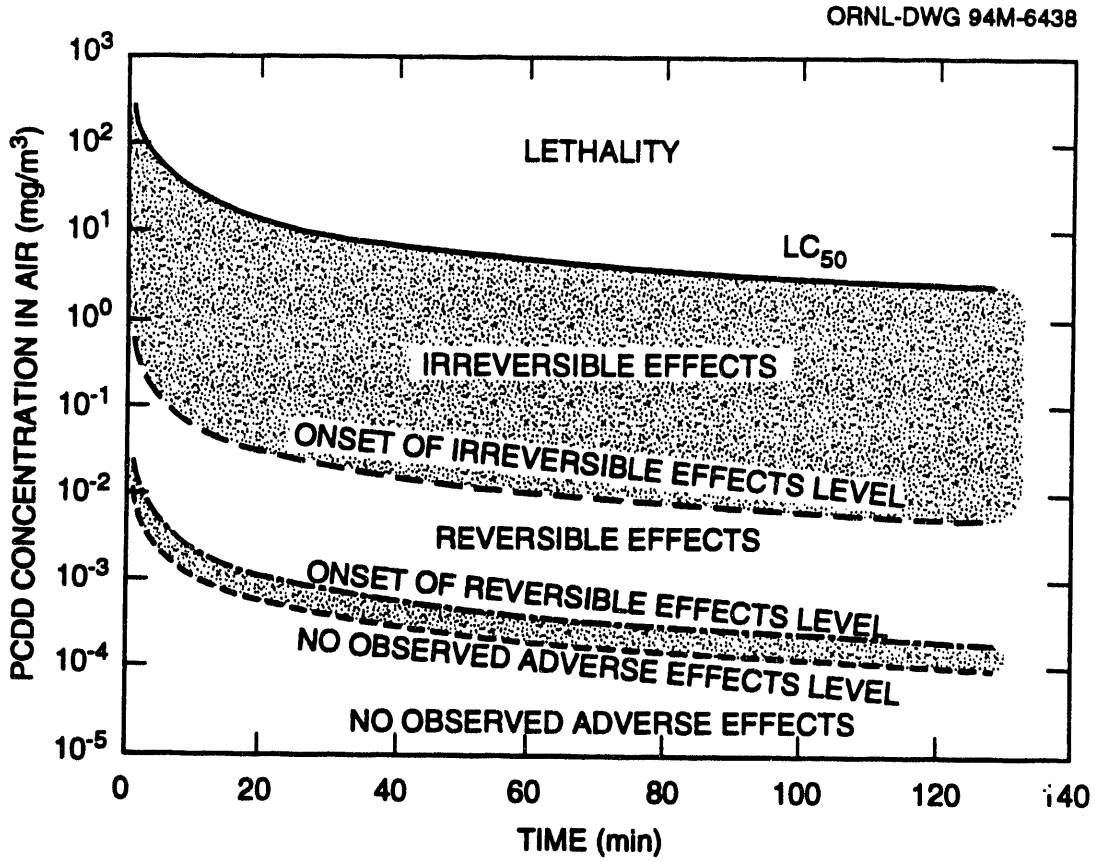

Fig. 5.4. Air levels of PCDDs that are estimated to result in accumulation of absorbed doses corresponding to NOAEL, reversible effects, irreversible effects, and LD_{50} levels for exposures of 1 to 120 min.

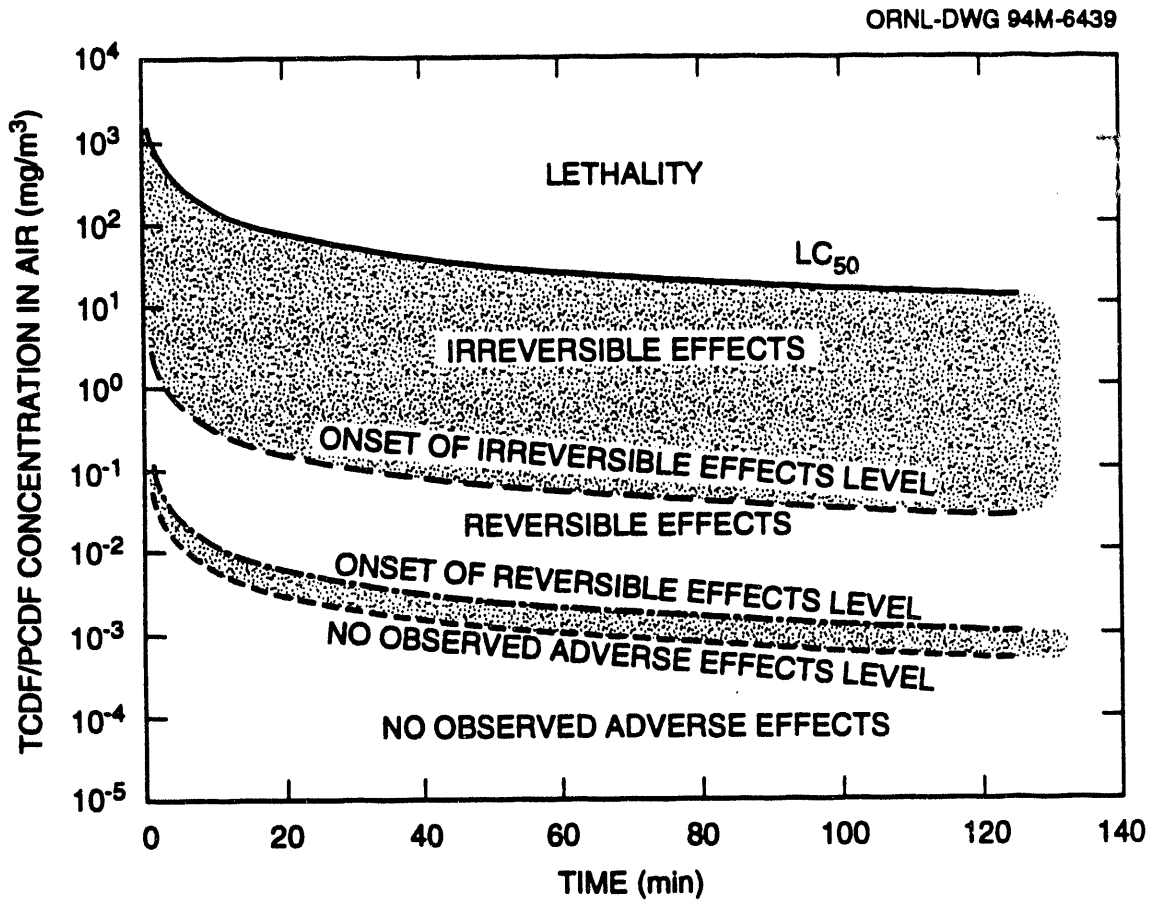

Fig. 5.5. Air levels of TCDF/PCDFs that are estimated to result in accumulation of absorbed doses corresponding to NOAEL, reversible effects, irreversible effects, and LD_{50} levels for exposures of 1 to 120 min.

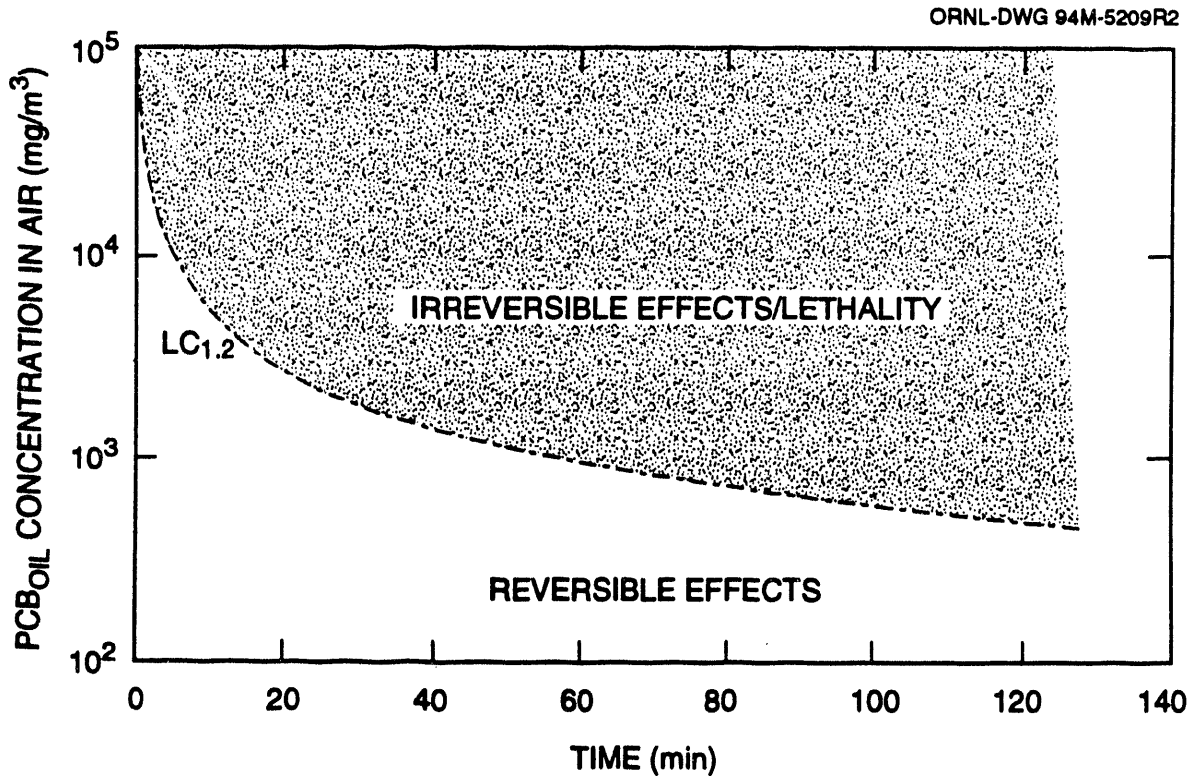

Fig. 5.6. Air levels of PCB_{oil} that are estimated to result in accumulation of absorbed doses corresponding to $LD_{1.2}$ level for exposures of 1 to 120 min.

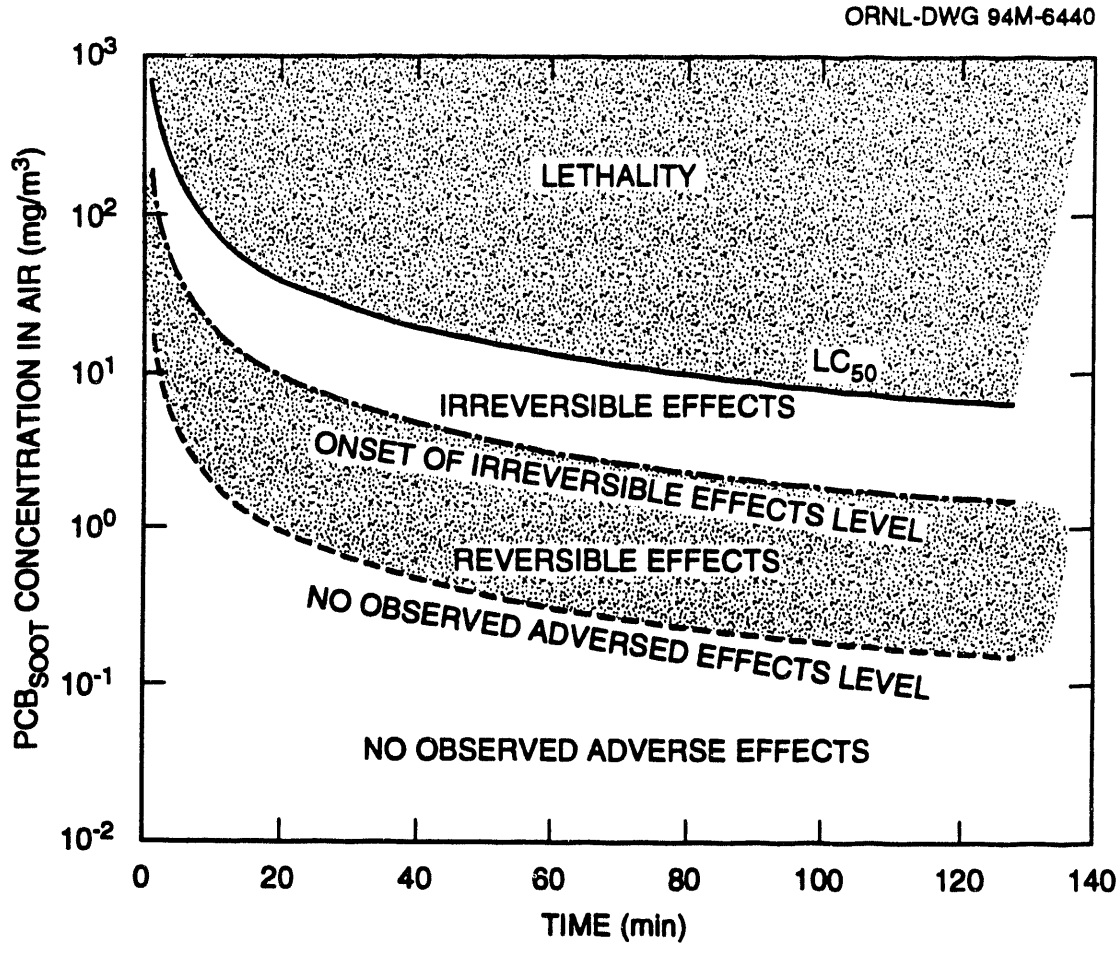

Fig. 5.7. Air levels of PCB_{soot} that are estimated to result in accumulation of absorbed doses corresponding to NOAEL, irreversible effects, and LD_{50} levels for exposures of 1 to 120 min.

