PNL-7505 Vol. 2
UC-350

18 J

Health Effects Associated with Energy Conservation Measures in Commercial Buildings

Volume 2: Review of the Literature

R. D. Stenner
M. C. Baechler

September 1990

Prepared for
the Bonneville Power Administration
under a Related Services Agreement
with the U.S. Department of Energy
Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
Operated for the U.S. Department of Energy
by Battelle Memorial Institute

Battelle

PNL-7505 Vol. 2

DISCLAIMER

PACIFIC NORTHWEST LABORATORY
operated by
BATTELLE MEMORIAL INSTITUTE
for the
UNITED STATES DEPARTMENT OF ENERGY
under Contract DE-AC06-76RLO 1830

Printed in the United States of America

Available to DOE and DOE contractors from the
Office of Scientific and Technical Information, P.O. Box 62, Oak Ridge, TN 37831;
prices available from (615) 576-8401. FTS 626-8401.

Available to the public from the National Technical Information Service,
U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

NTIS Price Codes, Microfiche A01

Printed Copy

Price Code	Page Range	Price Code	Page Range
A02	1- 10	A15	326-350
A03	11- 50	A16	351-375
A04	51- 75	A17	376-400
A05	76-100	A18	401-425
A06	101-125	A19	426-450
A07	126-150	A20	451-475
A08	151-175	A21	476-500
A09	176-200	A22	501-525
A10	201-225	A23	526-550
A11	226-250	A24	551-575
A12	251-275	A25	576-600
A13	276-300	A99	601-Up
A14	301-325		

PNL-7505 Vol. 2
UC-350

HEALTH EFFECTS ASSOCIATED WITH ENERGY CONSERVATION MEASURES IN COMMERCIAL BUILDINGS

VOLUME 2: REVIEW OF THE LITERATURE

R. D. Stenner
M. C. Baechler

September 1990

Prepared for
the Bonneville Power Administration
under a Related Services Agreement
with the U.S. Department of Energy
Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
Richland, Washington 99352

SUMMARY

Indoor air quality can be impacted by hundreds of different chemicals. More than 900 different organic compounds alone have been identified in indoor air. Health effects that could arise from exposure to individual pollutants or mixtures of pollutants cover the full range of acute and chronic effects, including largely reversible responses, such as rashes and irritations, to the irreversible toxic and carcinogenic effects. These indoor contaminants are emitted from a large variety of materials and substances that are widespread components of everyday life.

Pacific Northwest Laboratory conducted a search of the peer-reviewed literature on health effects associated with indoor air contaminants for the Bonneville Power Administration to aid the agency in the preparation of environmental documents.

Results are reported in two volumes. Volume 1 summarizes the results of the search of the peer-reviewed literature on health effects associated with a selected list of indoor air contaminants. In addition, the report discusses potential health effects of polychlorinated biphenyls and chlorofluorocarbons. All references to the literature reviewed are found in Volume 2. Volume 2 provides detailed information from the literature reviewed, summarizes potential health effects, reports health hazard ratings, and discusses quantitative estimates of carcinogenic risk in humans and animals.

Contaminants discussed in this report are those that

- have been measured in the indoor air of a public building or
- have been measured (significant concentrations) in test situations simulating indoor air quality (as presented in the referenced literature) and
- have a significant hazard rating.

This report reflects information currently available on the health effects associated with each of the selected contaminants. This information was obtained by conducting a comprehensive literature search on each of the selected contaminants. In addition, three active, professionally maintained and peer-reviewed on-line chemical databases were used to locate the latest

health effects information on each contaminant. The on-line databases used were the U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS), the National Library of Medicine's Hazardous Substance Data Bank (HSDB), and the National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemicals (RTECS).

It is recognized that the chemicals addressed in this report likely represent only a small number of the host of potential hazardous contaminants that may be found inside public buildings. In this report, public buildings are considered to be those commercial buildings that are open to the public.

CONTENTS

FIGURES

TABLES

TABLES (contd)

1.0 INTRODUCTION

The energy crisis of 1973 and its consequences focused attention on the problem of indoor air pollution. Among the measures taken to conserve energy have been the "tightening" of existing buildings and the design and construction of "tighter" new buildings. The tightening of buildings saves energy by activities such as reducing drafts around doors, windows, openings for pipes and ducts, through electrical outlets, cracks, and other openings. When people living and working in these tightened buildings began to complain in increased numbers about headaches and general malaise, investigations revealed accumulations of potentially toxic or carcinogenic chemicals because these buildings were insufficiently ventilated. In tightened buildings, indoor air concentrations of these chemicals can exceed outdoor values as well as national air-quality standards. Because the average person spends roughly 90% of his/her life indoors, the importance of indoor air quality for human health is readily apparent.

This report presents the best available information on the health effects associated with each of the selected contaminants. This information was obtained by conducting a comprehensive literature search on each of the selected chemicals. In addition, three active, professionally maintained and peer-reviewed on-line chemical databases were used to locate the latest health effects information on each contaminant. The on-line databases used were the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), the National Library of Medicine's Hazardous Substance Data Bank (HSDB), and the National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemicals (RTECS).

This report is presented in two volumes. Volume 1 summarizes the results of a search of the peer-reviewed literature on health effects associated with a selected list of indoor air contaminants. In addition, the report discusses potential health effects of polychlorinated biphenyls and chlorofluorocarbons. Volume 2 provides detailed information from the literature reviewed, summarizes potential health-effects, reports health hazard ratings, and discusses quantitative estimates of carcinogenic risk in humans and animals.

This report discusses only those contaminants that have been measured in the indoor air of a public building or measured (significant concentrations) in test situations simulating indoor air quality (as presented in the referenced literature) and that have a significant hazard rating. It is recognized that the chemicals addressed in this report are likely to represent only a small number of the host of potential hazardous contaminants that may be found inside public buildings. In this report public buildings are considered to be those commercial buildings that are open to the public.

1.1 DEFINITION OF TERMS

A glossary of definitions is appropriate to establish a common set of terms for discussing health effects of contaminants as they relate to the performance of risk assessments and health assessment evaluations. Definitions for the terms presented in this section were taken from the IRIS database for risk assessment information maintained by the EPA (IRIS 1990). These definitions are not intended to be all-encompassing, nor should they be construed to be "official" definitions. It is assumed that the user has some familiarity with risk assessment and health science. For terms that are not included in this glossary, the user should refer to standard health science, biostatistical, and medical textbooks and dictionaries.

Acceptable Daily Intake -- An estimate of the daily exposure dose that is likely to be without deleterious effect even if continued exposure occurs over a lifetime.

Acute exposure -- One dose or multiple doses occurring within a short time (24 hours or less).

Acute hazard or toxicity -- see Health hazard.

Added risk -- The difference between the cancer incidence under the exposure condition and the background incidence in the absence of exposure; AR = P(d) - P(0).

Anecdotal data -- Data based on descriptions of individual cases rather than on controlled studies.

Anemia -- A condition marked by significant decreases in hemoglobin concentration and in the number of circulating red blood cells.

Angina pectoris -- Constricting chest pain which may be accompanied by pain radiating down the arms, up into the jaw, or to other sites.

Anoxic stress -- Oxygen starvation.

Ataxia -- Loss of coordination.

Attributable risk -- The difference between risk of exhibiting a certain adverse effect in the presence of a toxic substance and that risk in the absence of the substance.

Benign -- Not malignant; remaining localized.

Bioassay -- The determination of the potency (bioactivity) or concentration of a test substance by noting its effects in live animals or in isolated organ preparations, as compared with the effect of a standard preparation.

Bioavailability -- The degree to which a drug or other substance becomes available to the target tissue after administration or exposure.

Bronchiolalveolitis -- Inflammation in the bronchi and alveoli.

Bronchospasm -- Temporary narrowing of the bronchi due to violent, involuntary contraction of the smooth muscle of the bronchi.

Carcinogen -- An agent capable of inducing a cancer response.

Carcinogenesis -- The origin or production of cancer, very likely a series of steps. The carcinogenic event so modifies the genome and/or other molecular control mechanisms in the target cells that these can give rise to a population of altered cells.

Case-control study -- An epidemiologic study that looks back in time at the exposure history of individuals who have the health effect (cases) and at a group who do not (controls), to ascertain whether they differ in proportion exposed to the chemical under investigation.

Chronic effect -- An effect that is manifest after some time has elapsed from initial exposure. See also Health hazard.

Chronic exposure -- Multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime.

Chronic hazard or toxicity -- see Health hazard.

Chronic study -- A toxicity study designed to measure the (toxic) effects of chronic exposure to a chemical.

Cohort study -- An epidemiologic study that observes subjects in differently exposed groups and compares the incidence of symptoms. Although ordinarily prospective in nature, such a study is sometimes carried out retrospectively, using historical data.

Confounder -- A condition or variable that may be a factor in producing the same response as the agent under study. The effects of such factors may be discerned through careful design and analysis.

Conjunctivitis -- Irritation of the conjunctiva, the mucous membrane lining the inner surface of the eyelids and covering the front part of the eyeballs.

Control group -- A group of subjects observed in the absence of agent exposure or, in the instance of a case/control study, in the absence of an adverse response.

Core grade(s) -- Quality ratings, based on standard evaluation criteria established by the Office of Pesticide Programs, given to toxicological studies after submission by registrants.

Critical effect -- The first adverse effect, or its known precursor, that occurs as the dose rate increases.

Cyanosis -- A bluish color in the skin and mucous membranes due to deficient levels of oxygen in the blood.

Developmental toxicity -- The study of adverse effects on the developing organism (including death, structural abnormality, altered growth, or functional deficiency) resulting from exposure prior to conception (in either parent), during prenatal development, or postnatally up to the time of sexual maturation.

Dose-response relationship -- A relationship between the amount of an agent (either administered, absorbed, or believed to be effective) and changes in certain aspects of the biological system (usually toxic effects), apparently in response to that agent.

Dyspnea -- Difficult or labored breathing.

Emphysema -- Swelling of the air sacs or the tissue connecting them in the lungs, accompanied by atrophy of the tissues and impaired breathing.

Endpoint -- A response measure in a toxicity study.

Erythema -- Skin redness.

Estimated exposure dose (EED) -- The measured or calculated dose to which humans are likely to be exposed considering exposure by all sources and routes.

Excess lifetime risk -- The additional or extra risk incurred over the lifetime of an individual by exposure to a toxic substance.

Extra risk -- The added risk to that portion of the population that is not included in measurement of background tumor rate; ER(d) = [P(d) - P(0)]/[1-P(0)].

Extrapolation -- An estimation of a numerical value of an empirical (measured) function at a point outside the range of data which were used to calibrate the function. The quantitative risk estimates for carcinogens are generally low-dose extrapolations based on observations made at higher doses. Generally, one has a measured dose and measured effect.

Fetotoxic -- Toxic to the fetus.

Gamma multi-hit model -- A dose-response model of the form

$$P(d) = \int_0^d \left\{[a^k][s^{(k-1)}][\exp(-as)]/G(u)\right\}ds$$

where $G(u) = \int_0^\infty [s^{(u-1)}][\exp(-s)]ds$

P(d) = the probability of cancer from a dose rate d
k = the number of hits necessary to induce the tumor
a = a constant

when k = 1, see the One-hit model.

Genotoxic -- Toxic to the genetic material within a person's cells [i.e., in the genes formed from the substance deoxyribonucleic acid (DNA), which make up the chromosomes in a person's cells].

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

Health hazard (types of) --

1. Acute toxicity -- The older term used to describe immediate toxicity. Its former use was associated with toxic effects that were severe (e.g., mortality) in contrast to the term "subacute toxicity" that was associated with toxic effects that were less severe. The term "acute toxicity" is often confused with that of acute exposure.

2. Allergic reaction -- Adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one.

3. Chronic toxicity -- The older term used to describe delayed toxicity. However, the term "chronic toxicity" also refers to effects that persist over a long period of time whether or not they occur immediately or are delayed. The term "chronic toxicity" is often confused with that of chronic exposure.

4. Idiosyncratic reaction -- A genetically determined abnormal reactivity to a chemical.

5. Immediate versus delayed toxicity -- Immediate effects occur or develop rapidly after a single administration of a substance, while delayed effects are those that occur after the lapse of some time. These effects have also been referred to as acute and chronic, respectively.

6. Reversible versus irreversible toxicity -- Reversible toxic effects are those that can be repaired, usually by a specific tissue's ability to regenerate or mend itself after chemical exposure, while reversible toxic effects are those that cannot be repaired.

7. Local versus systemic toxicity -- Local effects refer to those that occur at the site of first contact between the biological system and the toxicant; systemic effects are those that are elicited after absorption and distribution of the toxicant from its entry point to a distant site.

Hematopoietic -- Having to do with the blood-forming elements.

Hepatic -- Having to do with the liver.

Hemoptysis -- Discharge of blood from the larynx, trachea, bronchi or lungs.

Homologue -- One of a series of organic compounds that differ from each other by a CH_2, such as the methane series C_nH_{2n+2}, in which there is a similarity between the compounds in the series and a graded change of their properties.

Human equivalent dose -- The human dose of an agent that is believed to induce the same magnitude of toxic effect as that which the known animal dose has induced.

Hydranencephaly -- A congenital anomaly in which the brain is not fully developed.

Hyperchromic anemia -- Any of several blood disorders in which red blood cells show an increase in hemoglobin and a reduction in number.

Hypoxia -- Oxygen deficiency to a reduction of the blood's oxygen-carrying capacity.

Incidence -- The number of new cases of a disease within a specified period of time.

Incidence rate -- The ratio of the number of new cases over a period of time to the population at risk.

Individual risk -- The probability that an individual person will experience an adverse effect. This is identical to population risk unless specific population subgroups can be identified that have different (higher or lower) risks.

Initiation -- The ability of an agent to induce a change in a tissue which leads to the induction of tumors after a second agent, called a promoter, is administered to the tissue repeatedly. See also Promoter.

Interspecies dose conversion -- The process of extrapolating from animal doses to equivalent human doses.

Latency period -- The time between the initial induction of a health effect and the manifestation (or detection) of the health effect; crudely estimated as the time (or some fraction of the time) from first exposure to detection of the effect.

Limited evidence -- According to the EPA's Guidelines for Carcinogen Risk Assessment, limited evidence is a collection of facts and accepted scientific inferences which suggests that the agent may be causing an effect, but this suggestion is not strong enough to be considered established fact.

Linearized multistage procedure -- The modified form of the multistage model (see Multistage model). The constant q1 is forced to be positive (>0) in the estimation algorithm and is also the slope of the dose-response curve at low doses. The upper confidence limit of q1 (called q1*) is called the slope factor.

Logit model -- A dose-response model of the form

$$P(d) = 1/[1 + \exp -(a + b \log d)]$$

where P(d) is the probability of toxic effects from a continuous dose rate d, and a and b are constants.

Lowest-observed-adverse-effect level (LOAEL) -- The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

Lowest-effect level (LEL) -- Same as LOAEL.

Lymphocytes -- The principal cell type of the lymphs, comprising 20% to 30% of white blood cells.

Malignant -- Tending to become progressively worse and to result in death if not treated; having the properties of anaplasia, invasiveness, and metastasis.

Margin of Exposure (MOE) -- The ratio of the no observed adverse effect level (NOAEL) to the estimated exposure dose (EED).

Margin of Safety (MOS) -- The older term used to describe the margin of exposure.

Mesothelioma -- A tumor of the pleura (lining of the lung and chest cavity).

Metastasis -- The transfer of disease from one organ or part to another not directly connected with it; adj., metastatic.

Methemoglobinemia -- The presence of methemoglobin (oxidized hemoglobin) in the blood, which reduces the oxygen-carrying capacity of the blood.

Model -- A mathematical function with parameters that can be adjusted so that the function closely describes a set of empirical data. A "mathematical" or "mechanistic" model is usually based on biological or physical mechanisms, and has model parameters that have real-world interpretation. In contrast, "statistical" or "empirical" models are curve-fitting to data where the math function used is selected for its numerical properties. Extrapolation from mechanistic models (e.g., pharmacokinetic equations) usually carries higher confidence than extrapolation using empirical models (e.g., logit).

Modifying factor (MF) -- An uncertainty factor that is greater than zero and less than or equal to 10; the magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated with the standard uncertainty factors (e.g., the completeness of the overall database and the number of species tested); the default value for the MF is 1.

Multistage model -- A dose-response model often expressed in the form

$$P(d) = 1 - \exp(-[q(0) + q(1)d + q(2)d^{**}2 + \ldots + q(k)d^{**}k])$$

where P(d) is the probability of cancer from a continuous dose rate d, the q(i) are the constants, and k is the number of dose groups (or, if less, k is the number of biological stages believed to be required in the carcinogenesis process). Under the multistage model, it is assumed that cancer is initiated by cell mutations in a finite series of steps. A one-stage model is equivalent to a one-hit model.

Mutagenic -- Causing cell mutation, chromosome alternation, bacterial mutations, an DNA damage.

Nasopharyngeal -- Having to do with the nose and pharynx.

Neoplasm -- An aberrant new growth of abnormal cells or tissues; tumor.

Neurological sequelae -- A neurologic (nervous system) condition that results from or follows a disease, disorder or injury (i.e., complications of a neurologic injury).

No data -- According to the EPA Guidelines for Carcinogen Risk Assessment, "no data" describes a category of human and animal evidence in which no studies are available to permit one to draw conclusions as to the induction of a carcinogenic effect.

No evidence of carcinogenicity -- According to the EPA Guidelines for Carcinogen Risk Assessment, a situation in which there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies of adequate power and dose in different species.

No-observed-adverse-effect level (NOAEL) -- An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered as adverse, nor precursors to adverse effects. In an experiment with several NOAELs, the regulatory focus is primarily on the highest one, leading to the common usage of the term NOAEL as the highest exposure without adverse effect.

No-observed-effect level (NOEL) -- An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

One-hit model -- A dose-response model of the form

$$P(d) = a - \exp(-b\ d)$$

where P(d) is the probability of cancer from a continuous dose rate d, and b is a constant. The one-hit model is based on the concept that a tumor can be induced after a single susceptible target or receptor has been exposed to a single effective dose unit of a substance.

Organoleptic -- Affecting or involving a sense organ as of taste, smell, or sight.

Pheochromocytoma -- A tumor of the sympathetic nervous system composed principally of chromaffin cells; found most often in the adrenal medulla.

Pneumoconiosis -- Any lung disease caused by dust inhalation.

Principal study -- The study that contributes most significantly to the qualitative and quantitative risk assessment.

Probit model -- A dose-response model of the form

$$P(d) = 0.4\{\text{integral from minus infinity to } [\log(d - u)]/s \text{ of } [\exp-(y^{**}2)/2]dy\}$$

where P(d) is the probability of cancer from a continuous dose rate d, and u and s are constants.

Promoter -- In studies of skin cancer in mice, an agent that results in an increase in cancer induction when administered after the animal has been exposed to an initiator, which is generally given at a dose that would not result in tumor induction if given alone. A cocarcinogen differs from a promoter in that it is administered at the same time as the initiator.

Cocarcinogens and promoters do not usually induce tumors when administered separately. Complete carcinogens act as both initiator and promoter. Some known promoters also have weak tumorigenic activity, and some also are initiators. Carcinogens may act as promoters in some tissue sites and as initiators in others.

Proportionate mortality ratio (PMR) -- The number of deaths from a specific cause and in a specific period of time per 100 deaths in the same time period.

Prospective study -- A study in which subjects are followed forward in time from initiation of the study. This is often called a longitudinal or cohort study.

Pulmonary edema -- Fluid in the lungs.

q1* -- Upper bound on the slope of the low-dose linearized multistage procedure.

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

Registration (of a pesticide) -- Under FIFRA and its amendments, new pesticide products cannot be sold unless they are registered with the EPA. Registration involves a comprehensive evaluation of risks and benefits based on all relevant data.

Regulatory dose (RgD) -- The daily exposure to the human population reflected in the final risk management decision; it is entirely possible and appropriate that a chemical with a specific RfD may be regulated under different statutes and situations through the use of different RgDs.

Relative risk (sometimes referred to as risk ratio) -- The ratio of incidence or risk among exposed individuals to incidence or risk among nonexposed individuals.

Renal -- Having to do with the kidneys.

Reportable quantity -- The quantity of a hazardous substance is considered reportable under CERCLA. Reportable quantities are 1) one pound, or 2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Rhinitis -- Inflammation of the nasal mucous membrane.

Risk -- The probability of injury, disease, or death under specific circumstances. In quantitative terms, risk is expressed in values ranging from zero (representing the certainty that harm will not occur) to 1 (representing the certainty that harm will occur). The following are examples showing the

manner in which risk is expressed: E-4 = a risk of 1/10,000; E-5 = a risk of 1/100,000; E-6 = a risk of 1/1,000,000. Similarly, 1.3E-3 = a risk of 1.3/1000 = 1/770; 8E-3 = a risk of 1/125; and 1.2E-5 = a risk of 1/83,000.

Risk assessment -- The determination of the kind and degree of hazard posed by an agent, the extent to which a particular group of people has been or may be exposed to the agent, and the present or potential health risk that exists due to the agent.

Risk management -- A decisionmaking process that entails considerations of political, social, economic, and engineering information with risk-related information to develop, analyze, and compare regulatory options and to select the appropriate regulatory response to a potential chronic health hazard.

Safety factor -- See Uncertainty factor.

Short-term exposure -- Multiple or continuous exposures occurring over a week or so.

Slope Factor -- The slope of the dose-response curve in the low-dose region. When low-dose linearity cannot be assumed, the slope factor is the slope of the straight line from 0 dose (and 0 excess risk) to the dose at 1% excess risk. An upper bound on this slope is usually used instead of the slope itself. The units of the slope factor are usually expressed as 1/(mg/kg-day).

Standardized mortality ratio (SMR) -- The ratio of observed deaths to expected deaths.

Subchronic exposure -- Multiple or continuous exposures occurring usually over 3 months.

Subchronic study -- A toxicity study designed to measure effects from subchronic exposure to a chemical.

Sufficient evidence -- According to the EPA Guidelines for Carcinogen Risk Assessment, sufficient evidence is a collection of facts and scientific references which is definitive enough to establish that the adverse effect is caused by the agent in question.

Superfund -- Federal authority, established by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) in 1980, to respond directly to releases or threatened releases of hazardous substances that may endanger health or welfare.

Supporting studies -- Those studies that contain information that is useful for providing insight and support for the conclusions.

Systemic effects -- Systemic effects are those that require absorption and distribution of the toxicant to a site distant from its entry point, at which point effects are produced. Most chemicals that produce systemic toxicity do

not cause a similar degree of toxicity in all organs, but usually demonstrate major toxicity to one or two organs. These are referred to as the target organs of toxicity for that chemical.

Systemic toxicity -- See Systemic effects.

Tachypnea -- An abnormally fast rate of breathing.

Target organ of toxicity -- See Systemic effects.

Teratogen -- Causing rectal abnormalities, skeletal and visceral malformations, and functional/behavioral deviations.

Threshold -- The dose or exposure below which a significant adverse effect is not expected. Carcinogens are thought to be non-threshold chemicals, to which no exposure can be presumed to be without some risk of adverse effect.

Threshold limit values (TLVs) -- Recommended guidelines for occupational exposure to airborne contaminants published by the American Conference of Governmental Industrial Hygienists (ACGIH). The TLVs represent the average concentration (in mg/m^3) for an 8-hour workday and a 40-hour work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

Time-weighted average -- An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Toxicity value -- A numerical expression of a substance's dose-response relationship that is used in risk assessments. The most common toxicity values used in EPA risk assessments are reference doses (for noncarcinogenic effects) and slope factors (for carcinogenic effects).

Tumor progression -- The sequence of changes in which a tumor develops from a microscopic lesion to a malignant stage.

Uncertainty factor -- One of several, generally ten-fold factors, used in operationally deriving the Reference Dose (RfD) from experimental data. UFs are intended to account for 1) the variation in sensitivity among the members of the human population; 2) the uncertainty in extrapolating animal data to the case of humans; 3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure; and 4) the uncertainty in using LOAEL data rather than NOAEL data.

Unit Risk -- The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/L$ in water, or 1 $\mu g/m^3$ in air.

Upper bound -- An estimate of the plausible upper limit to the true value of the quantity. This is usually not a statistical confidence limit.

Weibull model -- A dose-response model of the form

$$P(d) = 1 - \exp [-b(d^{**}m)]$$

where P(d) is the probability of cancer due to continuous dose rate d, and b and m are constants.

Weight-of-evidence for carcinogenicity -- The extent to which the available biomedical data support the hypothesis that a substance causes cancer in humans.

1.2 THE NEPA PROCESS

The Bonneville Power Administration (Bonneville) has taken a leading role among federal agencies in assessing the environmental impacts of indoor air pollutants and designing appropriate program responses. These efforts have included extensive research programs into residential ventilation and indoor pollution characterization and monitoring. Bonneville has also prepared three environmental documents under the National Environmental Policy Act (NEPA) that focused on indoor air quality issues (BPA 1982, 1984, and 1988).

One of these documents, the 1982 *Environmental Assessment of Energy Conservation Opportunities in Commercial-Sector Facilities in the Pacific Northwest*, supported conservation programs in existing commercial buildings. Bonneville is now planning the implementation of aggressive commercial conservation acquisition programs in both new and existing buildings. Because of changing information, and because of the change in scope of the programs being designed, Bonneville is now reevaluating the potential environmental effects of conservation activities in commercial buildings. Pacific Northwest Laboratory[(a)] (PNL) prepared this review of information about health effects to aid Bonneville in its assessment of potential environmental effects.

1.3 SELECTION OF POLLUTANTS FOR HEALTH EFFECT ANALYSIS

The primary environmental concern identified for new energy-efficient buildings is the potential effect of increased levels of indoor pollutants on

---

(a) Pacific Northwest Laboratory is operated by Battelle Memorial Institute for the U.S. Department of Energy.

public health. A host of organic and other pollutants potentially exist in building materials and could be released to the indoor air of these public buildings. To maintain a degree of realism in this general health effects assessment report on the potential contaminants associated with the indoor air quality of public buildings, only those contaminants that have been measured in the indoor air of a public building or measured (significant concentrations) in test situations simulating indoor air quality situations were examined in this health effects study. An additional criterion applied was that the hazard rating (Sax and Lewis 1989) needed to be high enough for the contaminant to be considered a significant hazard. The contaminants found in building materials but not found in sampling efforts associated with public building were not included in the list to study. However, some of these contaminants will be briefly discussed in the section on Other Potential Contaminants. Table 1.1 contains a list of the contaminants examined in this contaminant health effects study.

This list was derived after reviewing current literature articles regarding studies of indoor air quality in public buildings, the National Aeronautics and Space Administration (NASA) test for potential contaminants to the atmosphere of spacecraft, and studies of building materials and consumer products (Baechler et al. 1989; Jungers and Sheldon 1987; Wallace et al. 1984; Wallace et al. 1987a and 1987b; Girman et al. 1982; Tichenor and Mason 1988; Molhave 1982; Krause et al. 1987; Wallace 1987; Wallace 1986; and Tichenor and Mason 1986).

1.4 STUDY METHODOLOGY

Upon establishing the list of contaminants to study, a comprehensive literature search was conducted to located the latest information on health effects associated with each of the chemicals on the list. In addition, three active, professionally maintained and peer-reviewed, on-line chemical information databases were used to located the latest health effect information on each contaminant on the list. The three databases accessed were 1) Integrated Risk Information System (IRIS), 2) Hazardous Substance Data Bank (HSDB), and 3) Registry of Toxic Effects of Chemicals (RTECS).

TABLE 1.1. Contaminants Examined in Health Effects Study

Benzene	Formaldehyde
Benzo(A)Pyrene	Methylethylketone
Biogenic particles	Nitrogen oxides
n-butylacetate	Octane
Carbitol	Octene
Carbon dioxide	α-Pinene
Carbon monoxide	Polychlorinated Biphenyls
Carbon tetrachloride	Propylbenzene
Chlorofluorocarbons	Radon/Radon daughters
Chloroform	Styrene
Decane	Synthetic fibers (Fiber Glass & Cellulose)
Dichlorobenzene	Tetrachloroethylene
Dichloromethane	Toluene
Dodecane	1,1,1-Trichloroethane
Environmental tobacco Smoke	Trichloroethylene
2-Ethoxyethylacetate	1,2,4-Trimethylbenzene
Ethylbenzene	Undecane
Ethylene glycol	Xylene

IRIS is an on-line database of chemical-specific risk information prepared by the EPA in order to serve as guidance for EPA risk assessments. IRIS currently contains summaries of hazards, dose-response assessments and reference citations on approximately 400 chemicals. The database provides information for carcinogenicity assessment such as human and animal carcinogenicity data, weight of evidence for carcinogenicity, oral and inhalation slope factors, unit risks and concentrations at specified risk levels for chronic exposures to carcinogens. It provides risk assessment information such as oral and inhalation reference doses (RfDs) for chronic noncarcinogenic health effects. The health assessment information contained in IRIS is peer-reviewed by an interdisciplinary review group of EPA scientists and health professionals (Sidhu 1989).

The HSDB is a factual, nonbibliographic databank focusing upon the toxicology of potentially hazardous chemicals. The HSDB is managed by the National Library of Medicine, MEDLARS Management Section. It is enhanced with data from such related areas as emergency handling procedures, environmental fate, human exposure, detection methods, and regulatory requirements. Data is

derived from a core set of standard texts and monographs, government documents, technical reports, and the primary journal literature. HSDB contains complete references for all data sources utilized. The HSDB file is fully peer reviewed by the Scientific Review Panel (SRP), a committee of experts drawn from the major subject disciplines within the databanks's scope. HSDB is organized by chemical record, with approximately 4,200 chemical substance records contained in the file (NIH 1989).

RTECS is an on-line file containing toxic effects data on over 96,000 chemicals. Both acute and chronic effects are covered, including data on skin/eye irritation, carcinogenicity, mutagenicity, and reproductive consequences. Selected federal regulatory requirements and exposure levels are also presented. References are available for all data. Toxicology and carcinogenic reviews, where available on any given chemical, are cited. Some reviews may come from the International Agency for Research on Cancer (IARC) Monograph Series or may be other general review articles from the open scientific literature. RTECS is built and maintained by the National Institute for Occupational Safety and Health (NIOSH) (NIH 1989).

The information obtained in the literature search and active databases were then combined to prepare this health effects assessment report. For the most part, an emphasis was placed on general health effects and the health effects associated with the airborne exposure pathway, since this is likely to be the most dominant pathway of exposure for individuals residing/working in public buildings. The health effect information available for each contaminant varied widely. Some of the contaminants, such as PCBs and formaldehyde, had a vast amount of health effect-related information available. Other contaminants, such as α-pinene and octene, had little or no health effect information available. It was considered important to use only well peer-reviewed and documented (by reliable sources) information on the health effects associated with the selected contaminants. Thus, although for some contaminants the information provided may be limited, the health effect information provided in this report should be considered the best available at this time.

2.0 INDOOR AIR QUALITY

Indoor air quality can be potentially impacted by conceivably hundreds of different chemicals. The health effects that could potentially arise from exposure to individual pollutants or mixtures of pollutants cover the full range of acute and chronic effects, including largely reversible responses, such as rashes and irritations, as well as irreversible toxic and carcinogenic effects. These indoor contaminants are emitted from a large variety of materials and substances that are widespread components of everyday life.

Asbestos, combustion gases, formaldehyde, and radon have been the focus of indoor air quality studies for some time. However, the understanding of complex mixtures of these and other commonly available chemicals is only in its infancy. As an example, environmental tobacco smoke contains over 3,800 different chemicals (NRC 1986). Similarly, the large number of volatile organics that emanate from a variety of consumer products, building materials, and furnishings are in the very early stages of quantitative study to relate specific organics to specific material sources (Tichenor 1989). In addition, a variety of biogenic contaminants are potentially available in public buildings that can affect occupants in many different ways.

This section discusses the health effects associated with the contaminants selected for this study, based on the criteria discussed earlier.

2.1 THE SICK BUILDING SYNDROME AND BUILDING-RELATED ILLNESS

A building is characterized as a sick building when its occupants complain of health and comfort problems that can be related to working or being in the building. The problems associated with sick buildings are sick building syndrome and building-related illness (EPA 1988). These terms generally apply to problems related to indoor air pollution. They are not normally used to characterize buildings where complaints stem solely from inadequate temperature or humidity control. A World Health Organization Committee estimates that up to 30% of new and remodeled buildings may have such problems.

A building is considered to manifest the sick building syndrome when a substantial percentage of the building occupants complain of symptoms associated with acute discomfort (e.g., headaches; eye, nose and throat irritations; dry cough; dry or itchy skin; dizziness and nausea; difficulty in concentrating; fatigue; sensitivity to odors), the cause of the symptoms is not known, and most of the complainants report relief upon leaving the building.

When occupant exposure to indoor contaminants results in a clinically defined illness, disease or infirmity, the building is said to manifest building-related illness. The characterization of building-related illness is by complaints of symptoms such as cough, chest tightness, fever, and muscle aches which can be associated with illness; the cause(s) of the symptoms are believed to be exposure to indoor pollutants; and complainants usually require prolonged recovery after leaving the building.

It is important to note that it is normal for a certain percentage of individuals in a building to experience one or more of the symptoms of sick buildings, and many of the complaints may be the result of illnesses contracted outside of the building or from stress-related circumstances. However, studies do show that such symptoms may be caused or heightened by indoor air contaminants.

Potential causes of sick buildings are inadequate ventilation, pollutants emitted inside the building, contaminants brought in from outside sources, and biological contamination. These causes usually act in combination and often supplement other occupant complaints, such as inadequate temperature, humidity, or lighting.