5.2 PHYSICOCHEMICAL PROPERTIES OF PCBs

Polychlorinated biphenyls (PCBs) (CAS Registry No. 1336-36-3) constitute a class of oily chlorine-substituted aromatic hydrocarbons whose stability, nonflammability, and good dielectric properties made them desirable as lubricants and as insulators in capacitors and electrical transformers as well as for other commercial applications. Commercial PCB production began in 1929; PCBs came into general use in the 1940s, with maximum use from 1957 to 1977 (Silberhorn, Glauert, and Robertson 1990; NIOSH 1986). Although production was banned in the United States in late 1977, PCBs continue to be of concern because their stability has led to widespread environmental contamination; furthermore, many PCB-laden capacitors and transformers are still in use, creating the potential for leakage or explosive PCB releases (NIOSH 1986).

These compounds were produced as complex isomeric mixtures whose trade names generally indicate their extent of chlorination; for example, Aroclor 1254 contains 54% chlorine by weight, Aroclor 1242 contains 42%, and so on. Silberhorn, Glauert, and Robertson (1990) have compiled data on the chlorine content and molecular weight of several American, German, and Japanese commercial PCB preparations. Commercial mixtures contain only about 100 of the 209 possible congeners in significant quantities (NIOSH 1986). Their boiling points range from 171 to 191°C (340 to 375°F), with a flash point of 195°C (383°F) (Lewis 1992). The solubilities of the PCBs in water are low (0.007 to 5.9 mg/L), while they are readily soluble in common organic solvents, oils, and fats (NIOSH 1986). Their vapor pressures are quite low (10^{-6} to 10^{-3} mm Hg at 20°C). More details of the physicochemical characteristics of commercial PCB mixtures are found in the *ATSDR Toxicological Profile for Selected PCBs* (ATSDR 1993). Aroclor 1254 was the major fluid used in the two largest U.S. capacitor plants from 1946 to the mid-1950s; Aroclor 1242 supplanted it until 1971, after which Aroclor 1016 was the primary fluid until 1977, when PCB use was discontinued (Brown et al. 1991).

The PCBs can be grouped into six structural classes, the toxicity of whose members varies with the number of chlorine substituents and molecular configuration, increasing generally with their degree of similarity to 2,3,7,8-TCDD (EPA 1991, Safe et al. 1985). Class I consists of four coplanar PCBs that are approximate isostereomers of 2,3,7,8-TCDD (see Fig. 5.8); Class II are mono-ortho-coplanar PCBs with a chlorine in a para position; Class III are mono-ortho-coplanars lacking a chlorine in that position. Class IV contains 13 diortho-substituted coplanar PCBs. The dioxin-like biological activity generally decreases with increasing class number (decreasing coplanarity), although Classes III and IV have about equivalent potency. Classes V and VI consist of tri- and tetraortho PCBs; these are not coplanar and exhibit little, if any, dioxin-like activity. Some PCBs possess nondioxin-like activity of toxicological

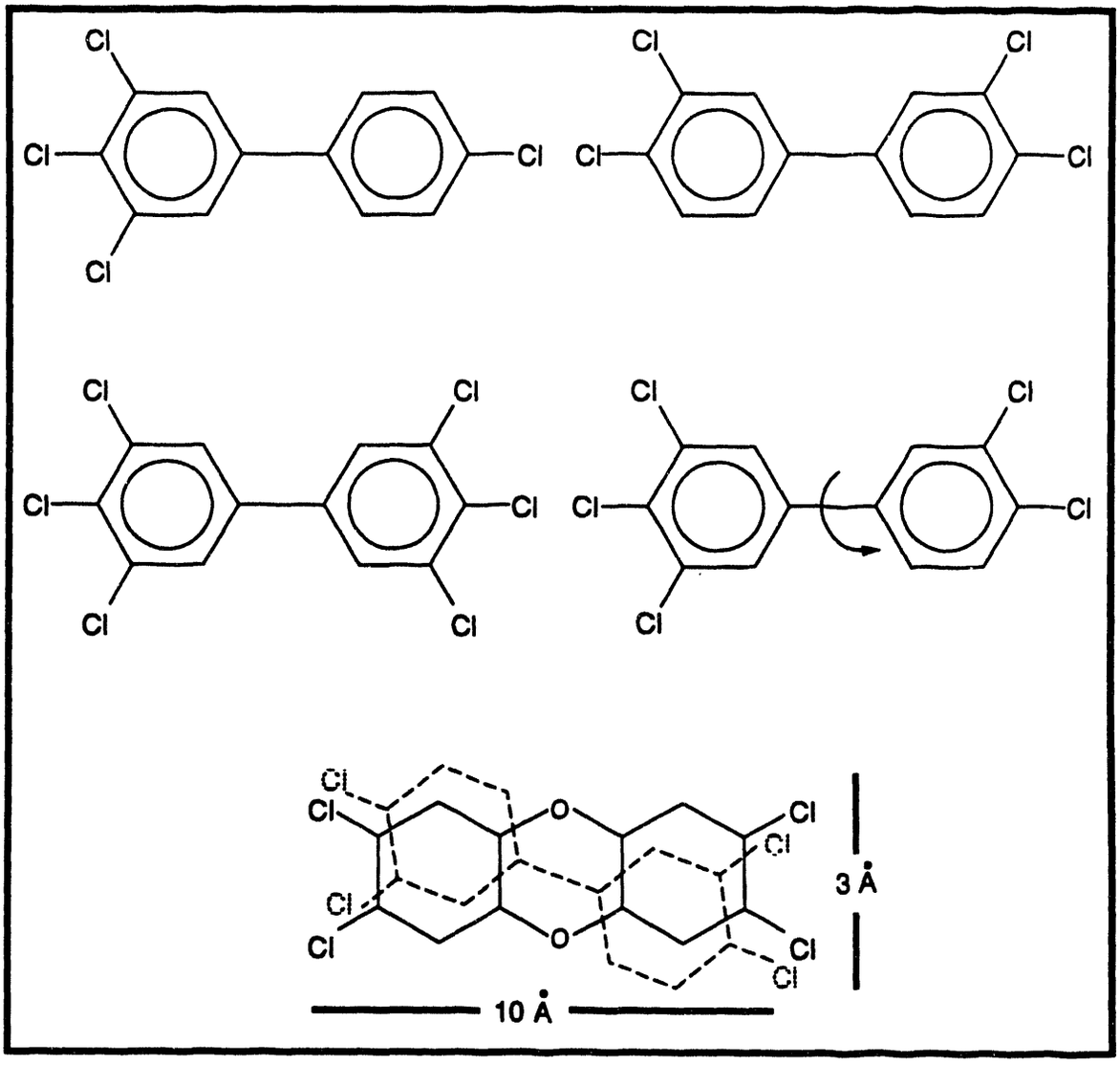

Fig. 5.8. Structures of the coplanar PCB congeners substituted in both para and two or more meta positions and their conformational similarity to 2,3,7,8-TCDD. *Source:* EPA 1991.

significance; such activity is not as well characterized or understood as the dioxin-like features, but includes developmental neurotoxicity and reproductive toxicity (EPA 1991, 1993).

The PCB preparations may contain impurities, including polychlorinated dibenzofurans (PCDFs) and chlorinated quaterphenyls (Kimbrough 1987). Pyrolysis of PCBs results in the formation of fluid or soot containing small but toxicologically significant amounts of PCDFs and often polychlorinated dibenzodioxins (PCDDs) (see Table 5.2) (Kimbrough 1987; NIOSH 1986).

The products of incomplete PCB combustion, PCDFs and PCDDs, are chemically similar to the PCBs, being relatively inert, nonpolar, lipid-soluble molecules with many possible congeners (see Fig. 5.9 for parent structures as well as congeners of high toxicity). Dioxins have 75 possible congeners, while dibenzofurans have 135 (Dickson and Buzik 1993). The chemical and physical properties of these compounds, as with the PCBs, vary with the number and position of chlorine substituents; the biological stability and potential for accumulation in fatty tissue increases with increasing chlorine substitution. Like the PCBs, the PCDFs and PCDDs are widely distributed in the environment, including in the human food chain.

Most people in industrialized countries carry a body burden of PCBs and several PCDF and PCDD congeners in their adipose tissue, especially those congeners with 2,3,7,8-substitution (Dickson and Buzik 1993). An Environmental Protection Agency (EPA) study found a mean 2,3,7,8-TCDD level of 5 ppt in 46 composite tissue samples prepared from 900 samples (number of donors not specified) (EPA 1986). An evaluation of several U.S. studies showed that 2,3,7,8-TCDD levels in human adipose tissue are log-normally distributed, increase with age, and exceed 12 ppt in over 10% of the population (Sielken 1987). Human milk also contains 2,3,7,8-TCDD and other PCDD and PCDF congeners (Bartmess 1988; Jensen 1983). These levels are much lower than those of the PCBs. For example, Kreiss (1985) reported mean PCB serum levels in the United States of about 5 to 7 ng/mL (ppb); adipose tissue levels of Canadian accident victims ranged from 0.9 to 9.4 mg/kg (ppm) (Mes, Davies, and Turton 1982). Levels of PCBs in human tissue and fluid samples are reviewed in some detail in the ATSDR *Toxicological Profile* (ATSDR 1993). Luotamo (1991) reports congener-specific profiles of PCBs in serum and adipose tissue from individuals with occupational, accidental, and environmental exposure.

Table 5.2. Concentrations of PCBs and related compounds following fire-related incidents in the United States

A. Fires

Date, location, and electrical equipment	Sampling date	PCBs in air (μg/m³)	Soot (μg/g)					Surface (μg/100 cm²)					Source
			PCBs	TCDF	PCDFs	TCDD	PCDDs	PCBs	TCDF	PCDFs	TCDD	PCDDs	
12/80; Cincinnati; Capacitor	03/81	ND						7,200	ND	ND	ND	ND	(1)
02/81; Binghamton, N.Y.; Transformer	02/81	80	200,000	12	2,160	0.6	19.9						(2)
10/81; Boston; Transformer	12/81		114,000	3	162	ND	ND						(3)
04/82; Miami; Transformer	04/82			ND	1.89	ND	ND	860					(4)
04/82; Tulsa, Okla.; Transformer	04/85	0.5	11	0.007	0.11	ND	0.16	1,100	8.5[a]	81.6[a]	ND	1.408[a]	(5)
06/82; Jersey City, N.J.; Capacitors		2.3						22	ND	0.14	ND	0.09	(6)
05/83; San Francisco; Transformer	05/83	1,500	86,000	6.3	28.9[b]	0.059	0.32[b]		29[a]	101.5[a]			(7)
09/83; Chicago; Transformer	09/83	58	39,100					3,263	0.41	12.2	ND	0.05	(8)
12/83; Tulsa, Okla; Transformer	01/84							1,607					(9)
03/84; Columbus, Ohio; Capacitors	04/84		6,415	3.2	46.4	0.016	4.1						(10)
05/84; Miami; Transformer	06/84		50,000	0.27	98.5	0.004	2.3						(11)

Table 5.2 (cont.)