2.2 VOLATILE ORGANIC COMPOUNDS

Considerable emphasis is being placed on the wide range of volatile organic compounds that may be found in indoor air. There are numerous sources of indoor volatile organic compounds. More than 350 different organic compounds have been identified in concentrations over 0.001 parts per million (ppm) in indoor air (Wallace et al. 1984). This large and ever-growing list of organic compounds make it difficult to associate health and well-being

problems associated with specific compounds. Actual exposures are to the various combinations of mixtures of these chemicals.

Organic compounds are part of almost all materials and products, such as construction materials, furnishings, combustion fuels, consumer products, and pesticides. A large variety of organic compounds are produced from combustion of cooking and heating fuels, tobacco, and human metabolism. Examples of organic compound types and their sources are listed in Table 2.1.

2.2.1 Benzene

Benzene is a clear, colorless liquid with a density of 0.8794 and a flash point of 12°F. Its molecular formula is C_6H_6, and its molecular weight is 78.12. It has a vapor pressure of 100 mm at 26.1°C. It has a hazard rating of 3 (Sax and Lewis 1989). The half-life of benzene in air is 6 days (EPA 1984a). Some of the more common synonyms for benzene are benzol, coal naphtha, cyclohexatriene, phene, phenyl hydride, polystream, and pyrobenzol. The threshold limit value (TLV), on a time weighted average (TWA) basis, for benzene is 10 ppm (ACGIH 1988).

2.2.1.1 Summary

The weight-of-evidence classification for benzene is "A; human carcinogen." Several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification (IRIS 1990). Both gavage and inhalation exposure of rodents to benzene have resulted in development of neoplasia.

Benzene and its metabolites inhibit both nuclear and mitochondrial replication and transcription. Deoxyriboneucleic acid (DNA) synthesis was inhibited in hemopoietic cells from mice exposed to a single dose of 3000 ppm benzene.

The inhalation slope factor is 2.9E-2/mg/kg/day. The inhalation unit risk is 8.3E-6/$\mu g/m^3$. The extrapolation method used was the one-hit model using pooled data. Table 2.2 shows air concentrations at specified risk levels (IRIS 1990).

TABLE 2.1. Examples of Organic Compounds and Sources

Pollutant type	Examples	Example Indoor Sources
Aliphatic and Oxygenated Aliphatic Hydrocarbons	α-pinene, n-decane, n-undecane, n-dodecane, propane, butane, n-butylacetate, ethoxyethylacetate	Cooking and heating fuels, aerosol propellants, cleaning compounds, paints, carpet, moldings, particle board, refrigerants, lubricants, flavoring agents, perfume base
Halogenated Hydrocarbons	Methyl chloroform, methylene chloride, polychlorinated biphenylss, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, chlorobenzene, dichlorobenzene	Aerosol propellants, fumigants, pesticides, refrigerants, adhesives, caulk, paint, linoleum tile, carpet, latex paint, and degreasing, dewaxing, and dry cleaning solvents
Aromatic Hydrocarbons	Xylenes, ethylbenzenes, trimethylbenzenes, ethyltoluenes, propylbenzenes, benzene, styrene, toluene	Paints, varnishes, glues, enamels, lacquers, cleaners, adhesives, molding, insulation, linoleum tile, carpet
Alcohols	Ethanol, methanol	Lacquers, varnishes, polish removers, adhesives
Ketones	Acetone, diethyl ketone, methyl ethyl ketone	Lacquers, varnishes, polish removers, adhesives, cleaners
Aldehydes	Formaldehyde, nonanal	Fungicides, germicides, disinfectants, artificial and permanent-press textiles, paper, particle boards, cosmetics, flavoring agents

2.2.1.2 Health Effects

Noncarcinogenic Effects - Benzene is on EPA's list of chemicals to be reviewed by an EPA work group for determining the Reference Dose for chronic oral exposure (RfDo) and for chronic inhalation exposure (RfDi).

TABLE 2.2. Benzene Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 $\mu g/m^3$
E-5 (1 in 100,000)	1E+0 $\mu g/m^3$
E-6 (1 in 1,000,000)	1E-1 $\mu g/m^3$

Effect on Replication and Transcription - Benzene and its metabolites inhibit both nuclear and mitochondrial replication and transcription. Deoxyribonucleic acid (DNA) synthesis was inhibited in hemopoietic cells from mice exposed to a single dose of 3000 ppm benzene. It was also inhibited in mouse L5178YS lymphoma cells after their exposure to the metabolites, but not to benzene, which is not bioactivated in these cells. The most potent inhibitor was p-benzoquinone, followed by hydroquinone, 1,2,4-benzenetriol, catechol, and phenol, all of which are metabolites of benzene, at concentrations that were not cytotoxic. Inhibition correlated with ease of oxidation. This correlation suggests that the oxidation of phenol or one of its metabolites produces the ultimate reactive compound that inhibits DNA synthesis (Kalf, Post, and Snyder 1987).

Hemopoietic Toxicity - Aplastic anemia from benzene poisoning could arise from toxic damage to one or more of the components of the hemopoietic system: stem cells, transit cells (progenitor cells in various degrees of differentiation), and/or bone marrow stroma or microenvironment (Kalf, Post, and Snyder 1987).

Human Carcinogenicity - The weight-of-evidence classification for benzene is "A; human carcinogen." Several studies of increased incidence of nonlymphocytic leukemia from occupational exposure, increased incidence of neoplasia in rats and mice exposed by inhalation and gavage, and some supporting data form the basis for this classification (IRIS 1990). Aksoy et al. (1974); as cited in IRIS (1990), reported effects of benzene exposure among 28,500 Turkish workers employed in the shoe industry. Mean duration of employment was 9.7 years and mean age was 34.2 years. Peak exposure was reported to be 210 to 650 ppm. Twenty-six cases of leukemia and a total of 34 leukemias or preleukemias were observed, corresponding to an incidence of

13/100,000 (by comparison to 6/100,000 for the general population). A followup paper (Aksoy 1980), as cited in IRIS, reported eight additional cases of leukemia as well as evidence suggestive of increases in other malignancies (IRIS 1990). Several cohort mortality studies were cited in IRIS which showed significant increases in cases of leukemia associated with benzene exposures. Wong et al. (1983) as cited in IRIS, reported the mortality of male chemical workers who had been exposed to benzene for at least 6 months during the years 1946-1975. The study population of 4062 persons was drawn from seven chemical plants, and jobs were categorized as to peak exposure. Those with at least 3 day/wk exposure (3036 subjects) were further categorized on the basis of an 8-hour time weighted average. Dose-dependent increases were seen in leukemia and lymphatic and hematopoietic cancer. The incidence of leukemia was responsible for the majority of the increase (IRIS 1990). IRIS mentioned that numerous other epidemiologic and case studies have reported an increased incidence or a causal relationship between leukemia and exposure to benzene. Numerous investigators have found significant increases in chromosomal aberrations of bone marrow cells and peripheral lymphocytes from workers exposed to benzene (IARC 1982, as cited in IRIS 1990). Benzene also induced chromosomal aberrations in bone marrow cells from rabbits (Kissling and Speck 1973; as cited in IRIS 1990), mice (Meyne and Legator 1980; as cited in IRIS 1990), and rats (Anderson and Richardson 1979; as cited in IRIS 1990). Several investigators have reported positive results for benzene in mouse micronucleus assays (Meyne and Legator 1980; as cited in IRIS 1990). Benzene was not mutagenic in several bacterial and yeast systems, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster, or in mouse lymphoma cell forward mutation assay (IRIS 1990).

Animal Carcinogenicity Data - Both gavage and inhalation exposure of rodents to benzene have resulted in development of neoplasia. Several studies were cited in IRIS regarding gavage doses with dose-related increases in the incidences of tumors. Slightly increased incidences of hematopoietic neoplasms were reported for male C57Bl mice exposed by inhalation to 300 ppm benzene 6 h/day, 5 day/wk for 488 days. There was no increase in tumor incidence in male AKR or CD-1 mice similarly exposed to 100 ppm or 300 ppm benzene, respectively (IRIS 1990).

Quantitative Estimate of Carcinogenic Risk From Inhalation Exposure - The inhalation slope factor is 2.9E-2/mg/kg/day. The inhalation unit risk is 8.3E-6/$\mu g/m^3$. The extrapolation method used was the one-hit model using pooled data. Table 2.2 shows air concentrations at specified risk levels (IRIS 1990).

The unit risk estimate is the geometric mean of four point estimates using pooled data from the Rinsky et al. (1981) and Ott et al. (1978) studies, which was then adjusted for the results of the Wong et al. (1983) study; all cited in IRIS (1990). The Rinsky data used were from an updated tape which reports one more case of leukemia than was published in 1981. Equal weight was given to cumulative dose and weighted cumulative dose exposure categories as well as to relative and absolute risk model forms. The results of the Wong et al. (1983) study were incorporated by assuming that the ratio of the Rinsky-Ott-Wong studies to the Rinsky-Ott studies for the relative risk cumulative dose model was the same as for other model-exposure category combinations and multiplying this ratio by the Rinsky-Ott geometric mean. The age-specific U.S. death rates for 1978 (the most current year available) were used for background leukemia and total death rates. It should be noted that a recently published paper (Rinsky et al. 1987), reported yet another case of leukemia from the study population. The unit risk should not be used if the air concentration exceeds 100 $\mu g/m^3$, since above this concentration the slope factor may differ from that stated (IRIS 1990).

Confidence of Inhalation Exposure Carcinogenicity - The pooled cohorts were sufficiently large and were followed for an adequate time period. The increases in leukemias were statistically significant and dose-related in one of the studies. Wong et al. 1983 as cited in IRIS (1990), disagrees that exposures reported in Rinsky et al. (1981) as cited in IRIS (1990), were within the recommended standards. For the five leukemia deaths in persons with 5 or more years exposure, the mean exposure levels (range 15 to 70 ppm) exceeded the recommended standard (25 ppm) in 75% of the work locations sampled. The risk estimate above based on reconsideration of the Rinsky et al. (1981) and Ott et al. (1978) studies; as cited in IRIS (1990), is very similar to that of 2.4E-2/ppm (cited in EPA 1980) based on Infante et al.

(1977a,b), Ott et al. (1978) and Aksoy et al. (1974); all cited in IRIS (1990). It was felt by the authors of U.S. EPA (1985); as cited in IRIS (1990), that the exposure assessment provided by Aksoy was too imprecise to warrant inclusion in the current risk estimate. A total of 21 unit risk estimates were prepared using six models and various combinations of the epidemiologic data. These range over slightly more than one order of magnitude. A geometric mean of these estimates is 2.7E-2/ppm. Regression models give an estimate similar to the geometric mean (IRIS 1990).

Toxicant Interactions - Benzene metabolism and therefore benzene toxicity is altered by simultaneous exposure to some other solvents (e.g., xylene, toluene) because these aromatic solvents are oxidized by many of the same hepatic enzyme systems. Reported hematotoxic effects of benzene in humans may be a synergistic result of simultaneous exposure to other solvents. Since benzene metabolites rather than the parent compound are suspected of inducing bone marrow toxicity, inhibition of benzene metabolism (hydroxylation) by toluene may result in increased toxic effects of the parent compound instead of benzene metabolites (EPA 1984a).

2.2.2 n-Butylacetate

The contaminant n-butylacetate is a colorless liquid with a density of 0.88 and a flash point of 72°F. Its molecular formula is $C_6H_{12}O_2$, and its molecular weight is 116.18. It has a vapor pressure of 15 mm at 25°C. It has a hazard rating of 2 (Sax and Lewis 1989). The TLV on a TWA basis, for n-butylacetate is 150 ppm. The TLV, on a short term exposure limit (STEL) basis, is 200 ppm (ACGIH 1988).

2.2.2.1 Summary

Butylacetates are irritations and narcotic in high concentrations. N-butylacetate has no notable systemic toxicity, but its vapor causes irritation of eyes and nose. The primary target organs for n-butylacetate are the eye, skin, and respiratory system..

Persons with skin disease, kidney disease, chronic respiratory disease, and liver disease may be at an increased risk from butylacetate exposure.

2.2.2.2 Health Effects

General Toxicity - n-butylacetate has no notable systemic toxicity, but its vapor causes irritation of eyes and nose. It may cause conjunctivitis. Concentrations of 1600 ppm have produced eye irritation in animals. Liquid application to rabbit eyes caused superficial injury graded 5 on a scale of 1 to 10. Workers exposed to greater than 200 ppm for 8 hours developed eye, nose, and throat irritations. n-butylacetate is normally first noticeable to humans at concentrations of 300 ppm in air and is objectionable at concentrations of 3300 ppm. Higher concentrations cause tearing and hyperemia of conjunctiva. Pulmonary edema has been reported in animals exposed to butyl acetates (HSDB 1990).

Butylacetates are narcotic in high concentrations. Concentrations of 1.4% caused death within 240 minutes in laboratory animals, and n-butylacetate has narcotic properties estimated at 1.7 times that of ethylacetate. Cerebral edema has occurred in laboratory animals (HSDB 1990).

Exposure of albino rabbits to 500 ppm for 20 days and to 1000 ppm for four days caused no corneal or conjunctival injury, as could be detected by slit-lamp biomicroscopy, and corneal sensation was not altered (HSDB 1990).

Slight central nervous system (CNS) depressant effects were noted in cats exposed for 6 hours at 6100 ppm of n-butylacetate. Slight irritation of eyes and salivation occurred at a concentration of 1600 ppm. The animals exposed 6 hours a day for 6 days at 3100 ppm concentration showed blood changes. Similar exposures at 4200 ppm resulted in slight irritation of the respiratory passages. Air nearly saturated with n-butylacetate (approximately 10,000 ppm) was fatal to six rats in an 8-hour period, but no deaths occurred, at this concentration, in 4 hours of exposure. Guinea pigs showed eye irritation at 3300 ppm concentrations of n-butylacetate. The guinea pigs became unconscious after 9 hours at a concentration of 7000 ppm and died following 4 hours of exposure at 14,000 ppm administered at a temperature of 30°C. In repeated inhalations of 3100 to 4200 ppm for 6 hours per day for 6 days, mice became habituated to the irritation but showed some fatigue and loss of weight. The blood picture of the exposed mice showed an increase in formed elements and hemoglobin. Mouse response to the inhalation of

n-butylacetate at concentrations of 7400 ppm for 3 hours resulted in CNS depression and recovery (HSDB 1990).

Effects on isolated tissue was demonstrated by combining butylacetate with choline. In combination with choline, butylacetate exhibited a contractile effect on isolated guinea pig ileum. Release of acetylcholine by butylacetate was indicated, and when butylacetate combined with muscle acetylcholine receptor, the response to acetylcholine was inhibited (HSDB 1990).

Chicken eggs were studied for teratogenic effects. When injected with a dose of 45 mg, eggs did not hatch. When 27 mg per egg were injected, 45% hatched, and with 9 mg, 60% hatched. Kidney damage and corneal lesions were observed in the chick embryos (HSDB 1990).

Hepatotoxicity - The HSDB contained a reference to a study conducted by Franco et al. for which a detection of hepatotoxicity was reported from occupational exposure to n-butylacetate (HSDB 1990).

Embryotoxicity - As part of a critical analysis of exploratory methods used in testing chemical agents for embryotoxicity, teratogenicity and mutagenicity, the oncogenic reaction of laboratory mice showed butylacetate to by embryotoxic when administered to DBA or C57BL pregnant mice (HSDB 1990).

Mutagenicity - The mutagenicity of 43 industrial chemicals, including n-butylacetate, in Salmonella typhimurium and Escherichia coli was examined. The mutation test was performed in the absence and presence of rat microsomal activation. No mutagenic activity was observed with n-butylacetate (HSDB 1990).

Symptoms and General Effects - The following are symptoms for various levels of exposure to n-butylacetate: 1) CNS - headache, muscle weakness, giddiness, ataxia, confusion, delirium, coma, 2) gastrointestinal - nausea, vomiting, diarrhea (odor of the alcohol in excreta), 3) irritation of skin, eyes, throat from vapor or liquid, 4) death from respiratory failure, 5) disturbances of cardiac rhythm, 6) occasional complications - gastrointestinal hemorrhage, renal damage with glycosuria, liver damage, cardiac failure, and pulmonary edema (HSDB 1990).

Inhalation of paint thinner containing acetate esters, including butylacetate, caused drunkenness and hallucination in human subjects. Blood chemistry was performed on workers who were exposed to a variety of fat solvents, including butylacetate. Normocytic normochronic anemia occurred and was attributed to butylacetate and butylalcohol. Plasma bicarbonate was also lowered because of liberation of acetic acid (HSDB 1990).

Toxicity Ranges - 10,000 ppm of n-butylacetate for 8 hours was 100% fatal in test animals. A 4-hour exposure to the same level showed no fatalities. Brief exposures of humans to 3,300 ppm of n-butylacetate caused marked irritation to eyes and nose. Mild irritation was reported after a brief exposure to 200 to 300 ppm concentrations. Throat irritations in human subjects were noticed at 200 ppm concentrations, and the throat irritations became quite severe at 300 ppm (HSDB 1990).

Toxicant Interactions - Tests of butylacetate vapor on animal eyes have been complicated by an admixture of butylalcohol. It is uncertain whether damage to the corneal epithelium reported to occur at high concentrations was caused by the butylacetate or the butylalcohol. Likewise, a report showed several cases of vacuolar keratitis among workers exposed to a mixture of vapor of butylacetate and isobutylalcohol; however, it is uncertain which compound -- the butylacetate or the isobutylalcohol -- was responsible.

2.2.3 Carbon Tetrachloride

Carbon tetrachloride is a heavy colorless liquid with an ethereal odor. It has a density of 1.597 and no registered flash point. Its molecular formula is CCl_4, and its molecular weight is 153.81. Carbon tetrachloride has a vapor pressure of 100 mm at 23.0°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, for carbon tetrachloride is 5 ppm (ACGIH 1988). Common synonyms for carbon tetrachloride are acritet, benzinoform, carbona, carbon chloride, carbon tet, freon 10, halon 104, methane tetrachloride, tetrachloromethane, perchloromethane, tetrafinol, tetraform, and tetrasol.

2.2.3.1 Summary

Carbon tetrachloride is toxic by all routes of exposure and is manifested by both liver and renal damage, which may be delayed for up to 2 to 3 days following exposure. Liver injury is probably greater following ingestion and can be permanent even from acute exposure. Neurological sequelae of cerebellar dysfunction can occur.

Carbon tetrachloride vapor is a narcotic and causes severe damage to the liver and kidneys. In humans, most fatalities have been the result of renal injury with secondary cardia failure. Liver damage occurs more often after ingestion of the liquid than after inhalation of the vapor. Human fatalities from acute renal damage have occurred after exposure for 1/2 to 1 hour to concentrations of 1,000 to 2,000 ppm. Cardiac arrhythmias have been reported (HSDB 1990).

The weight-of-evidence classification for carbon tetrachloride is "B2; probable human carcinogen." The basis for this classification is carcinogenicity in rats, mice and hamsters. There is inadequate human carcinogenicity data available. There have been three case reports of liver tumors developing after carbon tetrachloride exposure. Several studies of workers who may have used carbon tetrachloride have suggested that these workers may have an excess risk of cancer.

As little as 3 to 5 ml of carbon tetrachloride ingested orally has resulted in death. Toxicity via inhalation has been noted following a 30-minute exposure to 160 ppm. Systemic toxicity may follow dermal exposure.

Alcohol has been clearly shown to potentiate the toxicity of carbon tetrachloride.

2.2.3.2 Health Effects

Noncarcinogenic Effects - The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general the RfD is an estimate (with uncertainty spanning possibly an order of magnitude) of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. Oral

RfDs are available for carbon tetrachloride. Its critical effect is liver lesions and the RfDo is 7E-4 mg/kg/day. There is a medium confidence assigned to the RfDo. The principal study was well conducted and good dose-response was observed in the liver, which is the target organ for CCl_4. Therefore, a high confidence level is assigned to the study. Four additional subchronic studies support the RfDo, but reproductive and teratology endpoints are not well investigated. Thus, the database rates a medium confidence level, with the result being a medium confidence level in the RfDo. No Reference Dose for chronic inhalation exposure (RfDi) is available at this time (IRIS 1990).

Exposure to CCl_4 at 10 or 11 ppm for 180 minutes produced no effect on liver or kidney function. However, exposure to 49 ppm for 70 minutes produced an effect on liver function shown by a reduction of serum iron 1 to 2 days later in 2 of 4 subjects (HSDB 1990).

Individuals who have experienced short-term overexposure may experience delayed effects, including damage to the heart, liver, and kidneys. Symptoms of liver damage may result in jaundice and dark urine.

Human Carcinogenicity - The weight-of-evidence classification for carbon tetrachloride is "B2; probable human carcinogen." The basis for this classification is carcinogenicity in rats, mice, and hamsters. Human carcinogenicity data are inadequate. There have been three case reports of liver tumors developing after carbon tetrachloride exposure. Several studies of workers who may have used carbon tetrachloride have suggested that these workers may have an excess risk of cancer.

Animal Carcinogenicity - Carbon tetrachloride has proved carcinogenic to all species evaluated (rats, mice and hamsters), producing hepatocellular carcinomas in all of these species. Several studies were reported in IRIS confirming the carcinogenicity in these animals (IRIS 1990).

Carcinogenicity Supporting Data - Carbontetrachlorice was not mutagenic either for S. typhimurium or E. coli (McCann et al. 1975; Simmon et al. 1977; Uehleke et al. 1976; as cited in IRIS 1990). Carbon tetrachloride in low concentrations did not produce chromatic or chromosomal aberrations in an epithelial cell line derived from rat liver (Dean and Hodson-Walker 1979; as

cited in IRIS 1990). In vivo unscheduled DNA synthesis assays have likewise been negative (Mirsalis and Butterworth 1980; Mirsalis et al. 1983; as cited in IRIS 1990). Carbon tetrachloride produced mitotic recombination and gene conversion is cerevisiae, but only at concentrations which reduced viability to 10% (Callen et al. 1980; as cited in IRIS 1990). Carbon tetrachloride may be metabolized to reactive intermediates capable of binding to cellular nucleophilic macromolecules. Negative responses in bacterial mutagenicity assays may have been due to inadequate metabolic activation in the test systems (IRIS 1990).

Quantitative Estimate of Carcinogenic Risk - The inhalation slope factor is 1.3E-1/mg/kg/day. The inhalation unit risk is 1.5E-5/$\mu g/m^3$. The extrapolation method used was the linearized multistage procedure using extra risk. Table 2.3 shows air concentrations at specified risk levels (IRIS 1990).

Inhalation risk was calculated assuming an air intake of 20 m^3/day and 40% absorption rate by humans (EPA 1984; as cited in IRIS 1990). This absorption coefficient was based on 30% inhalation in monkeys, and 30% and 57% to 65% inhalation in humans. A range of estimates of unit risk for inhalation exposures for the four studies cited above was determined, with 1.5E-5/$\mu g/m^3$ calculated as the geometric mean for the unit risk. The unit risk should not be used if the air concentration exceeds 7E+2 $\mu g/m^3$, since above this concentration the slope factor may differ from that stated (IRIS 1990).

Hepatotoxicity - There is an age difference in susceptibility to carbon tetrachloride-induced hepatotoxicity. At intraperitoneal doses of 1 ml/kg, the increase in serum aspartate aminotransferase and triglyceride accumulation in the neonatal (1- to 14-day-old) rat was equivalent to that observed in the

TABLE 2.3. Carbon Tetrachloride Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (i in 10,000)	7E+0 $\mu g/m^3$
E-5 (1 in 100,000)	7E-1 $\mu g/m^3$
E-6 (1 in 1,000,000)	7E-2 $\mu g/m^3$

adult rat; however, there was much less macromolecular binding and lipid peroxidation in the young rats, whereas blood acetate levels were 3 to 5 times higher (HSDB 1990).

Response of specific forms of hepatic microsomal cytochrome p-450 to carbon tetrachloride was studied by immunohistochemical techniques to assess the localization and specificity of action for this hepatotoxin. Liver sections were taken from control, phenobarbital-pretreated, and 3-methylcholanthrene-pretreated male rats that had received acute (3-hour) treatment with carbon tetrachloride. Diminished fluorescence and loss of intracellular homogeneity fluorescence were found in the centrilobular cells of liver sections from carbon tetrachloride-challenged rats incubated with anti-p450b. In liver sections from 3-methylcholanthrene-pretreated, carbon tetrachloride challenged rates incubated with anti-p450c, fluorescence was diminished in periportal cells but did not show loss of intracellular homogenicity (HSDB 1990).

Rats were injected with carbon tetrachloride (0.2ml/kg body weight) twice weekly for 4 weeks. Carbon tetrachloride treatment caused a significant increase in hepatic lipid perodide levels and significant decrease in hepatic glutathione transferase activities. These results show that chronic carbon tetrachloride administration to rats leads to the stimulation of hepatic lipid peroxidation, which seems to be the consequence of impaired cellular defence by gluthione-related enzymes (HSDB 1990).

Teratogenicity - Carbon tetrachloride is not teratogenic to rats exposed orally, subcutaneously, or via inhalation (HSDB 1990).

Symptoms and General Effects - The following are symptoms for various levels of exposure to carbon tetrachloride: 1) prompt nausea, vomiting, and abdominal pain; after ingestion, hematemesis and diarrhea; 2) headache, dizziness, confusion, drowsiness, and occasionally convulsions; 3) visual disturbances, sometimes consisting of a concentric restriction of the color fields without central scotomata (toxic amblyopia); 4) rapid progression of central nervous depression with deepening coma and death from respiratory arrest or circulatory collapse; 5) occasionally sudden death due to ventricular fibrillation; 6) in massive exposures the above symptoms merge with

those outlined below, but central nervous depression may subside without sequelae, or an essentially asymptomatic interval of a few days may precede hepatorenal decompensation, 7) kidney and/or liver injury, 8) oliguria, albuminuria, anuria, gradual weight gain, edema. Death may occur within 1 week in the absence of effective supportive treatment, 9) anorexia, jaundice, and right upper quadrant pain due to an enlarged and tender liver, 10) carpopedal spasm that was relieved by calcium gluconate appears to be a very rare reaction (HSDB 1990).

Toxicity Ranges - As little as 3 to 5 ml of carbon tetrachloride ingested orally has resulted in death. Toxicity via inhalation has been noted following a 30 minute exposure to 160 ppm. Systemic toxicity may follow dermal exposure.

Inhalation Absorption Factors - Pertinent studies of pulmonary absorption of carbon tetrachloride in humans were not located in the available literature. A few studies on pulmonary absorption in experimental animals were found. Nielsen and Larsen 1965, as cited in EPA 1984b, stated that carbon tetrachloride is "readily absorbed" through the lungs, but the species studied was not reported. Lehmann and Hasegawa (1910), as cited in EPA 1984b, showed that the rate of absorption decreased with duration of exposure. Von Oettingen et al. (1949, 1950), as cited in EPA 1984b, studied blood concentrations in dogs following exposure to 15 or 20 g/L in air. Peak blood concentrations of ≈35 or ≈38 mg/L were attained after ≈300 minutes of exposure to 15 or 20 g/L in air, respectively (EPA 1984b).

Toxicant Interaction - Alcohol has been clearly shown to potentiate the toxicity of carbon tetrachloride. Traiger and Plass (1971), as cited in EPA 1984b, investigated the potentiation of carbon tetrachloride toxicity by methanol, ethanol and isopropanol in rats. The activity of serum glutonic pyruvic transaminase (SGPT) was monitored to evaluate hepatotoxicity. All three alcohols tested potentiated the toxicity of carbon tetrachloride, with isopropanol being the most potent. Neither carbon tetrachloride nor the alcohols alone elevated SGPT levels (EPA 1984b).

2.2.4 Chloroform

Chloroform is a heavy colorless liquid with an ethereal odor. It has a density of 1.49845 and no registered flash point. Its molecular formula is $CHCl_3$, and its molecular weight is 119.37. It has a vapor pressure of 100 mm at 10.4°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The half-life of chloroform in air is 80 days (EPA 1984c). From 49% to 77% of the chloroform present in the inspired air is absorbed by the lungs (EPA 1984c). The TLV, on a TWA basis, for chloroform is 10 ppm (ACGIH 1988).

2.2.4.1 Summary

Chloroform exposure may occur by oral, inhalation, or dermal routes. Chloroform is an irritant, and central nervous system and cardiac depressant. Delayed renal and hepatic toxicity may also occur. Conjunctivitis and blepharospasm may occur from exposure to vapors of chloroform. Respiratory depression, chemical pneumonitis, and pulmonary edema may occur. Central nervous system depression, headache, and anorexia have been noted from significant exposures to chloroform. Central hepatic necrosis has occurred 10 to 48 hours postingestion, and fatty degeneration and hepatomegaly have been noted. Renal damage and frequent urination have been reported. Chloroform may be embryotoxic, and it is listed as a suspected carcinogen (HSDB 1990).

Chloroform is classified as moderately toxic. A probable oral lethal dose for humans is 0.5 to 5 g/kg (between 1 ounce and 1 pint) for a 150-lb. person. The mean lethal dose is probably near 1 fluid ounce (44 g) (Gosselin et al. 1976, as cited in IRIS 1990). Also, it is a central nervous system depressant and a gastrointestinal irritant (Challen et al. 1958, as cited in IRIS 1990). Chloroform has caused rapid death attributable to cardiac arrest (IRIS 1990).

2.2.4.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate to the human population (including sensitive subgroups)

that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for chloroform is 1E-2/mg/kg/day, with the critical effect being fatty cyst formation in the liver. The confidence level assigned to this RfDo is medium. The critical study (Heywood et al. 1979, as cited in IRIS 1990), was of chronic duration, used a fairly large number of dogs and measured multiple endpoints; however, only two treatment doses were used and no NOEL was determined. Therefore, confidence in the study is rated medium. Confidence in the database is considered medium to low; several studies support the choice of a lowest-observed-adverse-effect level (LOAEL), but a no-observed-effect level (NOEL) was not found. Thus, confidence in the RfDo is also considered medium to low (IRIS 1990).

A 33-year-old male who habitually inhaled chloroform for 12 years has psychiatric and neurologic symptoms of depression, loss of appetite, hallucination, ataxia, and dysarthria. Other symptoms for habitual use are moodiness, mental and physical sluggishness, nausea, rheumatic pain, and delirium (HSDB 1990).

Worker exposure to concentrations of chloroform of over 112 mg/m^3 have been reported to result in depression, ataxia, flatulence, irritability, and liver and kidney damage. An increased incidence of cardiac arrhythmias has been demonstrated during surgery in patients anesthetized with chloroform as compared with other anesthetic agents at vapor concentrations of 22,500 ppm (HSDB 1990).

Human Carcinogenicity - The weight-of-evidence classification for chloroform is "B2; probable human carcinogen," based on increased incidence of several tumor types in rats and three strains of mice. The human carcinogenicity data are inadequate. There are no epidemiologic studies of chloroform itself. Chloroform and other trihalomethanes are formed from the interaction of chlorine with organic material found in water. Several ecological and case control studies of populations consuming chlorinated drinking water in which chloroform was the major chlorinated organic show small significant increases in the risk of rectal bladder or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies.

Animal Carcinogenicity - The animal carcinogenicity data are considered sufficient. Chloroform has been tested for carcinogenicity in eight strains of mice, two strains of rats and in beagle dogs.

In a gavage bioassay (NCI 1976, as cited in IRIS 1990), Osborne-Mendel rats and B6C3F1 mice were treated with chloroform in corn oil 5 times/wk for 78 weeks. Fifty male rats received 90 or 125 mg/kg/day; females initially were treated with 125 or 250 mg/kg/day for 22 weeks and 90 or 180 mg/kg/day at 18 weeks; females were dosed with 200 or 400, raised to 250 or 500 mg/kg/day. A significant increase in kidney epithelial tumors was observed in male rats, and increases in hepatocellular carcinomas were highly highly significant in mice of both sexes. Liver nodular hyperplasia was observed in low-dose male mice not developing hepatocellular carcinoma. Hepatomas have also developed in female strain A mice and NLC mice gavaged with chloroform (Eschenbrenner and Miller 1945; Rudali 1967; as cited in IRIS 1990).

Jorgenson et al. (1985); as cited in IRIS 1990, administered chloroform (pesticide quality and distilled) in drinking water to male Osborne-Mendel rats and female B6C3F1 mice at concentrations of 200, 400, 900, and 1800 mg/L for 104 weeks. These concentrations were reported by the author to correspond to 19, 38, 81, and 160 mg/kg/day for rats and 34, 65, 130, and 263 mg/kg/day for mice. A significant increase in renal tumors in rats was observed in the highest dose group. The increase was dose-related. The liver tumor incidence in female mice was not significantly increased. This study was specifically designed to measure the effects of low doses of chloroform (IRIS 1990).

Chloroform administered in toothpaste was not carcinogenic to male C57B1, CBA, CF-1 or female ICI mice or to beagle dogs. Male ICI mice administered 60 mg/kg/day were found to have an increased incidence of kidney epithelial tumors (Roe et al. 1979; Heywood et al. 1979; as cited in IRIS 1990). A pulmonary tumor bioassay in strain A/St mice was negative, as was one in which newborn C57X DBA2/F1 mice were treated subcutaneously on days 1 to 8 of life (Theiss et al. 1957; Roe et al. 1968; as cited in IRIS 1990).

Most tests for genotoxicity of chloroform have been negative. These negative findings include covalent binding to DNA, mutation in Salmonella, a Drosophila self-linked recessive, tests for DNA damage, a micronucleus test,

and transformation of BHK cells. By contrast, one study demonstrated binding of radiolabeled chloroform to calf thymus DNA following metabolism by rat liver microsome (DiRenzo 1982; as cited in IRIS 1990). Chloroform caused mitotic recombination in Saccharomyces (Callen et al. 1980; as cited in IRIS 1990) and sister chromatic exchange in cultured human lymphocytes and in mouse bone marrow cells exposed in vivo (Morimoto and Koizumi 1983; as cited in IRIS 1990).