B. Pressurized releases

Date, location, and electrical equipment	Sampling date	PCBs in air (pg/m³)	Fluid (µg/g)					Surface (µg/100 cm²)					Source
			PCBs	TCDF	PCDFs	TCDD	PCDDs	PCBs	TCDF	PCDFs	TCDD	PCDDs	
74; Wappingers Falls, NY; Transformer	02/84		117,000		0.97		ND	92					(12)
06/82; Washington, D.C.; Transformer	06/84			<.074[c]	<7.02[c]	ND	<1.3[c]	320,000	ND	<114[c]	ND	ND	(13)
06/82; Maplewood, Minn.; Transformer	06/82	90			ND		ND	5,000					(14)
12/83; Syracuse; Transformer	12/83	1.1						7.3	0.02[d]	0.17[b,d]	ND		(15)
06/85; Santa Fe, N.M.; Transformer	06/85	41.9	870,000	1.6	44.2	ND	ND	280,000	0.41	3.99	ND	0.19	(16)

Note: Values represent the highest measurements reported, as presented in NIOSH (1986); ND = none detected.

[a]Values expressed as nanograms per square meter (ng/m²).

[b]Values represent total tetrachlorinated forms only.

[c]Values represent results obtained in the presence of interfering chemicals.

[d]Values reported as µg per wipe sample (area undefined).

Sources: (1) NIOSH 1981; (2) Schecter 1983; (3) Melius 1985a; (4) NIOSH 1983; (5) Melius 1985b; (6) Port Authority 1985; (7) EPA 1984; (8) Melius 1985c; (9) Landsing Property Corporation 1985 (10) Melius 1985d; (11) Melius 1985e; (12) Melius 1885f; (13) Lees and Breysse 1983; (14) NIOSH 1984; (15) Melius 1985g; (16) Melius 1985h.

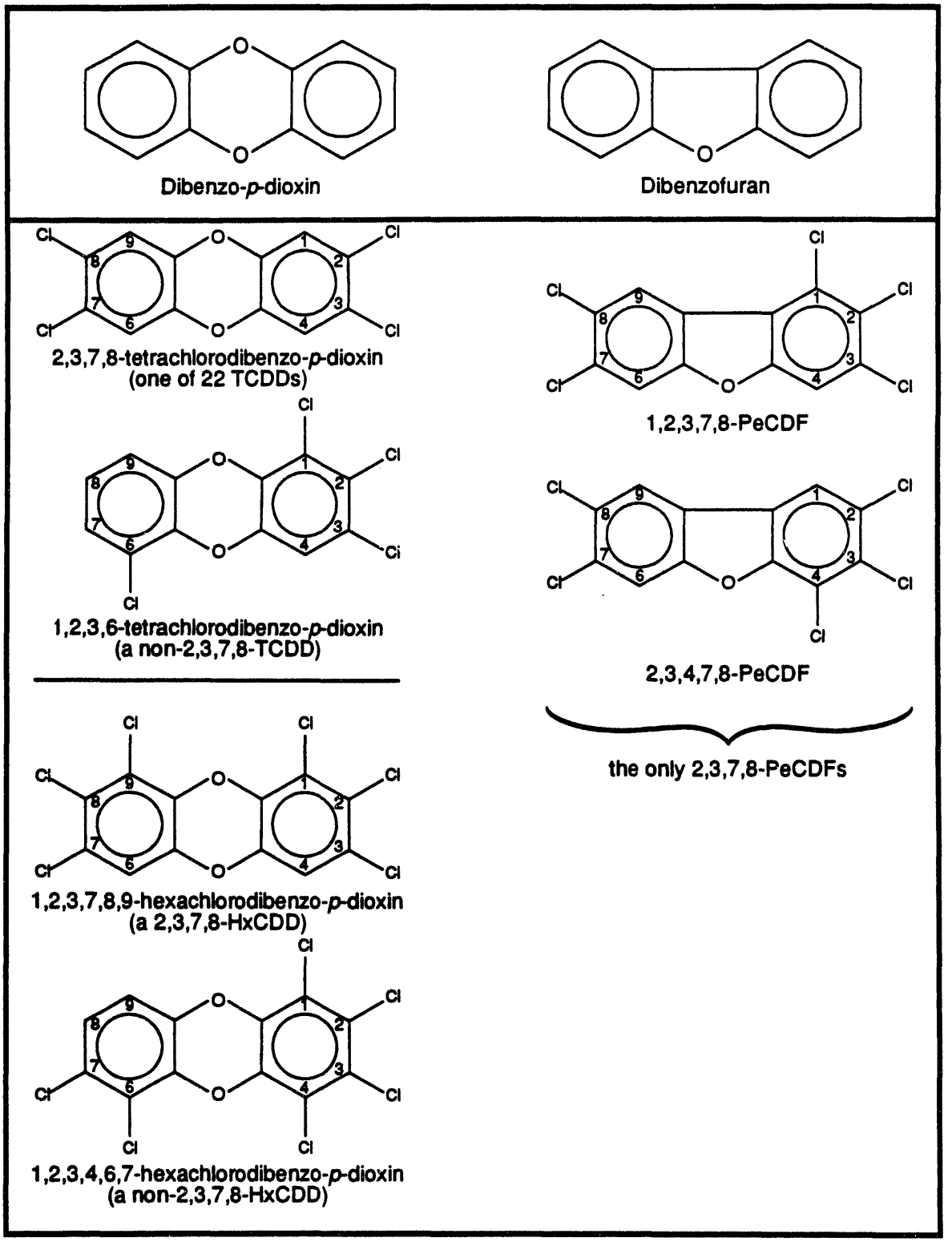

Fig. 5.9. Parent structures of dioxins and dibenzofurans and examples of 2,3,7,8- and non–2,3,7,8-substituted congeners. *Source:* Barnes, Kutz, and Bottimore 1989.

5.3 SUMMARY OF EXISTING TOXICITY DATA

5.3.1 PCBs

PCBs, PCDFs, and PCDDs have a wide range of deleterious health effects in humans and animals. Many of the health effects of PCBs are classed as dioxin-like and are thought to be mediated by binding with the aryl hydrocarbon cellular receptor (EPA 1991), as in the case of 2,3,7,8-TCDD (Andersen et al. 1993; Portier et al. 1993). Such effects may mimic or antagonize gonadal steroid hormone effects, adrenal hormones, or thyroid hormones (EPA 1993). The health effects of PCBs are reviewed in general by Kimbrough (1987), extensively in the ATSDR *Toxicological Profile* (1993), and the carcinogenic effects in detail by Silberhorn, Glauert, and Robertson (1990). Although species differences exist in sensitivity and in some endpoints, many similarities in toxic effects are observed.

Human responses to occupational or environmental (primarily from fish ingestion) exposure to PCBs include skin irritation, rashes, and chloracne; induction of liver enzymes, liver damage; developmental toxicity effects [slight effects on birth weight, head circumference, gestational age and/or neonatal behavior, memory, and attention (Jacobson et al. 1985; Tilson, Jacobson and Rogan 1990)]; peripheral sensory nerve damage (numbness in extremities); and possible carcinogenic effects (Kimbrough 1987; ATSDR 1993; EPA 1993). Recent evidence of genotoxic effects has been reported in PCB-exposed workers, as well as in animals (EPA 1993).

In various animal species, adverse effects include lethality, liver damage, and immunotoxicity (Holsapple et al. 1991; EPA 1993); reproductive, neuro-, and fetotoxicity; teratogenicity; and carcinogenicity (highly chlorinated isomers) (Kimbrough 1987; ATSDR 1993; Silberhorn, Glauert, and Robertson 1990; Golub, Donald, and Reyes 1991). Lethality is usually delayed and is preceded by a period of wasting that cannot be attributed only to appetite suppression; the immediate cause of death is usually not apparent. Based on animal studies, developmental neurotoxic effects are considered not to be dioxin-like effects and are associated with the ortho-substituted PCBs; they are very sensitive endpoints, possibly orders of magnitude more sensitive than most other endpoints (EPA 1991, 1993). Developmental neurotoxicity is evidenced by, for example, cognitive and behavioral deficits.

Wide variations in species sensitivity to PCBs exist, with nonhuman primates, guinea pigs, and mink among the most sensitive and rats, mice, and dogs less sensitive. Human beings appear to be among the less sensitive species with regard to some endpoints but the most sensitive with respect to developmental neurotoxicity (EPA 1993). Some have speculated that storage in adipose tissue may be protective (the more sensitive species tend to have less adipose tissue

than humans) (Kimbrough 1987, ATSDR 1993). Ability to store vitamin A may also correlate with lower sensitivity to PCBs.

5.3.2 PCDDs and 2,3,7,8-TCDD

The toxicity of PCDDs has been reviewed extensively by the EPA (1991, 1992). These compounds include the most toxic known substances, with acute median lethal doses (LD_{50}'s) in the microgram per kilogram range; of them, 2,3,7,8-TCDD is the most toxic. Sensitivity varies greatly among species and strains of animals, with acute LD_{50} values for 2,3,7,8-TCDD ranging from 0.0006 to 5.051 mg/kg (0.6 to 5051 µg/kg), a span of almost 4 orders of magnitude. Effects in animals include liver damage, microsomal enzyme induction, immunotoxicity, edema, systemic hemorrhage, bone marrow suppression, thymic atrophy, weight loss (wasting syndrome), teratogenicity, fetotoxicity, and carcinogenicity. Effects in human beings exposed to 2,3,7,8-TCDD as a contaminant in herbicides or other chlorinated compound mixtures are similar to those of animals. They include liver enzyme induction, liver damage, changes in lipid metabolism, porphyria cutanea tarda (an often reversible but potentially fatal alteration in porphyrin metabolism), neurotoxicity, hematologic changes, chloracne, hyperpigmentation, and developmental neurotoxicity. A group of children exposed pre- and postnatally to 2,3,7,8-TCDD as a result of maternal exposure in the Times Beach poisoning incident were evaluated for both immunological (15 subjects) and neurophysiological function (14 subjects). Preliminary reports indicate that at about 11 years of age, these children exhibited both persisting immunological abnormalities (Smoger et al. 1993) and functional (EEG) differences from normal in the frontal lobe regions (Cantor et al. 1993). The immunological abnormalities were associated with greatly increased frequencies of pneumonias and other infections (Swain 1993).

5.3.3 PCDFs and PCB/PCDF Mixtures

The toxicity of PCDFs has not been as extensively studied as that of PCBs and PCDDs, but the effects are similar in animals and show similar structure-activity relationships, with toxicity increasing as structural similarity to 2,3,7,8-TCDD increases.

Mixtures of PCBs in combination with highly chlorinated PCDFs in the Yu-Cheng rice-bran oil poisoning episode in Taiwan resulted in increased infant mortality (at least 20%) (Hsu et al. 1985); physical abnormalities of skin pigmentation, teeth, and nails; and slight growth retardation and developmental toxicity, including irreversible developmental neurotoxicity to children conceived during or for as much as 6 years after exposure ended (Yu et al. 1991; Chen et al. 1992). The developmental delays and neurotoxicity apparently resulted from in utero exposure, presumably during critical periods of neural development, since exposure to

breast milk had little further deleterious effect. The neurotoxicity resulted in modest effects on IQ, lowering it an average of 5 points by either of two standard tests. While the effect on the individual child was small, the resulting shift in the IQ distribution is of concern, as the number of children falling in the significantly impaired range of IQ ≤ 70 was tripled or quadrupled, depending on the scale used (Chen et al. 1992). The similar Yusho poisoning episode in Japan also resulted in perinatal mortality (Kuratsune 1980) and severe developmental neurotoxicity (Harada 1976, as cited in Chen et al. 1992).

The severity of toxic effects on the Yusho and Yu-Cheng infants is attributed largely to the PCDF contaminants. Babies born to PCB-exposed female capacitor workers with levels of serum PCBs as high as the Yusho and Yu-Cheng mothers (or higher) showed only slight growth retardation (girls) and physical changes such as skin pigmentation, dental caries, and nail deformities similar to the Yusho and Yu-Cheng infants but much less severe (Hara 1985). Their susceptibility to colds, respiratory complaints, and other ailments was also increased. No later evaluation of developmental status or neuropsychological functioning was made of these PCB-exposed children.