The carcinogenicity of chloroform may be a function of its metabolism to phosgene, which is known to cross-link DNA. A host-mediated assay using mice indicated that chloroform was metabolized in vivo to a form mutagenic to Salmonella strain TA1537. Likewise, urine extracts from chloroform-treated mice were mutagenic (Agustin and Lim-Sylianco 1979; as cited in IRIS 1990).

Quantitative Estimate of Risk - The inhalation slope factor is 8.1E-2/mg/kg/day. The inhalation unit risk is 2.3E-5/$\mu g/m^3$. The extrapolation method used was the linearized multistage procedure, using extra risk. Table 2.4 shows air concentrations at specified risk levels (IRIS 1990).

Dose-Response Data - Dose-response data for carcinogenicity, for inhalation exposure, is provided in IRIS 1990. The test animals were the B6C3F1 female mouse, administered with the oral and gavage routes. The tumor type was hepatocellular carcinoma. Table 2.5 shows the dose-response data (IRIS 1990).

This inhalation quantitative risk estimate is based on oral data. Above doses are TWA; at the end of the assay males weighed 35 g, and females 28 g. Exposure vehicle control animals were run concurrently and housed with test

TABLE 2.4. Chloroform Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	4 $\mu g/m^3$
E-5 (1 in 100,000)	4E-1 $\mu g/m^3$
E-6 (1 in 1,000,000)	4E-2 $\mu g/m^3$

TABLE 2.5. Chloroform Inhalation Exposure Dose-Response Data

Dose		
Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	Tumor Incidence
Female		
0	0	0/20
238	9.9	36/45
477	19.9	39/41
Male		
0	0	1/18
138	6.2	18/50
277	12.5	44/45

animals. All treated animals experienced decreased body weight gain. Survival was reduced in high-dose males and in all treated females (IRIS 1990).

Experimental data for this compound support complete absorption of orally administered chloroform under conditions of this assay. There are not apparent species differences in this regard. Extrapolation of metabolism-dependent carcinogenic responses from mice to humans on the basis of body surface area is supported by experimental data. The slope factor is the geometric mean calculated from male (3.3E-2) and female (2.0E-1) data. The unit risk should not be used if the air concentration exceeds 400 $\mu g/m^3$, since above this concentration the slope factor may differ from that stated. Slope factors derived from male rat kidney tumor data (2.4E-2) (NCI 1976; as cited in IRIS 1990) and studies by Roe et al. (1979); as cited in IRIS 1990, (1.0E-1) are generally supportive of the risk estimate (IRIS 1990).

Teratogenicity - Teratogenic effects (acaudia, imperforate anus, decreased crown-rump length, missing ribs, and delayed skeletal ossification) were seen in Sprague-Dawley rats (Schwetz et al. 1974; as cited in EPA 1984c) that inhaled chloroform for 7 h/day on days 6 to 15 of gestation at dose levels of 30, 100 and 300 ppm. When CF/1 mice (Murray et al. 1979; as cited

in EPA 1984c) were exposed to 100 ppm chloroform for 7 h/day on days 6 to 15 of gestation, there was a significantly increased incidence of cleft palate. When pregnant mice and rats were exposed to 100 ppm chloroform, their food consumption and body weight decreased, but their relative liver weight increased (EPA 1982, as cited in EPA 1984c). Ingestion of chloroform caused fetotoxicity but not teratogenicity, and only at levels that also produced severe maternal toxicity (Thompson et al. 1974, as cited in EPA 1984c).

Toxicity Ranges - As little as 10 ml in an acute ingestion of chloroform may result in central nervous system depression and death (HSDB 1990).

Symptoms - Signs of chloroform poisoning in humans include a characteristic sweetish odor on the breath, dilated pupils, cold and clammy skin, initial excitation alternating with apathy, loss of sensation, abolition of motor functions, prostration, unconsciousness, and eventual death.

Toxicant Interactions - The substrates that potentiate the toxic effects of chloroform are methyl n-butyl ketone, alcohol, carbon tetrachloride, chlordecone, DDT and phenobarbital (EPA 1984c). Methyl n-butyl ketone increases the toxicity of chloroform by lowering glutathione levels and by increasing the levels of hepatic cytochrome p-450, which in turn, increases the metabolism of chloroform to phosgene (Branchflower and Pohl 1981; as cited in EPA 1984c). Haris et al. (1982; as cited in EPA 1984c) reported that carbon tetrachloride potentiated the toxic effects of chloroform, because of increased phosgene formation and the initiation of lipid peroxidation. The mechanism of interaction for alcohol, chlordecone, DDT and phenobarbital was not discussed. Von Oettingen (1964; as cited in EPA 1984c) reported that high-fat/low-protein diets potentiated hepatotoxic effects of chloroform in animals (EPA 1984c).

2.2.5 Decane

Decane is a liquid with a density of 0.730 and a flash point of 115°F. Its molecular formula is $C_{10}H_{22}$, and its molecular weight is 142.29. It has a vapor pressure of 1 mm at 16.5°C. It has a Hazard Rating of 3 (Sax and Lewis 1989).

2.2.5.1 Summary

The most serious toxic effect following ingestion of decane is aspiration pneumonitis. Aspiration of hydrocarbons may also result in transient central nervous system depression or excitement. Secondary effects may include hypoxia, infection, pneumatocele formation, and chronic lung dysfunction. Inhalation may result in euphoria, cardiac dysrhythmias, respiratory arrest, and central nervous system toxicity.

2.2.5.2 Health Effects

The amount of information available regarding toxicological effects of decane is very limited. No specific studies involving the toxicology of decane were found.

Symptoms and General Effects - Coughing, choking, tachypnea, dyspnea, cyanosis, roles, hemoptysis, and pulmonary edema may occur following ingestion and aspiration. Transient central nervous system excitation followed by depression may occur, especially after inhalation. Liver injury, as manifested by elevated transaminases, may occur following ingestion, and renal injury, as manifested by tubular damage, may occur following ingestion (HSDB 1990).

Decane was oxidized by microsome from livers of mouse, rat, rabbit, beef, pigeon and chick embryo. Decanol, decanoic acid and decamethylene glycol were major metabolites of oxidation of decane (HSDB 1990).

Tumorigenic Data - The tumorigenic data provided in RTECS was very limited and sketchy. Mouse skin study with a low dose (25 gm/kg per 52 weeks) yielded that decane was an equivocal tumorigenic agent by Registry of Toxic Effects of Chemical Substances (RTECS) criteria. Tumors appeared at the site of application (RTECS 1987).

Toxicity Data - The toxicity data provided in RTECS were very limited and sketchy. Mouse inhalation studies yielded an LC50 of 72,300 mg/m^3/2 hr (RTECS 1987).

Toxicity Range - Less than 1 ml of some hydrocarbons, when directly aspirated into the lungs in animals, has produced severe pneumonitis (HSDB 1990).

Toxicant Interactions - Series of tobacco smoke components and related compounds were tested for carcinogenic activity on mouse skin. The compound was applied to mouse skin three times per week with low doses (5 μg/application) of benzo(a)pyrene [B(a)P]. Decane enhanced carcinogenicity of B(a)P (Van Douren et al. 1976, as cited in HSDB 1990).

2.2.6 1,2-Dichlorobenzene

1,2-Dichlorobenzene is a clear liquid with a density of 1.307 and a flash point of 151°F. Its molecular formula is $C_6H_4Cl_2$ and its molecular weight is 147.00. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, is 50 ppm. This TLV represents a ceiling limit. Some of the common synonyms for 1,2-dichlorobenzene are o-dichlorobenzene, chloroben, DCB, o-dichlor benzol, Dilantin D8, Dilatin DB, dizene, Dowtherm E, orthodichlorobenzene, orthodichlorobenzol, Termitkil, and ODB.

2.2.6.1 Summary

The RfDo is 9E-2 mg/kg/day, with no adverse critical effects observed (IRIS 1990). Inhalation of up to 400 ppm of o-dichlorobenzene was neither teratogenic nor fetotoxic in rats and neither o-dichlorobenzene or p-dichlorobenzene was teratogenic nor fetotoxic in rabbits at exposure levels up to 400 or 800 ppm, respectively (HSDB 1990).

A 55 year-old female received a non-occupational chronic repeated inhalation exposure to vapors from use of solution to clean clothes. The concentration was estimated at 1 to 2 L/yr. The result was acute myeloblastic leukemia (HSDB 1990).

2.2.6.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude)

of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo is 9E-2 mg/kg/day, with no adverse critical effects observed (IRIS 1990).

1,2-dichlorobenzene in corn oil was given by gavage to F344/N rats and B6C3F1 mice (50 males and 50 females/group) at doses of 0, 60, or 120 mg/kg/day, 5 day/wk for 103 weeks (NTP 1985, as cited in IRIS 1990). Survival of high-dose male rats was decreased compared with controls (19/50 versus 42/50, $P \geq 0.001$), but the difference appears largely because of deaths from gavage error (4 controls versus 20 high-dose). Although an increase ($P \geq 0.05$) in renal tubular regeneration in high-dose male mice was observed (control, 8/48; low-dose, 12/50; high-dose, 17/49), there was no other evidence of treatment-related renal lesions in either species. Further, control incidence of this lesion in male mice is below those of three similar control groups on study at the testing facility during approximately the same period (31/50, 15/50, 24/50). There was no other evidence of treatment-related effects in this study. Because the above differences between control and high-dose animals are questionable, a NOAEL of 120 mg/kg/day is concluded (IRIS 1990).

1,2-Dichlorobenzene in corn oil was given orally by gavage to F344/N rats and B6C3F1 mice (10 males and 10 females/group) at doses of 0, 30, 60, 125, 250, or 500 mg/kg/day, 5 day/wk for 13 weeks (NTP 1985; as cited in IRIS 1990). Liver necrosis was found in mice and rats given 250 mg/kg/day. Deaths, degeneration and necrosis in liver, lymphocyte depletion in spleen and thymus, renal tubular degeneration (male rats only), and slight decreases in hemoglobin, hematocrit and red blood cell counts (rats only) were induced with 500 mg/kg/day (IRIS 1990).

Necrosis (focal or individual hepatocyte) was observed in the livers of one male and three female rats given 125 mg/kg/day (NTP 1985, as cited in IRIS 1990). Increases ($P \geq 0.05$) in serum cholesterol were observed at all doses except 60 mg/kg/day in male rats and 30 and 60 in liver; increases in body weight ratios were observed in male and female rats, serum protein at all doses in female rats, and treatment-related liver effects at doses >125 mg/kg/day. However, no evidence of treatment-related liver pathology was

observed in rats and mice given 60 or 120 mg/kg/day, 5 day/wk in the 2-year National Toxicology Program (NTP 1985, as cited in Iris 1990), carcinogenicity bioassay and no increase ($P \geq 0.05$) in serum enzymes (SGPT, GGPT, alkaline phosphatase) are grounds for considering 125 mg/kg/day as a NOAEL in the 13-week study (IRIS 1990).

In rats dosed by gavage with 1,2-dichlorobenzene at 18.8, 188, or 376 mg/kg/day, 5 day/wk for 192 days, the NOAEL was 18.8 mg/kg/day, liver and kidney weights were increased at 188 mg/kg/day, and liver pathology and increased spleen weight were observed with 375 mg/kg/day (Hollingsworth et al. 1958; as cited in IRIS 1990).

Rats, guinea pigs, mice, rats, and monkeys were exposed by inhalation to 1,2-dichlorobenzene at levels of 49 or 93 ppm, 7 h/day, 5 day/wk for 6 to 7 months. At 93 ppm, body weight gain in rats and spleen weight in guinea pigs were reduced ($P \geq 0.05$) (Hollingsworth et al. 1958, as cited in IRIS 1990). Estimated daily doses with 49 ppm exposure are 387 mg/kg (mouse), 19.3 mg.kg (rat), 14.4 mg/kg (guinea pig), 15.9 mg/kg (rabbit), and 20.3 mg/kg (monkey) (IRRIS 1990).

Pregnant F344/N rats and New Zealand rabbits were exposed by inhalation to 0, 100, 200, or 400 ppm to 1,2-dichlorobenzene for 6 hours daily on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation (Hayes 1985, as cited in IRIS 1990). Body weight gain was lower ($P \geq 0.05$) in rats at all doses and in rabbits, during the first three days of exposure, at 400 ppm. Liver weight (absolute and relative to body weight) was increased in rats at 400 ppm. No developmental toxicity was evident at any dose. Estimated daily doses with 100 ppm exposure are 40 mg/kg (rat) and 32 mg/kg (rabbit) (IRIS 1990).

No RfDi is available at this time.

Seventeen chemicals (solvents, insecticides and intermediates used in the production of textiles and resins) were tested in a short-term in vitro system with human lymphocytes to determine their action. The parameters studied were tritiated thymidine uptake and cell viability in cultures grown

with or without a rat liver metabolizing system (S-9 mix). 1,3-dichlorobenzene, 1,2-dichlorobenzene, hexane, 1,2-diiodoethane, 1,4-dichlorobenzene, tetrachloroethylene, 2,3-dibromopropanol, chloromethyl methyl ether, 1,2- and 1,3-dibromopropane, in order, exerted the more toxic effects. The chemicals were non-toxic in the presence of the metabolizing system with exception of 1,2- and 1,3-dichlorobenzene which maintained, to some degree, their toxicity even in the presence of the S-9 mix (HSDB 1990).

Leukemia - A 55 year-old female received a non-occupational chronic repeated inhalation exposure to vapors from use of solution to clean clothes. The concentration was estimated at 1 to 2 L/yr. The result was acute myeloblastic leukemia (HSDB 1990).

Teratogenic Potential - o-dichlorobenzene (1,2-dichlorobenzene) and p-dichlorobenzene (1,4-dichlorobenzene) were evaluated for teratogenic potential in rats (o-dichlorobenzene only) and rabbits. Groups of bred rats and inseminated rabbits were exposed to 0, 100, 200, or 400 ppm of o-dichlorobenzene, while groups of inseminated rabbits were exposed to 0, 100, 300, or 800 ppm p-dichlorobenzene. The animals were exposed for 6 h/day on days 6 through 15 (rats) or days 6 through 18 (rabbits) of gestation. Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in all groups of o-dichlorobenzene exposed rats and liver weight was significantly increased in the 400 ppm o-dichlorobenzene exposed group. Slight maternal toxicity was observed in groups of rabbits exposed to 400 ppm o-dichlorobenzene or 800 ppm p-dichlorobenzene as indicated by significantly decreased body weight gain during the first three days of exposure. Inhalation of up to 400 ppm of o-dichlorobenzene was neither teratogenic nor fetotoxic in rats. Neither o-dichlorobenzene nor p-dichlorobenzene was teratogenic or fetotoxic in rabbits at exposure levels up to 400 or 800 ppm, respectively (HSDB 1990).

Toxicity Ranges - Toxic doses vary enormously with route and rate of exposure (HSDB 1990).

2.2.7 Dichloromethane

Dichloromethane is a colorless volatile liquid with a density of 1.326. Its molecular formula is CH_2Cl_2, and its molecular weight is 84.93. Dichloromethane has a vapor pressure of 380 mm at 22°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, for dichloromethane is 50 ppm (ACGIH 1988). Common synonyms for dichloromethane are methylene chloride, methane dichloride, DCM, 1,1-dichloromethane, Freon 30, methylene bichloride, and methylene dichloride.

2.2.7.1 Summary

The RfDo for dichloromethane is 6E-2mg/kg/day, with liver toxicity as the critical effect. The weight-of-evidence classification for dichloromethane is "B2; probable human carcinogen," based on inadequate data in humans and increased cancer incidence in rats and mice (IRIS 1990). The inhalation slope factor is 1.4E-2/mg/kg/day. The inhalation unit risk is 4.1E-6/$\mu g/m^3$. The extrapolation method used was linearized multistage procedure, with extra risk considered.

There is concern about consumer exposure to dichloromethane from products because the dichloromethane retained in inhalation is metabolized to carbon monoxide, leading to elevated levels of carboxyhemoglobin. At relatively high exposures, the resulting anoxic stress placed on individuals may pose a health hazard. In addition, a recent NTP inhalation bioassay found clear evidence of carcinogenicity in female rats and in both sexes of mice as well as "some evidence of carcinogenicity" in male rats (Girman and Hodgson 1986).

2.2.7.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for dichloromethane is 6E-2mg/kg/day, with liver toxicity as the critical effect.

The chosen study supporting the RfDo was a 24-month chronic toxicity and oncogenicity study of methylene chloride in rats (National Coffee Association 1982; as cited in IRIS 1990). This study appears to have been very well conducted, with 85 rats per sex at each of four nominal dose groups (i.e., 5, 50, 125, and 250 mg/kg/day) for 2 years. A high-dose recovery group of 25 rats per sex, as well as two control groups of 85 and 50 rats per sex, was also tested. Many effects were monitored. Treatment related histological alterations of the liver were evident at nominal doses of 50 mg/kg/day or higher. The low nominal dose of 5 mg/kg/day was a NOAEL (IRIS 1990).