Exposure of human beings to PCBs in combination with PCDFs in both the Yusho (Kuratsune 1980, 1989) and Yu-Cheng (Hsu et al. 1985) poisoning episodes also caused unusually severe and persistent chloracne, hyperpigmentation of the skin and nails, ocular effects, nausea and diarrhea, hepatomegaly, peripheral neuropathy (R.-C. Chen et al. 1985), and other signs and symptoms. Mortality of individuals other than infants also ensued, both from nonmalignant liver toxicity and other systemic effects, and from an excess of cancers (mainly liver) in the exposed groups (Hsu et al. 1985; Kuratsune 1980, 1989). Many of the deaths from neoplasms in the Yusho incident took place in the first 3 years after exposure (Kuratsune 1980) and in the Yu-Cheng incident, in the first 4 years after exposure (Hsu et al. 1985). As of 9 years after exposure, Kuratsune (1989) reported that in the Yusho victims, there was a sixfold excess of liver cancer mortality and a threefold excess of neoplasms of the lung, liver, and bronchi ($p < 0.01$) in adult men. A threefold excess of liver cancer was observed in women, but this did not reach statistical significance. Thus, it appears that combinations of PCBs and PCDF pyrolysis products may be carcinogenic to humans, although the dose ranges and mixture compositions are not precisely defined.

5.3.4 Delayed Effects from Acute Exposures

Because of the biological stability of PCBs, PCDFs, and PCDDs, many of these compounds are metabolized and eliminated from the body very slowly. In general, the more highly chlorinated PCBs are more resistant to metabolism (ATSDR 1993). For example, one hexachlorobenzene congener (2,2′,4,4′,5,5′,-hexa-CB) was the congener present in highest

concentration in human adipose tissue in one study, and in another, it decreased only by 10% over a period of 300 to 500 d in patients poisoned 7 to 12 months prior to the onset of measurements (ATSDR 1993). The PCDFs and PCDDs can be even more persistent. Thus, it would not be surprising to see delayed toxicity after acute exposure to such compounds.

Lethality in animals is often delayed by many days or weeks at lower lethal doses of PCBs or related compounds, although very high acutely lethal doses of 2,3,7,8-TCDD may cause death within a few days.

Dickson and Buzik (1993) summarize an instance in which three scientists who experienced "transient minimal exposure" to pure 2,3,7,8-TCDD in the course of its synthesis reported delayed signs and symptoms about 2 years later (Oliver 1975). In two of the men these signs and symptoms included fatigue, gastrointestinal irritation, visual and neuromuscular changes, loss of concentration, "personality changes," and hirsutism. All three scientists showed markedly elevated serum cholesterol levels. One subject with multiple delayed effects developed chloracne, as did (at a later time) the subject showing only elevated cholesterol levels. No liver damage, porphyrinuria, or other biochemical alterations were observed. Scientists working in the same laboratory and lacking only the exposure to 2,3,7,8-TCDD presented none of these signs or symptoms (Oliver 1975). The evidence is far from conclusive but is suggestive of delayed toxic effects of an acute exposure. No quantitative information is available regarding the level of exposure.

These effects of exposure are similar to prolonged signs and symptoms experienced by firefighters starting 2 d to 3 months after acute exposure to smoke and soot (inhalation and dermal exposures) after a PCB fire in which highly chlorinated PCDFs and other related combustion products were probably produced (Kilburn, Warsaw, and Shields 1989). The firefighters experienced extreme fatigue, headache, muscle weakness, aching joints, memory loss, impaired concentration, irritability, insomnia, impaired balance, and various impairments of cognitive functioning that persisted for many months. Another group of workers exposed to PCBs, PCDFs, mono- and dichloropyrenes, and possibly some 2,3,7,8-TCDF after a capacitor fire and explosion experienced nausea, headache, and intense perspiration within 1.5 h after the onset of exposure; later, some complained of odd feelings in their arms and legs. The exposed workers showed sensory nerve function defects at 2 months postexposure that were nearly repaired by 6 months postexposure (Seppalainen, Vuojolahti, and Elo 1985).

Children exposed acutely to 2,3,7,8-TCDD-contaminated phenoxy herbicides in the Seveso, Italy, accident responded by developing chloracne both soon (hours or days) and late (30 to 60 d) after exposure (Dickson and Buzik 1993; Caputo et al. 1988). Lesions developing late were more severe in individuals who had also developed early lesions.

On the basis of occupational studies suggestive of carcinogenicity and rat studies conclusive for carcinogenicity, the EPA (1988) has categorized PCBs as Group B2 (probable human carcinogens); NIOSH (1986) recommended that PCBs be regarded as potential carcinogens in the workplace and that exposures be controlled to the lowest feasible limit. The dioxin-like PCBs are strong promoters; some of the nondioxin-like PCBs also are carcinogenic in animals, but do not act by the same receptor-based mechanism as the dioxin-like PCBs (EPA 1991).

Animal feeding studies have shown 2,3,7,8-TCDD and hexachlorodibenzo-*p*-dioxins (HxCDDs) to be carcinogenic; no data are available on the effects of inhalation exposure. Human data on exposure to both 2,3,7,8-TCDD and HxCDDs are suggestive of carcinogenicity, and both are classified as probable human carcinogens (Group B2) by EPA (EPA 1992; Fingerhut et al. 1991). In association with phenoxyherbicides and/or chlorophenols, 2,3,7,8-TCDD is classed as a Group B1 (probable human carcinogen). In skin, liver, and lungs of rodents, the compound shows evidence of tumor-promoting activity with complex hormone dependency but questionable evidence of tumor-initiating activity (NAS 1994).

An increased incidence of malignant lymphomas and multiple myelomas has been reported for some individuals exposed to 2,3,7,8-TCDD in the Seveso, Italy, incident, which involved an explosion (Puntoni et al. 1986; Merlo and Puntoni 1986), as well as in agricultural and forestry workers exposed to phenoxy herbicides containing 2,3,7,8-TCDD as a contaminant (Hoar et al. 1986; Smith et al. 1984; Pearce, Smith, and Fisher 1985). A new study by the National Academy of Sciences' Institute of Medicine concludes that sufficient evidence exists for a statistical association between exposure to phenoxy herbicides such as Agent Orange and/or 2,3,7,8-TCDD and three types of cancer—soft tissue sarcoma, non-Hodgkin's lymphoma, and Hodgkin's disease. Sufficient evidence has also been found for an association with chloracne and porphyria cutanea tarda, and limited or suggestive evidence for an association with respiratory cancer, prostate cancer, and multiple myeloma (NAS 1994). However, in a recent critical review of the evidence for 2,3,7,8-TCDD carcinogenicity in humans and animals, Johnson suggests that cancers of the thyroid, lung, and other endocrine sites are more likely to result from 2,3,7,8-TCDD exposure than are malignant lymphomas or soft tissue sarcomas (1993). Evaluation of the carcinogenicity of 2,3,7,8-TCDD in humans is complicated by the fact that exposure to this chemical is always accompanied by exposure to other chemicals as well.

The likelihood that PCBs, PCDFs, and 2,3,7,8-TCDD and other PCDDs are human carcinogens means that, theoretically, any acute exposure could result in cancer later in life. Even if these substances act mainly by promotion, the long half-life in the body and the

already existing body burden mean that acute exposures are of concern. The production of neoplasms in humans by exposure to mixtures of highly chlorinated PCBs and PCDFs resulting from heating of PCBs in both the Yusho and Yu-Cheng poisoning episodes further suggests the likely carcinogenicity of mixtures of PCBs and their combustion products.

5.3.5 Workplace Standards

Exposure to PCBs in the workplace is enforceably regulated only for mixtures containing 42 and 54% chlorine (Aroclor 1242, CAS 53469-21-9, and Aroclor 1254, CAS 11097-69-1), as shown in Table 5.3. In view of the probable carcinogenicity of the PCBs, the National Institute of Occupational Safety and Health (NIOSH) recommends an air limit of 0.001 mg/m^3 for all PCBs (ACGIH 1986; Sax and Lewis 1989). The permissible exposure limits enforced by the Occupational Safety and Health Administration (OSHA) are in accord with the recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH)—a TLV-TWA (threshold limit value as time-weighted average for 8-h exposure) of 1 mg/m^3 for Aroclor 1242 and 0.5 mg/m^3 for Aroclor 1254. These levels are based primarily on providing protection from systemic toxicity, not on providing protection from skin irritation or chloracne (ACGIH 1986).

While the Aroclors exhibit a "typical aromatic odor" and are moderately irritating to eyes and skin, no quantitative odor or irritation thresholds have been identified (NIOSH 1978). Chronic exposure to levels as low as 0.1 mg/m^3 has caused mild to moderate skin irritation and acneiform eruptions in workers (NIOSH 1978); levels of 0.32 to 2.22 mg/m^3 for 5 to 23 years produced burning sensations of the eyes, face, and skin (Ouw, Simpson, and Siyali 1976); 10 mg/m^3 of Aroclor 1242 was reported to be unbearably irritating in an occupational setting (exposure duration unspecified, but presumably prolonged) (Elkins 1959 as cited in ACGIH 1986).

The OSHA levels identified as immediately dangerous to life and health (IDLH) (NIOSH 1990) appear to correspond to the level identified as unbearably irritating for Aroclor 1242 and presumably extrapolated to Aroclor 1254.

Sax and Lewis (1989) caution that heating any of the Aroclors to decomposition is accompanied by the release of the highly toxic Cl^- ion.

The PCDFs and PCDDs are not regulated, presumably because they are contaminants inadvertently produced in industrial processes or as a result of incomplete combustion of PCBs, not intentionally produced intermediates or end products.

Table 5.3. Regulations and guidelines for workplace exposure to PCBs

Agency	Description of guideline	42% Cl (Aroclor 1242) (mg/m^3)	54% Cl (Aroclor 1254) (mg/m^3)
OSHA	Permissible exposure limit (PEL)[a]	1	0.5
ACGIH	TLV-TWA[b]	1	0.5
NIOSH	Recommended limit[c]	0.001	0.001
OSHA	IDLH[c,d]	10	5

[a]Occupational Safety and Health Administration (OSHA), 29 CFR Pt. 1910.1000, Table Z-1-A (July 1, 1992, ed.)

[b]TLV-TWA = threshold limit value as a time-weighted average for 8-h exposure; American Conference of Governmental Industrial Hygienists (ACGIH 1992).

[c]Department of Health and Human Services/National Institute of Occupational Safety and Health (NIOSH 1990).

[d]IDLH = immediately dangerous to life and health.

No ERPG values have been identified for PCBs or their combustion products. Because these substances are not corrosive to tissues, acute exposure is hazardous primarily from a delayed and persistent toxicity standpoint.

Limited information from PCB fires or explosions suggests that firefighters or workers may experience deleterious effects that would affect performance, but even these effects appear to be somewhat delayed. For example, Seppalainen, Vuojolahti, and Elo (1985) report that after a capacitor explosion and fire, "clearing workers" became nauseated, experienced headache, and perspired intensely at about 1.5 h after the explosion; air concentrations of PCBs were not measured until 5.5 h after the explosion, at which time the maximum levels were 8 to 16 mg/m^3. Ten workers were hospitalized, but the immediate signs and symptoms subsided quickly. Other delayed effects are discussed in Sect. 5.3.4. It should be noted that the effects may be a result of exposure to substances other than PCBs and their combustion products or to a mixture, as other substances were almost certainly present.

A small group of firefighters was exposed for 15 to 30 min to smoke and fumes from a PCB fire in which a transformer exploded (Kilburn, Warsaw, and Shields 1989). Further intermittent inhalation and dermal exposure ensued, but air levels of PCBs or combustion products were not measured.

Headache, fatigue, weakness, and other signs and symptoms were reported but were not experienced until 2 d to 3 months after exposure. These and other delayed effects in this group are discussed in more detail in Sect. 5.3.4.

5.3.6 Summary of Health Effects Overview

- PCBs are ubiquitous environmental contaminants, as are their impurities and pyrolysis/combustion products, the PCDFs and PCDDs.
- Structure-activity relationships distinguish dioxin-like PCBs that are coplanar and whose chlorine substituents and molecular configuration mimic 2,3,7,8-TCDD from other classes that have significant toxic activity but act by different mechanisms.
- Most people in industrialized countries carry a body burden of PCBs and several PCDF and PCDD congeners that is concentrated in fatty tissues and fluids such as breast milk. This PCB body burden is near enough to toxic levels that the offspring of more highly-exposed mothers in two American populations with excess environmental exposure exhibited effects that included developmental neurotoxicity.
- Other human responses to occupational and environmental PCB exposure include skin irritation, rashes, and chloracne; induction of liver enzymes and liver damage; peripheral sensory nerve damage; and possible genotoxic and carcinogenic effects.
- Effects in animal species include weight loss (wasting); lethality; liver damage; immunotoxicity; reproductive, neuro-, and fetotoxicity; teratogenicity; and carcinogenicity.
- Wide variations are seen in species and strain sensitivities to PCBs, with humans among the least sensitive species for some endpoints, but the most sensitive for developmental neurotoxicity.
- 2,3,7,8-TCDD is the most toxic of the PCDDs, with an acute LD_{50} in the µg/kg range in some species; sensitivity varies almost 4 orders of magnitude among animal species and strains.
- Effects of the PCDDs in animals include liver damage, microsomal enzyme induction, immunotoxicity, edema, systemic hemorrhage, bone marrow suppression, thymic atrophy, weight loss, teratogencity, fetotoxicity, and carcinogenicity.
- PCDD effects in humans include liver damage, changes in lipid metabolism, porphyria cutanea tarda, neurotoxicity, hematologic changes, chloracne, hyperpigmentation, and developmental neuro- and immunotoxicity.
- The toxic effects of the PCDFs are similar to those of the PCDDs in animals and show similar structure-activity relationships; toxicity increases with increasing structural similarity to 2,3,7,8-TCDD.
- Exposure of two human populations to mixtures of highly chlorinated PCBs in combination with highly chlorinated PCDFs caused severe and persistent chloracne, hyperpigmentation,

ocular effects, nausea and diarrhea, hepatomegaly, peripheral neuropathy, carcinogenicity, and lethality; in one accident, increased infant mortality, developmental delays and developmental neurotoxicity from in utero exposure have been well-documented.

- Delayed effects of 2,3,7,8-TCDD exposure include chloracne, elevated serum cholesterol levels, hirsutism, and signs and symptoms of neurotoxicity; 2,3,7,8-TCDD and HxCDDs are considered probable human carcinogens.
- Workplace standards have been set only for two of the highly-chlorinated commercial PCB mixtures, Aroclors 1242 and 1254.
- No quantitative odor or irritation thresholds have been identified for PCBs or their combustion products; they have poor warning qualities.
- No ERPG levels have been established for PCBs or their combustion products.

5.4 ESTIMATES OF HEALTH EFFECTS

The following estimates of body burdens and associated air levels and concentration-time products are associated with significant but unquantifiable degrees of uncertainty. Many of the data for various endpoints and chemicals were obtained in animal studies using well-defined dose levels but small numbers of animals. The endpoints for which there are human data are based on much larger numbers of exposed individuals, but the exposures are much less well-defined both in terms of amount and mixture composition. In addition, assumption were made with regard to absorption and relevance of oral to inhalation exposure, as well as interspecies extrapolation. Furthermore, this analysis does not take into account the existing body burden of PCBs and related substances, as data on the local population are not at hand. The air levels calculated in subsequent sections corresponding to the toxicological endpoints of interest assume no previous exposure and, therefore, may not be protective. It would be desirable to obtain data on the distribution of PCBs, PCDFs, and PCDDs in tissues or fluids of individuals from this area or from an appropriate surrogate population and adjust the air levels corresponding to toxicological endpoints of concern accordingly.

5.4.1 PCBs

In general, quantitative data are not available relating human responses to acute (< 14-d) PCB exposure by inhalation, oral, or dermal routes (ATSDR 1993). Thus, animal studies must provide a basis for estimating exposures and doses corresponding to most of the endpoints of interest.

Regarding the desired endpoints, two general observations must be made. First, the data permit identification of a NOAEL but not a no-effects level. Second, the lowest observed adverse

effects level (LOAEL) is used here as the basis for the onset of reversible effects endpoint, with the assumption that the effect is reversible, although most studies were not designed to determine reversibility. The fact that most mild skin and liver enzyme effects in PCB-exposed workers appear to be reversible on cessation of exposure suggests that using the LOAEL in this way is reasonable.

5.4.1.1 No observed adverse effects level (NOAEL)

The only animal study providing acute PCB exposure data from which NOAEL values could be derived is that of Carter (1985), in which weanling rats were fed Aroclor 1254 incorporated into food at levels of 4 and 8 ppm for 4 d [equivalent to 0.5 and 1.0 mg/(kg · d)]. This exposure resulted in increased serum cholesterol levels and relative liver weights in the 1.0 mg/(kg · d) group (LOAEL) but not in the 0.5 mg/(kg · d) group (NOAEL). For this estimate, the total 4-d intake was used for the animal NOAEL and LOAELs, or 2 mg/kg and 4 mg/kg.

An equivalent human NOAEL is calculated from the rat data of Carter (1985) using the recently revised reference adult male body weight (ICRP 1994), as shown in Eq. 5.1:

$$AbsD_h = D_a \times BW_h \tag{5.1}$$

where

$AbsD_h$ = total absorbed dose of substance in human (mg),
D_a = absorbed dose of substance in animal per unit body weight (mg/kg),
BW_h = reference human body weight (73 kg).

The corresponding atmospheric levels that would result in a human absorbed dose approximating the animal NOAEL for exposures ranging from 1 to 120 min can be calculated based on a light-activity adult human ventilation rate of 25 L/min (ICRP 1994) or 0.025 m^3/min, assuming equivalent absorption by the inhalation and oral routes.

This assumption of equivalent absorption by oral and inhalation routes is based on limited experimental data in rats and monkeys that show most PCB congeners that were examined to be very well absorbed upon acute oral administration. Absorption was 90 to >99%, mostly >95%, for a number of congeners tested in rats by Albro and Fishbein (1972) and over 90% for Aroclor 1248 given to rhesus monkeys (Allen, Norback, and Hsu 1974). The physicochemical properties of PCBs are such that they would also be expected to be efficiently

absorbed on inhalation exposure (EPA 1993). One small inhalation study of six rats exposed for 2 h to 30 g/m^3 (Pydraul A200, 42% chlorine) showed that the PCBs were well and rapidly absorbed, but the data do not permit quantitation of the total amount absorbed (Benthe et al. 1972, as cited in ATSDR 1993).

A conservative assumption, therefore, is that the PCBs and related compounds are 100% absorbed by the oral and inhalation routes; as an example, the calculation of the air level is shown in Eq. 5.2:

$$HEC = \frac{AbsD_h}{\dot{V}_E \times t} \tag{5.2}$$

where

HEC = human equivalent concentration in air (mg/m^3),

$\dot{V}_E$ = ventilation rate (m^3/min); $\dot{V}_E = V_T \times f$, where V_T = tidal volume (m^3) and f = breathing frequency (breaths/min),

t = duration of exposure (min).

The NOAEL 10-min air level is 580 mg/m^3 and the corresponding concentration-time product is 5800 mg-min/m^3.

Similar calculations can be done, where appropriate data exist, to obtain absorbed doses and air levels corresponding to the onset of reversible effects levels, the onset of irreversible effects levels, and the LD_{50}/LC_{50}.

The PCBs, especially the highly chlorinated ones, are extensively absorbed and retained in the body and metabolized only slowly; their effects are often delayed and may be dependent on total dose. Therefore, it is reasonable to use Haber's law to calculate air levels corresponding to various exposure times resulting in the toxicological endpoint of concern once the absorbed dose corresponding to that endpoint has been determined. Safety factors to allow for interspecies extrapolation have not been applied to the animal data used in this analysis, as humans appear to be about as sensitive as the rat and much less sensitive than the guinea pig for systemic toxicity. Safety factors to allow for differences in individual sensitivity have generally not been used here as the purpose has been to develop estimates based on the average individual rather than the most sensitive members of the population.

The air levels for three durations of exposure corresponding to NOAEL, onset of reversible effects, and LD_{50} body burdens for PCBs are listed in Table 5.4 and illustrated for durations from 1 to 120 min in Fig. 5.1.

5.4.1.2 Detection threshold

PCBs have poor warning qualities; no quantitative odor detection or irritation thresholds have been identified. Chronic exposure to levels as low as 0.1 mg/m^3 have caused mild to moderate skin irritation and acneiform eruptions in workers; 10 mg/m^3 of Aroclor 1242 was unbearably irritating to workers (see Sect. 5.3.5).

5.4.1.3 Irritation/reversible effects

No human data are available on which to base an estimate of the onset of irritation (see Sect. 5.3.5). Therefore, the LOAEL of 4 mg/kg from the rat study of liver effects by Carter (1985) is used as the basis for estimating the onset of reversible effects level for humans. The corresponding human LOAEL is estimated to be 290 mg and the concentration-time product, 12,000 $mg\text{-}min/m^3$.

5.4.1.4 Irreversible effects

No animal data were found on which to base the onset of irreversible effects for liver or other types of systemic toxicity. As mentioned previously, most animal experiments have not been designed to determine the reversibility or irreversibility of the effects noted for PCBs.

A human data set has been located, however, on which to base both a NOAEL and an onset of irreversible effects level, at least for the general population. These may also be applied to the female worker population. The toxicological effect is in the category of developmental neurotoxicity and consists of deleterious effects on visual memory in infants and on verbal and quantitative short-term memory in the same population at age four. Tilson, Jacobson, and Rogan (1990) identified a NOAEL of 1.0 ppm in human breast milk and presented a method for estimating the corresponding body burden for these effects on human infants born to mothers with elevated PCB body burdens, presumably from ingestion of PCB-contaminated Lake Michigan fish. Jacobson, Jacobson, and Humphrey (1990) identified a threshold breast milk concentration of 1.25 ppm for the persisting cognitive effects at age four; this threshold is used together with the approach of Tilson, Jacobson, and Rogan (1990) to calculate the body burden associated with this threshold, which is equated with the onset of irreversible effects. These investigators have shown that the quantity of PCB-contaminated breast milk ingested is unrelated to the presence or degree of cognitive or other developmental deficits, indicating that

Table 5.4. Summary of effect levels for PCBs and PCB-combustion product mixtures: air concentrations resulting in absorbed doses of toxicants corresponding to endpoints

Substance and exposure time (min)	Air concentration by endpoint (mg/m^3)						
	NOAEL	Onset of reversible effects	Onset of irreversible effects	$LD_{1.2}$	LD_{50}	General population NOAEL[a]	General population onset of irreversible effects[a]
PCB[b]							
10	580	1,200			3.0×10^5	6	7.5
60	97	200			49,000	1	1.3
120	49	97			25,000	0.5	0.63
PCB_{oil}[c]							
10				5,800			
60				970			
120				490			
PCB_{soot}[d]							
10	1.9		19		79		
60	0.32		3.2		13		
120	0.16		1.6		6.6		
TCDF/PCDF[e]							
10	0.0058	0.012	0.31		146		
60	0.00097	0.0020	0.051		24		
120	0.00049	0.00097	0.026		12		

Table 5.4. (cont.)

Substance and exposure time (min)	Air concentration by endpoint (mg/m^3)						
	NOAEL	Onset of reversible effects	Onset of irreversible effects	$LD_{1.2}$	LD_{50}	General population NOAEL[a]	General population onset of irreversible effects[a]
PCDD[f]							
10	0.0012	0.0023	0.061		29		
60	0.00020	0.00039	0.010		4.9		
120	0.000097	0.00020	0.0051		2.4		
2,3,7,8-TCDD[g]							
10	0.00029	0.00058	0.015		7.3		
60	0.000049	0.000097	0.0026		1.2		
120	0.000024	0.000049	0.013		0.61		

[a]Female workers; based on human data for developmental neurotoxicity (Tilson, Jacobson, and Rogan 1990).

[b]Based on animal experimental data for liver toxicity and lethality.

[c]Based on human data from Yu Cheng poisoning episode (PCB/PCDF contamination of ingested rice-bran oil); based on estimated average intake of PCBs; also resulted in 20% perinatal mortality of infants conceived in 3-year postexposure period.

[d]Based on toxicity of Binghamton soot sample to female Hartley guinea pigs; calculated on measured PCB content of soot (0.5%), which was also rich in PCDF and PCDD/TCDD; adjusted for enhanced toxicity as if administered in oil.

[e]Based on potency of TCDF/PCDF relative to 2,3,7,8-TCDD.

[f]Based on potency of PCDD relative to 2,3,7,8-TCDD.