The supporting database is limited for the RfDo. A NOAEL of 87 mg/m^3 was reported in one inhalation study (Haun et al. 1972, as cited in IRIS 1990). The equivalent oral dose is about 28 mg/kg bw/day (i.e., 87 mg/m^3 x 0.05 x 0.223 m^3/day/0.35 kg; these exposure values are for rats (IRIS 1990).

The confidence rating for the dichloromethane RfDo is medium. The study supporting the RfDo is given a high confidence rating because a large number of animals of both sexes were tested in four dose groups, with a large number of controls. Many effects were monitored and a dose-related increase in severity was observed. The database is rated medium to low because only a few studies support the NOAEL. Thus, medium confidence in the RfDo follows.

The RfDi is not available at this time.

Human Carcinogenicity - The weight-of-evidence classification for dichloromethane is "B2; probable human carcinogen," based on inadequate data in humans and increased cancer incidence in rats and mice (IRIS 1990).

Human carcinogenicity data are inadequate. Neither of two studies of chemical factory workers showed an excess of cancers (Friedlander et al. 1978, 1985; Ott et al. 1983, as cited in IRIS 1990). In the former study, exposures were low, but the data provided some suggestion of an increased incidence of pancreatic tumors. The latter report was designed to examine cardiovascular effects, and the study period was too short to allow for latency of site-specific cancers (IRIS 1990).

Animal Carcinogenicity Data - The animal carcinogenicity data are considered sufficient. In a 2-year study (National Coffee Association 1982,

1983, as cited in IRIS 1990), F344 rats received 0, 5, 50, 125, or 250 mg dichloromethane/kg/day in drinking water. B6C3F1 mice consumed 0, 60, 125, 185, or 250 mg/kg/day in water. Female rats responded with increased incidence of neoplastic nodules or hepatocellular carcinomas, which was significant by comparison to matched but not to historical controls. Male rats did not show an increased incidence of liver tumors. Male mice had elevated incidences of combined neoplastic modules and hepatocellular carcinomas, but female mice did not. This increase was not statistically significant or dose-related. In a study by the NTP (1982), as cited in IRIS (1990), gavage study of rats and mice has not been published because of data discrepancies (IRIS 1990).

Inhalation exposure of male and female Syrian hamsters to 0, 500, 1500, or 3500 ppm dichloromethane for 6 h/day, 5 day/wk for 2 years did not produce neoplasia. Female Sprague-Dawley rats exposed under the same conditions experienced reduced survival at the highest dose. Increased incidences of mammary tumors were noted in both males and females. Male rats also developed salivary gland sarcomas (Burek et al. 1984, as cited in IRIS 1990). There is a question as to whether these doses were at or near the maximum tolerated dose (MTD). In a subsequent study (Burek et al. 1984, as cited in IRIS 1990) male and female rats were exposed to 0, 50, 200 or 500 ppm dichloromethane. No salivary tumors were observed, but the highest dose resulted in mammary tumors (IRIS 1990).

Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to dichloromethane 6 h/day, 5 day/wk for 2 years. Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. Survival of male rats was low, but apparently not treatment related; survival was decreased in a treatment-related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were increased in male and female rats as were mononuclear cell leukemias in female rats. Among treated mice of both sexes, there were increased incidences of hepatocellular adenomas and carcinomas and highly significant increases in alveolar/bronchiolar adenomas and carcinomas (NTP 1986, as cited in IRIS 1990).

Two inhalation assays using dogs, rabbits, guinea pigs, and rats were negative, but were not carried out for the lifetime of the animals (Heppel et al. 1944; MacEwen et al. 1972, as cited in IRIS 1990). Theiss et al. (1977), as cited in IRIS 1990, injected strain A male mice intraperitoneally with 0, 160, 400, or 800 mg/kg for 16-17 times. Pulmonary adenomas were found, but survival of animals was poor (IRIS 1990).

As supporting data for carcinogenicity, dichloromethane is mutagenic for Salmonella typhimurium with or without added hepatic enzymes (Green 1983, as cited in IRIS 1990) and produced mitotic recombination in yeast (Callen et al. 1980, as cited in IRIS 1990). Results in cultured mammalian cells have generally been negative, but dichloromethane has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells (Price et al. 1978; Hatch et al. 1983, as cited in IRIS 1990).

Quantitative Estimate of Carcinogenic Risk - The oral slope factor is 7.5E-3/mg/kg/day. The extrapolation method used was linearized multistage procedure, with extra risk considered. The inhalation unit risk is 4.7E-7/$\mu g/m^3$. An inhalation slope factor is not available because pharmacokinetic models were used to estimate the unit risk value. Table 2.6 shows air concentrations at specified risk levels (IRIS 1990).

Dose-Response Data - Inhalation dose-response data for carcinogenicity is provided in IRIS (1990). The test animal was the female B6C3F1 mouse; scientists looked at combined carcinomas and adenomas of the lung or liver. Table 2.7 shows the dose-response data (IRIS 1990).

Dose conversions used the mouse assay midpoint weight of 0.032 kg and estimated inhalation rate of 0.0407 m^3/day. To obtain estimates of unit risk

TABLE 2.6. Dichloromethane Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	2E+2 $\mu g/m^3$
E-5 (1 in 100,000)	2E+1 $\mu g/m^3$
E-6 (1 in 1,000,000)	2 $\mu g/m^3$

TABLE 2.7. Dichloromethane Inhalation Exposure Dose-Response Data

Dose		
Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	Tumor Incidence
Female		
0	0	5/50
1582	122	36/48
3164	244	46/57

for humans, an inhalation rate of 20 m^3/day was assumed. Dichloromethane was considered to be a well-absorbed vapor at low doses. A revision of the cancer risk assessment was released in September 1990. This revision contains a new inhalation unit risk based on the incorporation of information on pharmacokinetics and metabolism. This unit risk should not be used if the air concentration exceeds 2E+4 $\mu g/m^3$, because above this concentration, the slope factor may differ from that stated (IRIS 1990).

Adequate numbers of animals were observed and tumor incidences significantly increased in a dose-dependent fashion. Analysis, excluding animals that died before observation of the first tumors, produced similar risk estimates as did time-to-tumor analysis. However, significant uncertainty still exists in the inhalation unit risk because of uncertainty in the pharmacokinetic model for dichloromethane.

2.2.8 Dodecane

Dodecane has a molecular formula of $C_{12}H_{26}$, and a molecular weight of 170.38. It has a Hazard Rating of 3 (Sax and Lewis 1989). Some common synonyms for dodecane are adakane 12, bihexyl, dihexyl, n-dodecane, and duodecane.

2.2.8.1 Summary

Dodecane, which is not highly toxic, is a possible potentiator of skin tumorigenesis by B(a)P, decreasing the effective threshold dose by a factor of 10 (Patty 1981, as cited in HSDB 1990).

The RTECS database lists a mouse skin Toxic Dose Low (TDLo) of 11 g/kg/22 weeks.

2.2.8.2 Health Effects

The amount of information available regarding toxicological effects of dodecane is very limited. The HSDB database lists dodecane, but does not provide any information regarding human toxicity. The IRIS database does not list dodecane.

Tumoregenic Data - The RTECS database lists a mouse skin TDLo of 11 g/kg/22 weeks. RTECS has dodecane listed as a "equivocal tumorigenic agent by RTECS criteria" (RTECS 1987).

Non-Human Toxicity - An isolated perfused rabbit lung preparation was used to study the influence of pretreatment with a cocarcinogen, n-dodecane, on the metabolism of B(a)P. B(a)P was administered intratracheally to the isolated perfused lung following biweekly inhalation exposure of the rabbit to n-dodecane. N-dodecane appears to be as good an enzyme inducer as B(a)P in stimulating metabolism of B(a)P in isolated perfused rabbit lung (HSDB 1990).

A ratio of potencies of dodecane, a lymphocyte comitogen, has previously been found for promotion of mouse epidermal tumorigenesis. Maximum comitogenic activity was found when alkane and lectin were added to cultures simultaneously, the effect decreasing sharply when alkane addition was delayed relative to lectin. The existence of a cellular receptor with specificity for hydrophobic functions with chain length lying within a restricted range was suggested. Binding to this a receptor also appears to be a common early event in tumor promotion, comitogenicity, and comutagenicity, by agents of several chemical types (Baxter et al. 1981, as cited in HSDB 1990).

In an isolated rabbit heart, mitochondria incubation (at 15-38 degrees) with n-dodecane at 10-160 μg/mg mitochondrial protein resulted in uncoupling of oxidative phosphorylation, but only at 30-38 degrees. A slight inhibition of hydronicotinamide adenine dinucleotide (NADH) oxidase was also noted. N-dodecane exerted a biphasic action activation followed by inhibition of succinate oxidase (Borgatti et al. 1981, as cited in HSDB 1990).

Toxicant Interactions - Dodecane and phenyldodecane applied topically to progeny of rats treated with B(a)P, Chrysene or benzo(b)triphenylene on the 17th day of gestation produced tumors in offspring (Tanaka 1978, as cited in HSD8 1990).

Dodecane was shown to be a potentiator of some carcinogens above an apparent 0.02% threshold dose when, for example, B(a)P dissolved in decalin was applied to the mouse skin. Dodecane, which is not highly toxic, is a possible potentiator of skin tumorigenesis by B(a)P, decreasing the effective threshold dose by a factor of 10 (Patty 1981, as cited in HSDB 1990).

2.2.9 2-Ethoxyethylacetate

2-ethoxyethylacetate (cellosolve acetate) is a colorless liquid with a mild, pleasant ester-like odor. It has a density of 0.9748, and a flash point of 117°F. Its molecular formula is $C_6H_{12}O_3$ and its molecular weight is 132.18. It has a vapor pressure of 1.2 mm at 20°C. It has a Hazard Rating of 2 (Sax and Lewis 1989). The TLV, on a TWA basis, is 5 ppm (ACGIH 1988). There are several synonyms for 2-ethoxyethylacetate; some of the more common ones are cellosolve acetate, 2-ethoxyethanol acetate, ethylene glycol, ethyl ether acetate, ethylglycol acetate, and oytol acetate.

2.2.9.1 Summary

The amount of information regarding toxicological effects of 2-ethoxyethylacetate is very limited. No studies of human toxicology were found.

2.2.9.2 Health Effect

The amount of information regarding toxicological effects of 2-ethoxyethylacetate is very limited. No studies of human toxicology were found.

2-ethoxyethylacetate is moderately toxic by ingestion and intraperitoneal routes. It is mildly toxic by skin contact, inhalation and subcutaneous routes. It is a skin and eye irritant and an experimental teratogen (Sax and Lewis 1989).

General Toxicity - 2-ethoxyethylacetate is moderately toxic by ingestion and intraperitoneal routes. It is mildly toxic by skin contact, inhalation

and subcutaneous routes. It is a skin and eye irritant and an experimental teratogen. Other experimental reproductive effects have been observed (Sax and Lewis 1989).

2.2.10 Ethylbenzene

Ethylbenzene is a colorless liquid with an aromatic odor. It has a density of 0.8669, and a flash point of 59°F. Its molecular formula is C_8H_{10} and its molecular weight is 106.18. It has a vapor pressure of 10 mm at 25.9°C (Sax and Lewis 1989). The TLV, on a TWA basis, for ethylbenzene is 100 ppm. The TLV, on a short-term exposure basis (STEL) basis, is 125 ppm (ACGIH 1988). Some of the common synonyms for ethylbenzene are aethylbenzol, EP, ethylbonzol, and phenylethane.

2.2.10.1 Summary

The RfDo for ethylbenzene is 1E-1mg/kg/day, with the critical effect of liver and kidney toxicity. The LOAEL of 408 mg/kg/day is associated with histopathologic changes in liver and kidney (IRIS 1990).

Prolonged exposure to vapors of ethylbenzene may result in functional disorders, increase in deep reflexes, irritation of the upper respiratory tract, hematological disorders (leukopenia and lymphocytosis, in particular), and hepatobiliary complaints (HSDB 1990). Aspiration of even a small amount of ethylbenzene may cause severe injury because its low viscosity and surface tension cause it to spread over a large surface of pulmonary tissue (HSDB 1990).

Ethylebenzene produces an irritant effect from chronic inhalation at 100 ppm/8 h (Patty 1981, as cited in HSDB).

It has been shown that the concentration of 1 mg/L and even 0.1 mg/L of ethylbenzene may be dangerous and may produce functional and organic disturbances (i.e., nervous system disorders, toxic hepatitis and upper respiratory tract complaints). Concentrations as low as 0.01 mg/L may lead to inflammation of upper respiratory tract mucosa (HSDB 1990).

Ethylbenzene vapor has a transient irritant effect on human eyes at 200 ppm in air. At 1000 ppm on the first exposure, it is very irritating and

caused tearing, but tolerance rapidly develops. At 2000 ppm, eye irritation and lacrimation are immediate and severe. Concentrations of 5000 ppm cause intolerable irritation of the eyes and nose (HSDB 1990).

The weight-of-evidence classification for ethylbenzene is "D; not classifiable as to human carcinogenicity."

2.2.10.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for ethylbenzene is 1E-1 mg/kg/day, with the critical effect of liver and kidney toxicity. The criteria considered in judging the toxic effects on the test animals were growth, mortality, appearance and behavior, hematologic findings, terminal concentration of urea nitrogen in the blood, final average organ and body weights, histopathologic findings, and bone marrow counts. The LOAEL of 408 mg/kg/day is associated with histopathologic changes in liver and kidney (IRIS 1990).

The confidence in the RfDo is low (IRIS 1990). Confidence in the chosen study is low because rats of only one sex were tested and the experiment was not of chronic duration. Confidence in the supporting database is low because other oral toxicity data were not found.

The RfDi is not available at this time.

Erythema and inflammation of skin may result from contact of the skin with liquid (Sax and Lewis 1989).

Prolonged exposure to vapors of ethylbenzene may result in functional disorders, increase in deep reflexes, irritation of the upper respiratory tract, hematological disorders (leukopenia and lymphocytosis, in particular), and hepatobiliary complaints (HSDB 1990).

Aspiration of even a small amount of ethylbenzene may cause severe injury because its low viscosity and surface tension cause it to spread over a large surface of pulmonary tissue (HSDB 1990).

Ethylebenzene produces an irritant effect from chronic inhalation at 100 ppm/8 h (Patty 1981, as cited in HSDB).

It has been shown that the concentration of 1 mg/L and even 0.1 mg/L of ethylbenzene may be dangerous and may produce functional and organic disturbances (i.e., nervous system disorders, toxic hepatitis and upper respiratory tract complaints). Concentrations as low as 0.01 mg/L may lead to inflammation of upper respiratory tract mucosa (HSDB 1990).

Ethylbenzene vapor has a transient irritant effect on human eyes at 200 ppm in air. At 1000 ppm on the first exposure, it is very irritating and caused tearing, but tolerance rapidly develops. At 2000 ppm, eye irritation and lacrimation are immediate and severe. Concentrations of 5000 ppm cause intolerable irritation of the eyes and nose (HSDB 1990).

Human Carcinogenicity - The weight-of-evidence classification for ethylbenzene is "D; not classifiable as to human carcinogenicity." Ethylbenzene is nonclassifiable because of lack of animal bioassays and human studies (IRIS 1990). No human carcinogenicity data are available.

Animal Carcinogenicity - There are no data for animal carcinogenicity assessment. NTP has plans to initiate a bioassay. Metabolism and excretion studies at 3.5, 35 and 350 mg/kg are to be conducted as well.

Carcinogenicity Supporting Data - The metabolic pathways for humans and rodents are different (Engstrom et al. 1984, as cited in IRIS 1990). Major metabolites in humans, mandelic acid and phenylglyoxylic acid, are minor metabolites in rats and rabbits (Kiese and Lenk 1974, as cited in IRIS 1990). The major animal metabolites were not detected in the urine of exposed workers (Engstrom et al. 1984, as cited in IRIS 1990).

Ethylbenzene at 0.4 mg/plate was not mutagenic for Salmonella strains TA98, TA1535, TA1537 and TA1538 with or without Aroclor 1254 induced rat liver homogenates (S) (Nestmann et al. 1980, as cited in IRIS 1990). Ethhylbenzene was shown to increase the mean number of sister chromatic exchanges in human

whole blood lymphocyte culture at the highest dose examined without any metabolic activation system (Norppa and Vainio 1983, as cited in IRIS 1990).

Dean et al. (1985), as cited in IRIS 1990, used a battery of short-term tests including bacterial mutation assays, mitotic gene conversion in Saccharomyces cerevisiae JD1 in the presence and absence of S9, and chromosomal damage in a cultured rat liver cell line. Ethylbenzene was not mutagenic in the range of concentrations tested (0.2, 2, 20, 50, and 200 μg/plate) for S. typhimurium TA98, TA100, TA1535, TA1537, and TA1538 or for Escherichia coli WP2 and WPSuvrA. Ethylbenzene also showed no response in the S. cerevisiae JD1 gene conversion assay. In contrast, ethylbenzene hydroperoxide showed positive responses with E. coli WP2 at 200 μg/plate in the presence of S9 and an equally significant response with the gene conversion system of yeast (IRIS 1990).