[g]Based on animal experimental data for liver enzyme induction, developmental male reproductive toxicity, and lethality.

the toxic effect results from in utero exposure. Because of the persistence of PCBs in the body, any female of childbearing age or within several years of puberty is a potential target whether or not she is pregnant at the time of exposure. The 15-mg NOAEL body burden for visual recognition memory for a 25-year-old, 60-kg, 25% body-fat, primiparous female calculated from the 1.0 ppm breast-milk PCB levels [using the method of Tilson, Jacobson, and Rogan (1990)] and that calculated in this analysis for the onset of irreversible effects (19 mg) were adjusted by a safety factor of 10 [as recommended by Tilson, Jacobson, and Rogan (1990)] to allow for variations in body weight, body fat content, number of previous pregnancies, and sensitivity. This adjustment was necessary because of the assumptions employed in calculating body burdens from breast-milk PCB concentrations; therefore, the body burdens are estimated to be 1.5 mg (NOAEL) and 1.9 mg (onset of irreversible effects). The corresponding PCB air levels for 10, 60, and 120-min exposures are displayed in Table 5.4 and for 1 to 120-min time periods, in Fig. 5.2. The corresponding concentration-time products are 60 (NOAEL) and 75 mg-min/m^3 (irreversible effects).

5.4.1.5 Lethal dose or concentration at 50% (LD_{50}/LCt_{50})

Single-dose oral LD_{50} values are available for mink (750 mg/kg, Aroclor 1221) (Aulerich and Ringer 1977) and rats (1010 mg/kg, Aroclor 1254 in corn oil) (Garthoff et al. 1981). Because Aroclor 1254 is a more highly-chlorinated mixture than Aroclor 1221 and human beings appear to have a PCB sensitivity more like the rat than the highly sensitive mink, an equivalent human LD_{50} absorbed dose of 74,000 mg was calculated from the rat value; the corresponding concentration-time level is 3.0×10^6 mg-min/m^3.

5.4.1.6 Summary

- No data are available on which to base a quantitative estimate of a detection threshold.
- The LOAEL for PCBs is based on a rat feeding study; the LOAEL for increased relative liver weight was found to be 1.0 mg/(kg · d) or 4 mg/kg. The equivalent human body burden is estimated to be 290 mg for a 73-kg adult male. The corresponding concentration-time product is 12,000 mg-min/m^3.
- A NOAEL body burden of 1.5 mg and an onset of irreversible effects body burden of 1.9 mg for the general public and female workers are based on human data for irreversible developmental neurotoxicity (deficits in visual recognition memory in infants, deficits in verbal and quantitative short-term memory at age four in the same children). The corresponding concentration-time product for the NOAEL is 60 and for irreversible effects is 75 mg-min/m^3. No animal data were identified as a basis for the irreversible effects level for systemic effects.

- The acute oral LD_{50} value for rats of 1010 mg/kg for Aroclor 1254 exposure was selected as the basis for estimating the equivalent human LD_{50} body burden value of 74,000 mg and the corresponding concentration-time value of 3.0×10^6 mg-min/m^3.

5.4.2 Toxicological Endpoints: Acute Exposure to TCDD, PCDD, and TCDF/PCDF

The makeup of toxic mixtures resulting from accidental releases of PCB pyrolysis products or products of incomplete PCB combustion cannot be predicted. Therefore, the air levels of pure 2,3,7,8-TCDD and related polychlorinated compounds resulting in accumulation of absorbed doses corresponding to the endpoints of interest have been identified here by relative potency consideration for comparison with those of PCBs. These air levels can also be compared with those of a PCB/PCDF mixture for which a human response can be quantitated (Sect. 5.4.3.1) and with a PCB/PCDD/PCDF-laden soot mixture that has been tested in guinea pigs and analyzed for chemical constituents (Sect. 5.4.3.2). The soot sample resulted from a PCB transformer fire at Binghamton, New York; soot from that incident contained the most toxic constituents of soots from a number of incidents evaluated and tabulated in a mid-1980s NIOSH report (NIOSH 1986). Table 5.2 lists the constituents of soots from PCB incidents including the Binghamton fire, as compiled by NIOSH (1986). This table could be used to estimate the amounts of combustion products that might form in a fire. Additional detailed information on soot composition from PCB accidents is found in a review by O'Keefe and Smith (1989).

5.4.2.1 2,3,7,8-TCDD

NOAEL. Neubert (1991) identifies the animal NOAEL for liver enzyme induction from single dose exposure as 1 ng/kg body weight (0.000001 mg/kg), based on data from several investigators (Kitchin and Woods 1979; Abraham, Krowke, and Neubert 1988; Kruger et al. 1990). Derivation of an equivalent human NOAEL absorbed dose of 0.000073 mg is based upon these studies in both rats and marmoset monkeys. The corresponding concentration-time value is 0.0029 mg-min/m^3.

Onset of reversible effects. A LOAEL of 0.002 µg/kg (0.000002 mg/kg) for reversible liver enzyme induction in female SD rats (Kitchin and Wood 1979) was selected as the basis for estimating the human absorbed dose of 0.00015 mg corresponding to the onset of reversible effects. The rats were exposed by single gavage dosing with 2,3,7,8-TCDD in corn oil. The corresponding concentration-time value is 0.0058 mg-min/m^3.

Onset of irreversible effects. No data for liver enzyme induction or other systemic toxicity was found upon which to base a value for the onset of irreversible toxicity. However,

administration of a single oral dose of 2,3,7,8-TCDD in corn oil/acetone (19:1, v/v) to pregnant Holzman rats (SD-derived) on day 15 of gestation has been shown to alter the neuroendocrine control pattern of pituitary luteinizing hormone secretion and control of male sexual behavior in male offspring (Mably et al. 1992a). An even more sensitive endpoint in the male offspring was found to be spermatogenesis, with a decrease to 57–74% of the control value observed at the highest dose tested (Mably et al. 1992b). The lowest dose tested, 0.064 µg/kg (0.000064 mg/kg), had a statistically significant effect on spermatogenesis that persisted through age 120 d, the time when maximum sperm production is normally attained in the rat. While the reductions in spermatogenesis were not sufficient to alter reproductive performance in the rat, which produces 10 times more sperm than necessary for fertility, reproductive efficiency in human males is relatively low compared to the rat and other mammalian species, usually with only 2–4 times the number of sperm needed for fertility (Working 1988). Thus, reductions in spermatogenesis in human males, even if small, could have a significant effect on fertility, particularly in oligospermic men. The human absorbed dose corresponding to the onset of irreversible effects is estimated to be 0.0038 mg; the related concentration-time value is 0.15 mg-min/m^3.

LD_{50}. The 2,3,7,8-TCDD rat LD_{50} selected upon which to base a calculated equivalent human LD_{50} absorbed dose of 1.8 mg is 25 µg/kg (0.025 mg/kg). This is based on a value of 25 µg/kg for female and weanling male SD rats given a single intraperitoneal (IP) dose in olive oil (Beatty, Vaughn, and Neal 1978), and on a value of 22 µg/kg for acute oral exposure of Sherman rats (Schwetz et al. 1973). The corresponding concentration-time value is 73 mg-min/m^3.

The air levels of 2,3,7,8-TCDD resulting in attainment of absorbed doses corresponding to the toxicologic endpoints of concern are displayed graphically in Fig. 5.4. The absorbed doses and concentration-time products corresponding to these endpoints are listed in Table 5.1.

Summary. The following list provides a summary of the information pertinent to 2,3,7,8-TCDD exposures.

- No data are available on which to base a quantitative estimate of a detection threshold.
- The acute NOAEL of 1 ng/kg body weight (0.000001 mg/kg) for liver enzyme induction in rats and marmoset monkeys has been selected as the basis for a calculation of an equivalent human NOAEL of 0.000073 mg. The corresponding concentration-time value is 0.0029 mg-min/m^3.
- The onset of reversible effects value of 0.00015 mg in humans is based on the acute oral LOAEL of 0.002 µg/kg (0.000002 mg/kg) for reversible liver enzyme induction in female SD rats. The corresponding concentration-time value is 0.0058 mg-min/m^3.

- The onset of irreversible effects absorbed dose estimate for humans of 0.0038 mg is based on production of developmental reproductive toxicity (inhibition of spermatogenesis) by acute oral exposure of pregnant rats at 0.000064 mg/kg. The corresponding concentration-time product for humans is 0.15 mg-min/m^3.
- The LD_{50} absorbed dose estimate for humans of 1.8 mg is based on a rat value of 25 µg/kg (0.025 mg/kg) for acute oral exposure. The corresponding concentration-time product for humans is 73 mg-min/m^3.

5.4.2.2 Other PCDDs and PCDFs

Values for equivalent toxicological endpoints were calculated from those of 2,3,7,8-TCDD using factors derived from a relative potency analysis for dioxins and dibenzofurans used recently by Owen (1990). This analysis was based on the *RA*pid *S*creening of *H*azard (RASH) methodology developed at Oak Ridge National Laboratory (ORNL) by Jones et al. (1985, 1988). The method uses published toxicity data to derive an array of relative potency values characterizing the toxicity potential of a chemical or substance compared to a reference standard. The results of the RASH analysis for relative potency of dioxins and dibenzofurans are shown in Table 5.5. It can be seen from this table that the TCDDs (epitomized by 2,3,7,8-TCDD) are the most toxic congeners, with the PCDDs being about one-fourth and the chlorinated dibenzofurans about one-twentieth as toxic as 2,3,7,8-TCDD.

Table 5.5. Relative potency of dioxin and dibenzofuran congeners

Congener	Relative potency[a]
TCDD	1
PCDD	0.25
TCDF	0.05
PCDF	0.05

[a]Owen 1990.

EPA is developing its own approach to assessing the toxicity of mixture of dioxins, furans, and PCBs in terms of toxicity equivalency factors (Barnes, Kutz, and Bottimore 1989; EPA 1991; Safe, Yao, and Davis 1990). However, this approach is still under development, and the current set of factors is generally less conservative than those arrived at by RASH analysis. Thus, the RASH approach is preferred here.

Absorbed doses and corresponding concentration-time products of PCDDs and TCDF/PCDFs related to various toxicological levels for acute exposure are listed in Table 5.1. Corresponding air levels are displayed graphically for PCDDs in Fig. 5.4 and for TCDF/PCDFs in Fig. 5.5.

5.4.3 Toxicological Endpoints: PCBs and Combustion Products

5.4.3.1 Exposure to PCB/PCDF-contaminated rice-bran oil

In the Yusho and Yu-Cheng incidents discussed previously, two human populations were exposed orally to PCB/PCDF-contaminated rice-bran cooking oils over a period of months as a result of leakage of PCB-laden heat-exchanger fluid into the oil; the PCBs had been exposed to elevated temperatures sufficient to cause the formation of highly chlorinated PCBs and PCDFs (230°C at 2–3 mm Hg) (Miyata et al. 1985; P. H. Chen et al. 1985; Chen et al. 1992). Exposure estimates for the Yu-Cheng incident allow calculation of a body burden value for the level causing 1.2% lethality in the exposed population ($LD_{1.2}$). Using the estimated average intake of 1 g PCB (Chen et al. 1992) [intake range: 0.7–1.84 g (Hsu et al. 1985)] and an average body weight of 50 kg (Masuda et al. 1985), a PCB body burden of 1.46 g (≈1500 mg) for a reference Caucasian male can be estimated. It should be kept in mind that this is an exposure to more highly chlorinated PCBs than those contained by the unheated commercial preparation or even typical used (heated) Kanechlor 400 (Miyata et al. 1985). The intake of 1 g of PCBs was accompanied by an estimated average intake of 3.8 mg of PCDFs and 586 mg of polychlorinated quaterphenyls (PCQs) (P. H. Chen et al. 1985). The PCQs are not thought to have contributed much to the toxic effects resulting from the exposure (Kashimoto et al. 1985). For purposes of this analysis, the $LD_{1.2}$ body burden of 1500 mg and corresponding concentration-time product (58,000 mg-min/m^3) air levels are based only on the PCB intake. The air levels corresponding to 10-, 60-, and 120-min exposures are shown in Table 5.4 and for exposures of 1 to 120 min, in Fig. 5.6.

- The onset of lethality ($LD_{1.2}$) estimated body burden of 1500 mg for PCBs in rice-bran oil is based on human data from the Yu-Cheng incident. The corresponding concentration-time product is 58,000 mg-min/m^3.

5.4.3.2 Acute exposure to PCBs, 2,3,7,8-TCDD, PCDDs, and PCDFs in Binghamton soot

Silkworth and colleagues (1982) reported the results of acute oral administration of soot from the Binghamton, New York, fire in an aqueous 0.75% methyl cellulose suspension to guinea pigs. The soot had been shown to contain toxicologically significant amounts of 2,3,7,8-TCDD and 2,3,7,8-TCDF contaminants in addition to PCBs (Smith et al. 1981). The acute NOAEL from this study was 10 mg/kg for effects on body weight, relative organ weights, hematologic

values, and serum chemistry values. At the next dose tested, 100 mg/kg, effects on body weight and relative organ weights of thymus and kidneys as well as other effects were judged significant enough to select this as the onset of irreversible effects, particularly as some deaths occurred at the next dose level, 250 mg/kg. Thus, no LOAEL can be identified from this study on which to base the onset of reversible effects. The LD_{50} value was determined both by administration of soot suspension and also by administration of benzene extracts of soot. The value derived from the aqueous suspension, 410 mg/kg, was selected as the basis for estimating the equivalent human body burden for this report, for consistency with the other endpoints. For comparison to the PCB_{oil} $LD_{1.2}$ data, the doses were adjusted based on the measured PCB content of the soot (0.5%) and to reflect the increased toxicity of the constituents had they been administered in an oil vehicle. [This adjustment was based on the enhanced toxicity of pure 2,3,7,8-TCDD in this study given in corn oil (LD_{50} = 2.5 µg/kg) as compared to the aqueous methyl cellulose suspension (LD_{50} = 19 µg/kg) (Silkworth et al. 1982).] The latter adjustment was made for purposes of comparison with the endpoints for pure 2,3,7,8-TCDD (and the values for PCDD and PCDF/TCDF obtained with reference to 2,3,7,8-TCDD) in which the animal data were obtained by oral administration of the compound in oil.

The air concentrations for 10-, 60-, and 120-min exposure durations required to produce human body burdens corresponding to the NOAEL, irreversible effects, and LD_{50} values (0.48, 4.8, and 20 mg, respectively) are presented in Table 5.4 and shown for times ranging from 1 to 120 min in Fig. 5.7. The corresponding concentration-time values are 19 mg-min/m^3, 190 mg-min/m^3, and 790 mg-min/m^3, respectively, and are listed in Table 5.1.

Silkworth et al. (1982) calculated the amounts of 2,3,7,8-TCDD (0.5 µg) and 2,3,7,8-TCDF (20 µg) in the LD_{50} dose of soot based on previous chemical analyses of the sample used in the toxicity study (Smith et al. 1981) and concluded that if the toxicities were additive, these components were not sufficient alone or together to be responsible for the observed level of toxicity in the LD_{50} study. They suggested that other highly chlorinated PCDDs and PCDFs shown by others to be present in the soot contributed to the observed toxicity.

5.4.3.3 Summary

- The NOAEL absorbed dose estimate of 0.48 mg for PCBs in soot is based on acute oral exposure of female guinea pigs to soot from the Binghamton, New York, PCB fire in an aqueous 0.75% methyl cellulose suspension. The corresponding concentration-time product is 19 mg-min/m^3.
- No data were identified as a basis for estimating the onset of reversible effects level.

- The human absorbed dose estimate of 4.8 mg for onset of irreversible effects is based on the effects of 100 mg/kg Binghamton soot in female guinea pigs. The corresponding concentration-time product is 190 mg-min/m^3.
- The LD_{50} absorbed dose estimate for humans of 20 mg is based on the acute oral LD_{50} in female guinea pigs of aqueous soot suspension at 410 mg/kg. The corresponding concentration-time product is 790 mg-min/m^3.

5.5 REFERENCES

Abraham, K., R. Krowke, and D. Neubert 1988. "Pharmacokinetics and Biological Activity of 2, 3, 7, 8-Tetrachlorodibenzo-*p*-Dioxin. 1. Dose-Dependent Tissue Distribution and Induction of Hepatic Ethoxyresorufin O-Deethylase in Rats Following a Single Injection," *Arch. Toxicol.* **62**, 359–68.

Agency for Toxic Substances and Disease Registry (ATSDR) 1993. *Toxicological Profile for Selected PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016)*, ATSDR/TP-92/16. ATSDR, U.S. Public Health Service, Atlanta.

Albro, P. W., and L. Fishbein 1972. "Intestinal Absorption of Polychlorinated Biphenyls in Rats," *Bull. Environ. Contam. Toxicol.* **8**, 26.

Allen, J. R., D. H. Norback, and I. C. Hsu 1974. "Tissue Modifications in Monkeys as Related to Absorption, Distribution, and Excretion of Polychlorinated Biphenyls," *Arch. Environ. Contam. Toxicol.* **2**, 86–95.

American Conference of Governmental Industrial Hygienists (ACGIH) 1986. *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th ed., American Conference of Governmental Industrial Hygienists, Cincinnati, pp. 128–29.

American Conference of Governmental Industrial Hygienists (ACGIH) 1992. *1992–1993 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, American Conference of Governmental Industrial Hygienists, Cincinnati.

Andersen, M. E., et al. 1993. "Modeling Receptor-Mediated Processes with Dioxin: Implications for Pharmacokinetics and Risk Assessment," *Risk Anal.* **13**, 25–36.

Aulerich, R. J., and R. K. Ringer 1977. "Current Status of PCB Toxicity, Including Reproduction to Mink," *Arch. Environ. Contam. Toxicol.* **6**, 279.

Barnes, D. G., F. W. Kutz, and D. P. Bottimore 1989. *1989 Update to the Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Debenzo-*p*-Dioxins and- Dibenzofurans (CDDs and CDFs)*, Part II, Risk Assessment Forum, EPA, Washington, D.C.

Bartmess, J. E. 1988. "The Risk of Polychlorinated Dibenzodioxins in Human Milk," *J. Human Lact.* **4**, 105–07.

Beatty, P. W., W. K. Vaughn, and R. A. Neal 1978. "Effect of Alteration of Rat Hepatic Mixed-Function Oxidase (MFO) Activity on the Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD)," *Toxicol. Appl. Pharmacol.* **45**, 513–19.

Benthe, H. F., J. Knop, and A. Schmoldt 1972. "Absorption and Distribution of Polychlorinated Biphenyls (PCB) After Inhalatory Application," *Arch. Toxicol.* **29**, 85.

Brown, J. F., Jr., et al. 1991. "Assessing the Human Health Effects of PCBs," *Chemosphere* **23**, 1811–15.

Cantor, D. S., et al. 1993. "In Utero and Postnatal Exposure to 2,3,7,8-TCDD in Times Beach, Missouri: 2. Impact on Neurophysiological Functioning," *Proceedings of DIOXIN '93: The International Conference of Organohalogen Compounds.*

Caputo, R., et al. 1988. "Cutaneous Manifestations of Tetrachlorodibenzo-*p*-Dioxin in Children and Adolescents: Follow-up 10 Years After the Seveso, Italy, Accident," *J. Amer. Acad. Dermet.* **19**, 812–19.

Carter, J. W. 1985. "Effects of Dietary PCBs (Aroclor 1254) on Serum Levels of Lipoprotein Cholesterol in Fischer Rats," *Bull. Environ. Contam. Toxicol.* **34**, 427–31.

Chemical contamination associated with car 643 fire. [Report submitted to the Port Authority of New York and New Jersey by Arthur D. Little, Inc., Cambridge, Massachusetts, contract no. 88162, May 1983:1-10].

Chen, P. H., et al. 1985. "Polychlorinated Biphenyls, Dibenzofurans, and Quaterphenyls in Toxic Rice-Bran Oil and in the Blood and Tissues of Patients with PCB Poisoning (Yu-Cheng) in Taiwan," *Environ. Health Perspect.* **59**, 59–65.

Chen, R.-C., et al. 1985. "Polychlorinated Biphenyl Poisoning: Correlation of Sensory and Motor Nerve Conduction, Neurologic Symptoms, and Blood Levels of Polychlorinated Biphenyls, Quaterphenyls, and Dibenzofurans," *Environ. Res.* **37**, 340–48.

Chen, Y.-C. J., et al. 1992. "Cognitive Development of Yu-Cheng (Oil Disease) Children Prenatally Exposed to Heat-Degraded PCBs," *JAMA* **268**, 3213–18.

Dickson, L., and S. Buzik 1993. "Health Risks of Dioxins: A Review of Environmental and Toxicological Considerations," *Vet. Hum. Toxicol.* **35**, 68–76.

Elkins, H. B. 1959. *Chemistry of Industrial Toxicology*, 153, Wiley & Sons, New York.

Fingerhut, M. A., et al. 1991. "Cancer Mortality in Workers Exposed to 2, 3, 7, 8-Tetrachlorodibenzo-*p*-Dioxin," *N. Engl. J. Med.* **324**, 212–18.

Garthoff, L. H., F. E. Cerra, and E. M. Marks 1981. "Blood Chemistry Alteration in Rats After Single and Multiple Gavage Administration of Polychlorinated Piphenyls," *Toxicol. Appl. Pharmacol.* **60**, 33–44.

Golub, M. S., J. M. Donald, and J. A. Reyes 1991. "Reproductive Toxicity of Commercial PCB Mixtures: LOAELs and NOAELs from Animal Studies," *Environ. Health Perspect.* **94**, 245–53.

Hara, I. 1985. "Health Status and PCBs in Blood of Workers Exposed to PCBs and of Their Children," *Environ. Health Perspect.* **59**, 85–90.

Harada, M. 1976. "Intrauterine Poisoning: Clinical and Epidemiological Studies of the Problem," *Bull. Inst. Constitutional Med.* **25**, 1–60.

Hoar, S. K., et al. 1986. "Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma," *J. Am. Med. Assoc.* **256**, 1141.

Holsapple, M. P., et al. 1991. "A Review of 2, 3, 7, 8-Tetrachlorodibenzo-*p*-Dioxin-Induced Changes in Immunocompetence: 1991 Update," *Toxicology* **69**, 219–55.

Hsu, S.-T. et al. 1985. "Discovery and Epidemiology of PCB Poisoning in Taiwan: A Four-Year Followup," *Environ. Health Perspect.* **59**, 5–10.

International Commission on Radiological Protection (ICRP) 1994. Human Respiratory Tract Model for Radiological Protection, ICRP Publication 66. *Ann. ICRP* **24**.

Jacobson, J. L., S. W. Jacobson, and H. E. B. Humphrey 1990. "Effects of In Utero Exposure to Polychlorinated Biphenyls and Other Contaminants on Cognitive Functioning in Young Children," *J. Pediatr.* **116**, 38–45.

Jacobson, S. W. et al. 1985. "The Effect of Intrauterine PCB Exposure on Visual Recognition Memory," *Child Dev.*, **56**, 853–60.

Jensen, A. A. 1983. "Chemical Contaminants in Human Milk," pp. 104–7 in *Residue Reviews*, ed. F. A. Gunther, Springer-Verlag, New York.

Johnson, E. S. 1993. "Important Aspects of the Evidence for 2,3,7,8-TCDD Carcinogenicity in Man," *Environ. Health Perspect.* **99**, 383–90.

Jones, T. D., P. J. Walsh, and E. A. Zeighami 1985. "Permissible Concentrations of Chemicals in Air and Water Derived from RTECS Entries: A RASH Chemical Scoring System," *Toxicol. Ind. Health* **1**, 213–34.

Jones, T. D., et al. 1988. "Chemical Scoring by a *Ra*pid *S*creening of *H*azard (RASH) Method," *Risk Anal.* **8**, 99–118.

Kashimoto, T., et al. 1985. "PCBs, PCQs and PCDFs in Blood of Yusho and Yu-Cheng Patients," *Environ. Health Perspect.* **59**, 73–78.

Kilburn, K. H., R. H. Warsaw, and M. G. Shields 1989. "Neurobehavioral Dysfunction in Firemen Exposed to Polychlorinated Biphenyls (PCBs): Possible Improvement After Detoxification," *Arch. Environ. Health* **44**, 345–50.

Kimbrough, R. D. 1987. "Human Health Effects of Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs)," *Ann. Rev. Pharmacol. Toxicol.* **27**, 87–111.