2.2.11 Formaldehyde

Formaldehyde is a clear, water-white, very slightly acid gas or liquid with a pungent odor. It has a density of 1.0, and a flash point of (15% methanol-free) 122°F. Its molecular formula is CH_2O and it has a molecular weight of 30.03. It has a Hazard Rating of 3 (Sax and Lewis 1989). Formaldehyde has a vapor pressure of 10 mm at -88°C (Patty 1963, as cited in IRIS 1990). The TLV, on a TWA basis, is 1 ppm. The TLV, on a STEL basis, is 2 ppm (ACGIH 1988).

2.2.11.1 Summary

The weight-of-evidence classification for formaldehyde is "B1; probable human carcinogen," based on limited evidence in humans and sufficient evidence in animals.

Effects in women include menstrual disorders and secondary sterility (IARC 1972-1985, as cited in IRIS 1990). Solutions splashed in eyes have caused injuries ranging from severe, permanent congeal opacification and loss of vision to minor discomfort (Grand 1974, as cited in IRIS 1990).

Medical conditions generally are aggravated by exposure to formaldehyde. In people sensitized to formaldehyde, late asthmatic reactions may be provoked by brief exposures at approximately 3 ppm (Hendrick 1982, as cited in IRIS 1990).

In a study to analyze the relation of chronic respiratory symptoms and ventilatory function, levels of Peak Expiratory Flow Rates (PEFR) in children decreased linearly as formaldehyde concentration increased. In adults, only morning PEFR levels were related to formaldehyde exposure.

The inhalation slope factor is 4.5E-2/mg/kg/day. The inhalation unit risk is 1.3E-5/$\mu g/m^3$. The extrapolation method used was the linearized multistage procedure using additional risk.

The main signs and symptoms of exposure are irritation of the eyes, nose and throat; tearing; cough; bronchospasm; pulmonary irritation; and dermatitis (Proctor and Hughes 1978, as cited in IRIS 1990). Severe pain, vomiting and diarrhea result from ingestion. After absorption, formaldehyde depresses the central nervous system and symptoms similar to alcohol intoxication result. It can also cause a reduction in body temperature (Environment Canada 1982, as cited in IRIS 1990).

2.2.11.2 Health Effects

Noncarcinogenic Effects - A risk assessment for formaldehyde is under review by an EPA work group.

Effects in women include menstrual disorders and secondary sterility (IARC 1972-1985, as cited in IRIS 1990). Solutions splashed in eyes have caused injuries ranging from severe, permanent congeal opacification and loss of vision to minor discomfort (Grand 1974, as cited in IRIS 1990).

Medical conditions generally are aggravated by exposure to formaldehyde. In people sensitized to formaldehyde, late asthmatic reactions may be provoked by brief exposures at approximately 3 ppm (Hendrick 1982, as cited in IRIS 1990).

Eight symptomatic individuals chronically exposed to indoor formaldehyde at low concentrations (0.07-0.55 ppm) were compared to eight nonexposed

subjects with respect to 1) presence of IgG and IgE antibodies to formaldehyde conjugated to human serum albumin (F-HSA); 2) the percentage of venous bolls T- and B-cells by E- and EAC-resetting; and 3) the ability of T- and B-cells to undergo mitogen (phytohemogglutin and pokeweed) stimulated blastogenesis as measured by the incorporation of tritiated thymidine. Anti-F-HSA, IgG, but not IgE, antibodies were detected in the sera of the eight exposed subjects; none were found in seven of the controls. T-lymphocytes were decreased in the exposed (48%) compared to the control (65.9%) subjects (P,0.01). B-cells were 12.6% (exposed group) and 14.75% (controls) (P,0.05). The incorporation of labeled thymidine by T-cells (phytohemagglutin) was decreased: 17,882 cpm (exposed group) and 28.576 cpm (controls) (p,0.01). T- and B-cell blastogenesis (poleweed) was 9,698 cpm (exposed group) and 11,219 (controls) (p,0.1) (HSDB 1990).

In a study to analyze the relation of chronic respiratory symptoms and ventilatory function, levels of PEFR in children decreased linearly as formaldehyde concentration increased. In adults, only morning PEFR levels were related to formaldehyde exposure. In nonsmokers, this effect was linear and much smaller than that found in children, even with concentrations of 100 parts per billion (ppb), the decrement due to this exposure was barely 1% of the normal morning value. In smokers the relation was quadratic and the decrease in PEFR with formaldehyde was found only for concentrations over 40 ppb. Data indicate an increased prevalence of chronic respiratory disease, chronic bronchitis or asthma, in children 6-15 years of ages living in houses with formaldehyde concentrations between 60 and 140 ppb. No threshold level was found for concentrations affecting ventilatory function (Krzyzanowski, Quickenboss, and Lebowitz 1989).

Human Carcinogenicity - The weight-of-evidence classification for formaldehyde is "B1; probable human carcinogen," based on limited evidence in humans, and sufficient evidence in animals. Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. An increased incidence of nasal squamous cell carcinomas was

observed in long-term inhalation studies in rats and in mice. The classification is supported by in vitro genotoxicity data and structural relationships to other carcinogenic aldehydes such as acetaldehyde (IRIS 1990).

The human carcinogenicity data are limited. At least 28 epidemiologic studies have been carried out relevant to formaldehyde. Among these, two cohort (Blair et al. 1986, 1987; Stayner et al. 1988, as cited in IRIS 1990) and one case-control (Vaughn et al. 1986a,b, as cited in IRIS 1990) were well conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks. Blair et al. studied workers at ten plants in some way exposed to formaldehyde (largely through resin formation) and observed significant excesses in lung and nasopharyngeal cancer deaths. Despite a lack of significant trends with increasing intensity or cumulative formaldehyde exposure, lung cancer mortality was significantly elevated in analyses with or without a 20-year latency allowance. No explicit control was made for smoking status. Stayner et al. reported statistically significant excesses in mortality from buccal cavity tumors among formaldehyde-exposed garment workers. The highest mortality was for workers with long employment duration (exposure) and follow-up period (latency). The Vaughn et al. nasal and pharngeal cancer case-control study examined occupational and residential exposures, controlling for smoking and alcohol consumption in analysis. It showed a significant association between nasopharyngeal cancer and having lived 10 or more years in a mobile home. People for whom this association was drawn had lived in mobile homes built in the 1950s to 1970s, a period of increasing formaldehyde-resin usage, but no measurements were directly available or used (IRIS 1990).

The 25 other reviewed studies had limited ability to detect small to moderate increases in formaldehyde risks because of small sample sizes, small numbers of observed site-specific deaths, and insufficient follow-up. Even with these potential limitations, 6 of the 25 studies (Acheson et al. 1984; Hardell et al. 1982; Hayes et al. 1986; Liebling et al. 1984; Olsen et al. 1984; Stayner et al. 1985, all as cited in IRIS 1990) reported significant associations between excess site-specific respiratory (lung, buccal cavity and pharyngeal) cancers and exposure to formaldehyde. Some of these studies

looked at such potential confounders as wood-dust exposure in greater detail; their resolution could not discern sinonasal cancer incidence excesses of the size predicted. Others (Liebling et al. 1984; Stayner et al. 1985, as cited in IRIS 1990) overlapped the three first-mentioned studies, the improved design and nonoverlapping portions of the later studies (Blair et al. 1986; Stayner et al. 1988, as cited in IRIS 1990) reinforce the conclusions of the earlier studies. Analysis of the remaining 19 studies indicates a possibility that observed leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated. Although the common exposure in all of these studies was formaldehyde, the epidemiologic evidence is categorized as "limited" primarily because of possible exposures to other agents. Such exposures could have contributed to the findings of excess cancers (IRIS 1990).

Animal Carcinogenicity - The animal carcinogenicity data are considered sufficient. Consequences of inhalation exposure to formaldehyde have been studied in rats, mice, hamsters, and monkeys. The principal evidence comes from positive studies in both sexes of two strains of rats (Kerns et al. 1983; Albert et al. 1982; Tobe et al. 1985, all as cited in IRIS 1990) and males of one strain of mice (Kerns et al. 1983, as cited in IRIS 1990), all showing squamous cell carcinomas (IRIS 1990).

For Chemical Industry Institute of Toxicology (CIIT), Kerns et al. (1983), as cited in IRIS 1990, exposed about 120 animals per sex per species (Fischer 344 rats and B6C3F1 mice) to 0, 2, 5.6 or 14.3 ppm, 6 h/day, 5 day/wk for 24 months. Sacrifices of 5 per group were carried out at 6 and 12 months and 20 per group were killed at 18 months. At 24 and 27 months, the number sacrificed is unclear. The studies were terminated at 30 months. From the 12th month on, male and female rats in the highest dose groups showed mortality significantly increased over controls. In the 5.6 ppm group, male rats showed a significant increase from 17 months on. Female mice showed generally comparable survival across dose groups, as did male mice, but the male mice as a whole had survival decreased by housing-related problems. Squamous cell carcinomas were seen in the nasal cavities of 51 males and 52

females of the 117 male and 115 female rats at 14.3 ppm evaluated by experiments (as many as 35 had been identified in males by month 18 based on contemporaneous EPA analysis notes and Kerns Chart 8). Two rats (one male, one female) of 119 males and 116 females examined at 5.6 ppm showed squamous cell carcinomas of the nasal cavity. No such tumors were seen at 0 or 2 ppm. Polupoid adenomas of the nasal mucosa were seen in rats at all doses in a significant dose-related trend, albeit one that falls off after a peak. Among the mice, squamous cell carcinomas were seen in two males at 14.3 ppm. No other lesions were noteworthy.

Sellakumar et al. (1985), as cited in IRIS 1990, exposed male Sprague-Dawley rats, 100/group, 6 h/day, 5 day/wk for a lifetime, to a premix of 10 ppm HCL and 14 ppm formaldehyde, a combined exposure wherein HCl and formaldehyde were administered simultaneously but separately, 14 ppm formaldehyde alone, 10 ppm HCl alone, and an air control. An equal number of rats received no treatment. HCl was administered to determine whether tumor response was enhanced by an additional irritant effect or by the combining of formaldehyde and HCl to form bis-(chloromethyl)ether (BCME). Groups receiving formaldehyde alone or mixed with HCl were observed to have increased nasal squamous cell carcinomas; those without formaldehyde were free of carcinomas and other tumors (0/99 in each group), although rhinitis and hyperplasia were of comparable incidence (IRIS 1990).

A 28-month study of male Fischer 344 rats (begun about 2 weeks younger than those in Kerns et al. 1983; as cited in IRIS 1990) was carried out by Tobe et al. (1985), as cited in IRIS 1990. Groups of 32 rats were exposed 6 h/day, 5 day/wk to 15 ppm formaldehyde, 2, 0.3, or 3.3 ppm aqueous solution methanol (vehicle); an unexposed group of 32 was raised concurrently. Groups were compared to the methanol control and 12-, 18- and 24-month sacrifices were performed. Mortality was highest in the 15 ppm group, reaching 88% by month 24 when exposure to this group ceased. In the other groups, mortality by 28 months ranged from 60% (unexposed) to 32% (0.3 ppm). Squamous cell carcinomas were seen in 14/27 rats at 15 ppm surviving past 12 months and in no other rats (control incidence was 0/27). No polypoid adenomas were

observed. Rhinitis and hyperplasia, while most prevalent at 15 ppm, were seen at increasing incidence across doses (IRIS 1990).

While these three rodent studies are principal in the weight of evidence, inhalation studies have been carried out in other strains and species. Dalbey (1982), as cited in IRIS (1990), as part of a promotion experiment, exposed male Syrian golden hamsters to 10 ppm formaldehyde five times per week, 5 hours per day throughout their lifetimes, with 132 animals as untreated controls. While survival time was significantly reduced in the treated group, no tumors were observed in either group. Rusch et al. (1983), as cited in IRIS (1990), carried out a one-half year toxicity study in six male cynomolgus monkeys, 40 F344 (10 male and 10 female) rats and 20 Syrian golden hamsters (20 male and 20 female) with higher than 2.95 ppm, with corresponding controls. The short duration of the assay, the small sample sizes and, possibly, the concentrations tested, limited the sensitivity of the assay to discern tumors. In the highest dose group in both rats and monkeys, incidence of squamous metaplasia/hyperplasia of the nasal turbinates was significantly elevated (IRIS 1990).

Carcinogenicity Supporting Data - Mutagenic activity of formaldehyde has been demonstrated in viruses, Escherichia coli, Pseudomonas florescence, Salmonella typhimurium and certain strains of yeast, fungi, Drosophila, grasshopper and mammalian cells (Ulsamer et al. 1984, as cited in IRIS 1990). Formaldehyde has been shown to cause gene mutations, single strand breaks in DNA, DNA-protein crosslinks, sister chromatic exchanges and chromosomal aberrations. Formaldehyde produces in vitro transformation in BALB/c 3T3 mouse cells, BHK21 hamster cells and C3H-10T1/2 mouse cells, enhances the transformation of Syrian hamster embryo cells by SA7 adenovirus, and inhibits DNA repair (Consensus Workshop of formaldehyde 1984, as cited in IRIS 1990).

Quantitative Carcinogenic Risk - The inhalation slope factor is 4.5E-2/mg/kg/day. The inhalation unit risk is 1.3E-5/$\mu g/m^3$. The extrapolation method used was the linearized multistage procedure using additional risk. Table 2.8 shows air concentrations at specified risk levels (IRIS 1990).

TABLE 2.8. Formaldehyde Air Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	$8/\mu g/m^3$
E-5 (1 in 100,000)	$8E\text{-}1/\mu g/m^3$
E-6 (1 in 1,000,000)	$8E\text{-}2/\mu g/m^3$

Dose-Response Data - Inhalation dose-response data for carcinogenicity are provided in IRIS (1990). The test animal was the male F344 rat; scientists looked at squamous cell carcinoma. Table 2.9 shows the dose-response data (IRIS 1990).

Rats that died prior to appearance of the first squamous cell carcinoma at 11 months were not consider at risk. Those sacrificed at 12 and 18 months were treated as though they would have responded in the same proportion as rats remaining alive at the respective sacrifice times. Those living beyond 24 months were included with animals sacrificed at 24 months. From the estimates of the probability of death with tumor within 24 months and its variance, the number of animals at risk and the number with tumors were derived for a 24-month study with no 12- or 18-month kills. These rounded numbers are shown above and were used for significance tests and modeling. The unit risk should not be used if the air concentration exceeds 8E+2 $\mu g/m^3$, because above this concentration, the slope factor may differ from that stated (IRIS 1990).

The experimental range is close to expected human exposures. Estimated lifetime excess risks from six epidemiologic studies are close to upper bound risks based on animal data (usually within 1 order of magnitude for four types of estimated occupational and residential exposure). Animal-based estimates derived using time in the model were similar but would have required the use of more assumptions in calculation. Three non-zero doses were used in addition to controls in the study on which calculations are based, with a large number of animals per group. Male and female incidences were close throughout the exposure groups (IRIS 1990).

Toxicity Ranges - The probable oral lethal dose for humans is 0.5-5 g/kg, or between 1 ounce and 1 pint for a 150-lb person (Gosselin 1976,

TABLE 2.9. Formaldehyde Inhalation Exposure Dose-Response Data

Dose		
Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	Tumor Incidence
Male		
0	0	0/156
2	2	0/159
5.6	5.6	2/153
14.3	14.3	94/140

as cited in IRIS 1990). Below 1 ppm, the odor of formaldehyde is perceptible to most people. At 2-3 ppm, mild tingling of the eyes occurs. At 4-5 ppm, increased discomfort with mild lacrimation occurs. At 10 ppm, profuse lacrimation occurs and can be withstood only for a few minutes. At 10-20 ppm, breathing difficulties, cough, and severe burning of nose and throat occur. At 50-100 ppm, acute irritation of respiratory tract occurs and very serious injury are likely. There is a delayed sensitization dermatitis (Proctor and Hughes 1978, as cited in IRIS 1990).

Table 2.10 shows the acute health effects from a Cleveland health effects study (Nied and TerKonda 1983).

Symptoms - The main signs and symptoms of exposure are irritation of eyes, nose and throat, tearing, cough, bronchospasm, pulmonary irritation, dermatitis (Proctor and Hughes 1978, as cited in IRIS 1990). Severe pain, vomiting and diarrhea result from ingestion. After absorption, formaldehyde depresses the central nervous system and symptoms similar to alcohol intoxication. It can also cause a reduction in body temperature (Environment Canada 1982, as cited in IRIS 1990).