Kitchin, K. T., and J. S. Woods 1979. "2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) Effects on Hepatic Microsomas Cytochrome P-448-Mediated Enzyme Activities," *Toxicol. Appl. Pharmacol.* **47**, 537–46.

Kreiss, K. 1985. "Studies on Populations Exposed to Polychlorinated Biphenyls," *Environ. Health Perspect.* **60**, 193–99.

Kruger, N., et al. 1990. "Induction of Caffeine-Demethylations by 2,3,7,8-TCDD in Marmoset Monkeys Measured with a CO-Breath Test," *Chemosphere* **20**, 1173–76.

Kuratsune, M. 1980. "Yusho, pp. 287–302 in *Topics in Environmental Health*, Vol. 4, *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, 1st ed., ed. R. D. Kimbrough, Elsevier/North-Holland Biomedical Press, Amsterdam.

Kuratsune, M. 1989. "Yusho, with Reference to Yu-Cheng," pp. 381–400 in *Topics in Environmental Health*, Vol. 4, *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, 2nd ed., eds. R. D. Kimbrough and A. A. Jensen, Elsevier/North-Holland Biomedical Press, Amsterdam.

Landsing Property Corporation 1985. Comments in Response to EPA Proposed rule, "Polychlorinated Biphenyls (PCBs); Manufacture, Processing, Distribution in Commerce and Use Prohibitions, Use in Electrical Transformers" (*Federal Register* **49**, 39966-89 October 11, 1984), EPA docket no. OPTS 62035-N5.

Lees, P. S. J., and P. N. Breysse 1983. *Industrial Hygiene Assessment: PCB Exposure of GSA Switchgear Operators*, submitted to General Services Administration, Washington, D.C., by Johns Hopkins University, Center for Occupational and Environmental Health, Baltimore.

Lewis, R. J., Sr. 1992. *Sax's Dangerous Properties of Industrial Materials*, 8th ed., Van Nostrand Reinhold, New York.

Luotamo, M. 1991. "Congener Specific Assessment of Human Exposure to Polychlorinated Biphenyls," *Chemosphere* **23**, 1685–98.

Mably, T. A., et al. 1992a. "*In Utero* and Lactational Exposure of Male Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. 2. Effects on Sexual Behavior and the Regulation of Luteinizing Hormone Secretion in Adulthood," *Toxicol. Appl. Pharmacol.* **114**, 108–17.

Mably, T. A., et al. 1992b. "*In Utero* and Lactational Exposure of Male Rats to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin. 3. Effects on Spermatogenesis and Reproductive Capability," *Toxicol. Appl. Pharmacol.* **114**, 118–26.

Masuda, Y., et al. 1985. "PCB and PCDF Congeners in the Blood and Tissues of Yusho and Yu-Cheng Patients," *Environ. Health Perspect.* **59**, 53–58.

Melius, J. M. 1985a. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCB's in Boston, Massachusetts. U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati, Ohio.

Melius, J. M. 1985b. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Tulsa, Oklahoma, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Melius, J. M. 1985c. Memorandum to Richar A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Chicago, Illinois, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati, Ohio.

Melius, J. M. 1985d. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Columbus, Ohio, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Melius, J. M. 1985e. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Miami, Florida, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Melius, J. M. 1985f. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Wappingers Falls, New York, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Melius, J. M. 1985g. Memorandum to Richard A. Lemen, NIOSH, regarding analyses following a fire-related incident involving PCBs in Syracuse, New York, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Melius, J. M. 1985h. Memorandum to Richard to Lemen, NIOSH, regarding enalyses following a fire-related incident involving PCBs in Santa Fe, New Mexico, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies, Cincinnati.

Merlo, F., and R. Puntoni, 1986. "Soft-Tissue Sarcomas, Malignant Lymphomas, and 2,3,7,8-TCDD Exposure in Seveso," *Lancet* **2**, 1455.

Mes, J., D. J. Davies, and D. Turton 1982. "Polychlorinated Biphenyl and Other Chlorinated Hydrocarbon Residues in Adipose Tissue of Canadians," *Bull. Environ. Contam. Toxicol.* **28**, 97–104.

Miyata, H., et al. 1985. "PCBs, PCQs and PCDFs in Tissues of Yusho and Yu-Cheng Patients," *Environ. Health Perspect.* **59**, 67–72.

Institute of Medicine/National Academy of Sciences (NAS) 1994. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*, National Academy Press, Washington, D.C.

National Institute for Occupational Safety and Health (NIOSH) 1978. *Occupational Health Guideline for Chlorodiphenyl (42%Chlorine)*, U.S. Department of Health and Human Services (DHHS)/NIOSH, Cincinnati, 1–5.

National Institute for Occupational Safety and Health (NIOSH) 1981. *Health Hazard Evaluation—Our Lady of Visitation Elementary School, Cincinnati, Ohio*, 81-237-915, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati.

National Institute for Occupational Safety and Health (NIOSH) 1983. *Health Hazard Evaluation—Miami Fire Department, Miami, Florida*, 82-224-1336, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati.

National Institute for Occupational Safety and Health (NIOSH) 1984. *Health Hazard Evaluation—Hill-Murray High School, Maplewood, Minnesota*, 82-310-1475, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati.

National Institute for Occupational Safety and Health (NIOSH) 1986. *NIOSH Current Intelligence Bulletin 45: Polychlorinated Biphenyls (PCB's): Potential Health Hazards from Electrical Equipment Fires or Failures*, DHHS (NIOSH) Publication No. 86-111, DHHS/NIOSH, Cincinnati.

National Institute for Occupational Safety and Health (NIOSH) 1990. *NIOSH Pocket Guide to Hazardous Chemicals*, DHHS/NIOSH, Cincinnati, 66.

Neubert, D. 1991. "Animal Data on the Toxicity of 2,3,7,8-TCDD and Special Aspects of Risk Assessment," paper presented at a WHO Consultation on Tolerable Daily Intake of PCDDs and PCDFs from Food, Bilthoven, The Netherlands, 1990.

O'Keefe, P.W., and R. M. Smith 1989. "PCB Capacitor/Transformer Accidents," in *Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, Vol. 4 of *Topics in Environmental Health*, 2nd ed., eds. R. D. Kimbrough and A. A. Jensen, Elsevier/North Holland Biomedical Press, Amsterdam, 417–44.

Oliver, R. M. 1975. "Toxic Effects of 2,3,7,8-Tetrachlorodibenzo 1,4 Dioxin in Laboratory Workers," Br. J. Ind. Med., **32**, 49–53.

Ouw, H. K., G. R. Simpson, and D. S. Siyali 1976. "Use and Health Effects of Aroclor 1242, a Polychlorinated Biphenyl, in an Electrical Industry," *Arch. Environ. Health* **31**, 189–94.

Owen, B. A. 1990. "Criteria Development for Evaluation of HCB, PCB, PCDF, and PCDD Emissions from the K-25 TSCA Incinerator," Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.

Pearce, N. E., A. H. Smith, and D. O. Fisher 1985. "Malignant Lymphoma and Multiple Myeloma Linked with Agricultural Occupations in a New Zealand Cancer Registry-Based Study," *Am. J. Epidemiol.* **121**, 225–37.

Port Authority of New York and New Jersey 1983. *Chemical Contamination Associated with Car 643 Fire*, contract no. 88162, A. D. Little, Inc., Cambridge, Mass., May.

Portier, C., et al. 1993. "Ligand/Receptor Binding for 2,3,7,8-TCDD: Implications for Risk Assessment," *Fund. Appl. Toxicol.* **20**, 48–56.

Puntoni, R., et al. 1986. "Soft Tissue Sarcomas in Seveso," *Lancet* **1**, 525.

Safe, S., et al. 1985. "PCBs: Structure-Function Relationships and Mechanism of Action," *Environ. Health Perspect.* **60**, 47–56.

Safe, S., C. Yao, and D. Davis 1990. "Development of Toxic Equivalency Factors for Polychlorinated Biphenyls (PCBs)," *Proceedings DIOXIN '90: The International Conference of Organohalogen Compounds, Bayreuth, Sept. 10–14, Short papers*, Vol 2, Ecoinforma Press, Bayreuth, FRG, 55–59.

Sax, N. I., and R. J. Lewis, Sr. 1989. *Dangerous Properties of Industrial Materials*, 7th ed., Vol. 3, Van Nostrand Reinhold, New York, 2815–19.

Schecter, A. 1983. "Contamination of an Office Building in Binghamton, New York, by PCBs, Dioxins, Furans, and Biphenylenes after an Electrical Panel and Electrical Transformer Incident," *Chemosphere* **12**, 669–80.

Schwetz, B. A., et al. 1973. "Toxicology of Chlorinated Dibenzo-*p*-Dioxins," *Environ. Health Perspect.* **5**, 87–99.

Seppalainen, A., P. Vuojolahti, and O. Elo 1985. "Reversible Nerve Lesions After Accidental Polychlorinated Biphenyl Exposure," *Scand. J. Work Environ. Health* **11**, 91–95.

Sielken, R. L., Jr. 1987. "Statistical Evaluations Reflecting the Skewness in the Distribution of 2,3,7,8-TCDD Levels in Human Adipose Tissue," *Chemosphere* **16**, 2135–40.

Silberhorn, E. M., H. P. Glauert, and L. W. Robertson 1990. "Carcinogenicity of Polyhalogenated Biphenyls: PCBs and PBBs," *Crit. Rev. Toxicol.* **20**, 397–426.

Silkworth, J., et al. 1982. "Acute Toxicity in Guinea Pigs and Rabbits of Soot from a Polychlorinated Biphenyl–Containing Transformer Fire," *Toxicol. Appl. Pharmacol.* **65**, 425–39.

Smith, A. H., et al. 1984. "Soft Tissue Sarcoma and Exposure to Phenoxyherbicides and Chlorophenols in New Zealand," *J. Natl. Cancer Inst.* **73**, 1111.

Smith, R. M., et al. 1981. *Analysis of a Binghamton Soot Sample for Tetrachlorodibenzofurans and Tetrachlorodibenzo-p-dioxins*. N.Y. State Department of Health Report, October 1, Albany, N.Y.

Smoger, G. H., et al. 1993. "In Utero and Postnatal Exposure to 2,3,7,8-TCDD in Times Beach, Missouri. 1. Immunological Effects: Lymphocyte Phenotype Frequencies," Presented at DIOXIN '93.

Swain, W. R. 1993. Ecologic International, Inc., personal communication to N. B. Munro, Health Sciences Research Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.

Tilson, H. A., J. L. Jacobson, and W. J. Rogan 1990. "Polychlorinated Biphenyls and the Developing Nervous System: Cross-Species Comparisons," *Neurotoxicol. Teratol.* **12**, 239–48.

U.S. Environmental Protection Agency (EPA) 1984. *Exposure Assessment: Fires Involving PCB Transformers*, contract no. 68-01-6271, Versar, Inc., Springfield, Va., March.

U.S. Environmental Protection Agency (EPA) 1986. *Broad Scan Analysis of the FY 82 National Human Adipose Tissue Survey Specimens*, Vol. 3, *Semi-Volatile Organic Compounds*, EPA-560/5-86-037, Office of Toxic Substances, EPA, Washington, D.C.

U.S. Environmental Protection Agency (EPA) 1988. *Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs)*, Office of Drinking Water, EPA, Washington, D.C.

U.S. Environmental Protection Agency (EPA) 1991. *Workshop Report on Toxicity Equivalency Factors for Polychlorinated Biphenyl Congeners*, EPA/625/3-91/020, Risk Assessment Forum, EPA, Washington, D.C.

U.S. Environmental Protection Agency (EPA) 1992. *Dioxin Reassessment, Chapter 3. Acute, Subchronic, and Chronic Toxicity*, EPA/600/AP-92/001c, Office of Health and Environmental Assessment, Washington, D.C.

U.S. Environmental Protection Agency (EPA) 1993. *Workshop Report on Developmental Neurotoxic Effects Associated with Exposure to PCBs*, EPA/630/R-92/004, EPA, Washington, D.C.

Working, P. K. 1988. "Male Reproductive Toxicology: Comparison of the Human to Animal Models," *Environ. Health Perspect.* **77**, 37–44.

Yu, M.-L., et al. 1991. "In Utero PCB/PCDF Exposure: Relation of Developmental Delay to Dysmorphology and Dose," *Neurotoxicol. Teratol.* **13**, 195–202.

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