2.2.12 Methylethylketone

Methylethylketone is a colorless liquid with an acetone-like odor. It has a density of 0.80615 and a flash point of 22°F. Its molecular formula is C_4H_8O and its molecular weight is 72.12. Methylethylketone has a vapor

TABLE 2.10. Formaldehyde Concentrations from Cleveland Health Effects Study

Health Effects Reported	Average Formaldehyde Concentration (ppm)
No effects	0.02 - 0.26
Eye irritation	0.02 - 0.38
Nose and mucous membrane irritation	0.02 - 0.38
Neurophysiological effects	0.02 - 0.38
Upper airway irritation	0.03 - 0.38
Lower airway irritation	0.06 - 0.11
Dermatitis	0.04 - 0.14
Nausea and vomiting	0.03 - 0.13

pressure of 71.2 mm at 20°C (Sax and Lewis 1989). The TLV, on a TWA basis, for methylethylketone is 200 ppm. The TLV, on a STEL basis, is 300 ppm (ACGIH 1988). The most common synonym for methylethylketone is 2-butanone, with others such as MEK, ethylmethylketone, and methylacetone commonly used.

2.2.12.1 Summary

Methylethylketone is moderately toxic by ingestion, skin contact and intraperitoneal routes. Human systemic effects by inhalation include conjunctive irritation and unspecified effects on the nose and respiratory system. It is considered a strong irritant with human eye irritation at 350 ppm. Methylethylketone affects the peripheral nervous system and central nervous system. It has a Hazard Rating of 3 (Sax and Lewis 1989).

The RfDo is 5E-2mg/kg/day with a critical effect statement that no adverse effects were observed. The NOAEL listed for methylethylketone is 235 ppm, and the LOAEL listed is 130.5 mg/kg/day (IRIS 1990).

The weight-of-evidence classification for methylethylketone is "D; not classifiable as to human carcinogenicity." This classification is based on the fact that there are no human carcinogenicity data available and the animal data are considered inadequate (IRIS 1990).

2.2.12.2 Health Effects

General Toxicity Information - Methylethylketone is moderately toxic by ingestion, skin contact and intraperitoneal routes. Human systemic effects by inhalation include conjunctiva irritation and unspecified effects on the nose and respiratory system. Methylethylketone is an experimental teratogen. It has experimental reproductive effects. It is considered a strong irritant with human eye irritation at 350 ppm. Methylethylketone affects the peripheral nervous system and central nervous system (Sax and Lewis 1989).

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. An RfDo is available for methylethylketone. The RfDo is 5E-2mg/kg/day with a critical effect statement that no adverse effects were observed. The NOAEL listed for methylethylketone is 235 ppm, and the LOAEL listed is 130.5 mg/kg/day (IRIS 1990).

Adequate chronic toxicity testing has not been performed with methylethylketone. Although several more recent subchronic studies have been conducted (Freddi et al. 1982; Cavender et al. 1983; Takeuchi et al. 1983, all as cited in IRIS 1990), only the NOAEL of LaBelle and Brieger (1955), as cited in IRIS 1990, provides the lowest and most protective dose for deriving an RfD. In this study, 25 rats were exposed to 235 ppm of methylethylketone for 7 h/day, 5 day/wk for 12 weeks. No effects were observed, but only a few parameters were measured. Methylethylketone has also been tested for teratogencity (Schwetz et al. 1974; Deacon et al. 1981, as cited in IRIS 1990), and the observed LOAELs for fetotoxicity were higher than the NOAELs of LaBelle and Breiger (1955), as cited in IRIS 1990. The route extrapolation introduced uncertainty because of differences in pharmacokinetic parameters, notably absorption and elimination (IRIS 1990).

The study is given medium to low confidence because only 25 rats were exposed to only one dose, and the sex, strain, and amount of control animals

were low because four different studies lent some support to the chosen NOAEL. Confidence in the RfD can also be considered medium to low (IRIS 1990).

Human Carcinogenicity - The weight-of-evidence classification for methylethylketone is "D; not classifiable as to human carcinogenicity." This classification is based on the fact that there are no human carcinogenicity data available and the animal data are considered inadequate.

Animal Carcinogenicity - The animal carcinogenicity data are considered inadequate. No data were available to assess the carcinogenic potential of methylethylketone by the oral or inhalation routes. In a skin carcinogenesis study, two groups of 10 male C3H/He mice received dermal applications of 50 mg of a solution containing 25 or 29% methylethylketone in 70% dodecylbenzene twice a week for 1 year. No skin tumors developed in the group of mice treated with 25% methylethylketone. After 27 weeks, a single skin tumor developed in 1 of 10 mice receiving 29% methylethylketone (Horton et al. 1965, as cited in IRIS 1990).

Carcinogenicity Supporting Data - methylethylketone was not mutagenic for Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 with or without rat hepatic homogenates (Florin et al. 1980; Douglas et al. 1980; as cited in IRIS 1990). Methylethylketone induced aneuploidy in the diploid D61, M strain of Saccharomyces cerevisiae (Zimmermann et al. 1985; as cited in IRIS 1990). Low levels of methylethylketone combined with low levels of nocodazile (another inducer of aneuploidy) also produced significantly elevated levels of aneuploidy in the system (Mayer and Goin 1987, as cited in IRIS 1990).

Quantitative Estimate of Carcinogenic Risk - No carcinogenic risk estimates are available for either the inhalation or oral routes of exposure.

2.2.13 Octane

Octane is a clear liquid with a density of 0.7036 and a flash point of 56°F. Its molecular formula is C_8H_{18}, its molecular weight 114.26. Octane has a vapor pressure of 10mm at 19.2°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, for octane is 300 ppm. The TLV, on a STEL basis, is 375 ppm (ACGIH 1988).

2.2.13.1 Summary

The amount of toxicological information available for octane is very limited. No specific studies involving human toxicology of octane were found.

Direct aspiration into the lungs of paraffins with carbon numbers C_6 to C_{16} may cause chemical pneumonitis, pulmonary edema, and hemorrhaging (HSDB 1990).

Octane is rated moderately toxic. It has a probable oral lethal dose for humans of 0.5 to 5 g/kg [i.e., between 1 oz. and 1 pint (or 1 pound) for a 70 kg (150 lb.) person] (HSDB 1990).

Rabbits with acute intoxication by inhaling carbon monoxide alone or in association with octane at concentrations of 5,000 ppm were compared by the Physiogram Method. Hydrocarbons aggravated the cardiovascular phenomena caused by carbon monoxide, and although they are central excitants, they further degraded electroencephalogram (EEG) activity (HSDB 1990).

2.2.13.2 Health Effects

The amount of toxicological information available for octane is very limited. No specific studies involving human toxicology of octane were found.

General Toxicological Effects - Octane is rated moderately toxic. It has a probable oral lethal dose for humans of 0.5 to 5 g/kg [i.e., between 1 oz. and 1 pint (or 1 pound) for a 70 kg (150 lb.) person] (HSDB 1990).

There may be epileptiform seizures months after an acute episode of octane. Pathological examination of tissues from fatal cases of octane exposure gives evidence for widespread microhemorragic phenomena. Irritation of the upper and lower respiratory tract and visceral damage have also been described (HSDB 1990).

Direct aspiration into the lungs of paraffins with carbon numbers C_6 to C_{16} may cause chemical pneumonitis, pulmonary edema, and hemorrhaging (HSDB 1990).

Mice exposed at concentrations of 6,600 to 13,700 ppm octane demonstrated central nervous system depression within 30 to 90 minutes and respiratory arrest at 16,000 (1 of 4) to 32,000 ppm (4 of 4) in 5 to 3 minutes,

respectively (isooctane). The authors stated that the central nervous system depressant concentration was 10,000 ppm, which put the concentration at 8,000 ppm and the fatal concentration at 13,500 ppm. From these data on acute toxic response, it can reasonably be inferred that octane is from 1.2 to 2 times more toxic than haptene (HSDB 1990).

Orally, octane may be more toxic than its lower homologous. If the material is aspirated into the lungs, it may cause rapid death from cardiac arrest, respiratory paralysis, and asphyxia. The potency of Octane is approximately that of haptene, but does not appear to exhibit the central nervous system effect as to the two lower homologous (HSDB 1990).

The minimal concentration that causes loss of righting reflexes in mice was 35 mg/L, and total loss of reflexes occurred at 50 mg/L. A concentration of 95% causes loss of reflexes in mice in 125 minutes; however, a concentration of up to 1.9% appears to be tolerated for 143 minutes, with reversible effects (HSDB 1990).

Some effects of acute exposure to octane vapors on schedule-controlled responding in mice were detected. Cumulative concentration-effect curves were determined by comparing responding before and during exposure. The concentrations were incrementally increased at 40-minute intervals until responding completely ceased. Octane did not generally decrease responding until concentrations of approximately 1,000 ppm were obtained. Responding progressively decreased with increasing concentrations of up to 7,000 ppm (HSDB 1990).

Toxicant Interactions - Rabbits with acute intoxication by inhaling carbon monoxide alone or in association with octane at concentrations of 5,000 ppm were compared using the Physiogram Method. Hydrocarbons aggravated the cardiovascular phenomena caused by carbon monoxide, and although they are central excitants, they further degraded EEG activity (HSDB 1990).

2.2.14 α-Pinene

α-Pinene is a liquid with an odor of turpentine. It has a density of 0.8592 and a flash point of 91°F. Its molecular formula is $C_{10}H_{16}$ and its molecular weight is 136.26. α-Pinene has a vapor pressure of 10 mm at 37.3°C. It has a Hazard Rating of 3 (Sax and Lewis 1989).

2.2.14.1 Summary

The amount of toxicological information available for α-pinene is very limited. No specific studies involving human toxicology of α-pinene were found.

α-Pinene, in significant quantities, is considered a deadly poison by inhalation and moderately toxic by ingestion (Sax and Lewis 1989). It is also considered an eye, mucous membrane, and severe skin irritant. It has an oral rat LD50 of 3700 mg/kg. Its inhalation LCLo concentrations for rats, mice, and guinea pigs are 625 $\mu g/m^3$, 364 $\mu g/m^3$, and 572 $\mu g/m^3$ respectively (Sax and Lewis 1989).

2.2.14.2 Health Effects

The amount of toxicological information available for α-pinene is very limited. No specific studies involving human toxicology of α-pinene were found.

General Toxicity Information - α-Pinene, in significant quantities, is considered a deadly poison by inhalation and moderately toxic by ingestion (Sax and Lewis 1989). It is also considered an eye, mucous membrane, and severe skin irritant. It has an oral rat LD50 of 3700 mg/kg. Its inhalation LCLo concentrations for rats, mice, and guinea pigs are 625 $\mu g/m^3$, 364 $\mu g/m^3$, and 572 $\mu g/m^3$, respectively (Sax and Lewis 1989).

α-Pinene irritates the skin and mucous membranes. It can cause skin eruption, gastrointestinal (GI) tract irritation, delirium, ataxia, kidney damage and coma. Inhalation can cause palpitation, dizziness, nervous disturbances, chest pain, bronchitic, nephritis. α-Pinene can be absorbed through the skin, lungs, and intestine. It can also cause benign skin tumors from chronic contact (HSDB 1990).

α-Pinene has essentially the same toxicity as turpentine. As little as 15 ml (1/2 oz.) has proved fatal to a child, but a few children have survived 2 and even 3 ounces. The mean lethal dose in an adult probably lies between 4 and 6 ounces (HSDB 1990).

Toxicity Ranges - In an adult a dose of 140 ml may be fatal. A dose of 15 ml was fatal in a 2-year-old child; however, benzene was present in the mixture. Children have ingested 2 to 3 ounces and survived (HSDB 1990).

Symptoms and General Effects - The following symptomatology is associated with α-pinene: 1) burning pain in the mouth and throat, abdominal pain, nausea, vomiting and occasionally diarrhea; 2) mild respiratory tract symptoms (e.g., coughing, choking, dyspnea and even cyanosis) and pulmonary edema and pneumonitis from aspiration or systemic absorption; 3) transient excitement, ataxia, delirium and finally stupor, which is the commonest severe symptom; occasionally occurring convulsions, usually not until several hours after ingestion, when they may interrupt a deep coma; 4) occasionally occurring painful urination, albuminuria, and hematuria; urine may have an odor resembling violets; renal lesions are usually transient, 5) an odor of turpentine on breath and in vomitus; 6) fever and tachycardia; and 7) death from respiratory failure (HSDB 1990).

2.2.15 Propylbenzene

Propylbenzene (isocumene) is a clear liquid that is insoluble in water, but miscible in alcohol and ether. It has a density of 0.862 and a flash point of 86°F. Its molecular formula is C_9H_{12} and its molecular weight is 120.21. It has a vapor pressure of 10 mm at 43.4°C. Its most common synonym is isocumene, with 1-phenylpropane and n-propylbenzene also common synonyms. It has a Hazard Rating of 3 (Sax and Lewis 1989).

2.2.15.1 Summary

The amount of toxicological information available for propylbenzene (isocumene) is very limited. No specific studies involving human toxicology of propylbenzene were found.

Propylbenzene is considered mildly toxic by ingestion and inhalation (Sax and Lewis 1989). The rat oral LD50 is 6040 mg/kg. The mouse inhalation LCLo is 20 g/m^3 (RTECS 1987).

2.2.15.2 Health Effects

The amount of toxicological information available for propylbenzene (Isocumene) is very limited. No specific studies involving human toxicology of propylbenzene were found.

General Toxicity Information - Propylbenzene is considered mildly toxic by ingestion and inhalation (Sax and Lewis 1989). The rat oral LD50 is 6040 mg/kg. The mouse inhalation LCLo is 20 g/m^3 (RTECS 1987).

RTECS indicates that the toxic effects of propylbenzene have not yet been reviewed.

2.2.16 Radon/Radon Daughters

Radon is a colorless, odorless, inert gas that is very dense. It has a density, as a gas at 1 atmosphere 0 degrees, of 9.73 g/L, and, as a liquid at boiling point, of 4.4. It has a Hazard Rating of 3 (Sax and Lewis 1989). Radon is a decay product of uranium and it, in turn, decays to form radioactive progeny that may attach to dust particles or remain unattached. If these progeny are inhaled, they can be drawn into the lungs, where they emit alpha energy and may cause lung cancer.

2.2.16.1 Summary

The EPA has withdrawn its carcinogen assessment for radon and its daughters in IRIS pending further review. A new carcinogen summary is in preparation by the CRAVE Work Group (IRIS 1990). Thus, information presented for radon/radon-daughters is subject to change as a result of the new carcinogen summary by EPA.

The major health effects in the experimental studies that simulate exposures in the uranium mine environment are pulmonary emphysema, pulmonary fibrosis (pneumoconiosis), lung cancer, and lifespan shortening. In general, pulmonary fibrosis, emphysema, and lifespan shortening are not produced to any significant extent until radon-daughter exposures exceed about 5,000 working level months (WLM). However, lung cancer is produced in these studies using rats exposed to radon at levels down to 20 WLM, which are typical, average,

human, lifetime, environmental exposure levels. Respiratory carcinoma, therefore, is the most prominent health effect associated with radon-daughter exposures (DOE 1987).

Risk-projection models have been developed to estimate lifetime lung-cancer risk for radon exposure in underground miners and for environmental exposures. The range of lifetime risk coefficients for most models lies between 1 and 5 lung cancers per 10,000 persons exposed per WLM. A plausible range for environmental exposures at the 10- to 20-WLM lifetime exposure level is from 0 (if a threshold exists) to about 5 per 10,000 per WLM (if all environmental lung cancer in nonsmokers is radon-daughter related). When calculating an incremental risk from increased environmental exposure, the age at exposure should be considered. A person aged 60, if exposed to an elevated radon-daughter level for the remainder of life (an average of 24 years), will have a lower risk than an individual aged 30 exposed similarly for 24 years because of the potential for more years of risk expression. The National Council on Radiation Protection and Measurements (NCRP) has developed tables that allow age at exposure to be taken into account (NCRP 1984a, as cited in DOE 1987). In general, except for persons over age 60, the lifetime risk appears to be between 1 and 2 per 10,000 per WLM. Although this is a small risk, the large number of persons exposed in the United States yields a significant number of lung cancers (DOE 1987).

The lifetime risk coefficient data developed by the NCRP for environmental exposures of radon are 9.1E-3/WLM/year and 3.6E-3/pCi radon/L for exposure from infancy to death. The equivalent values for exposures of populations having an age distribution equal to that in the United States in 1975 are 5.6E-3 and 2.1E-3, respectively. The values for populations are somewhat smaller because the number of years at risk following radon exposure is reduced compared to exposures starting at infancy (DOE 1987).

The International Commission on Radiological Protection (ICRP) draft report on environmental exposures (ICRP 1985, as cited in DOE 1987) recommends a lifetime individual-risk coefficient of E-2/WLM/year. This is in very good agreement with the 9.1E-3/WLM/year recommended by the NCRP (NCRP 1984a, as cited in DOE 1987).

The data are not yet fully consistent nor developed, but most indicate that tobacco smoke in conjunction with radon exposure acts mainly as a cancer promoter. The U.S. uranium-miner data indicate that smokers have a shorter induction-latent period and a higher incidence of lung cancer than nonsmokers.

2.2.16.2 Health Effects

General Toxicological Information - In animals exposed to radon daughters, lesions observed in organs other than the lung are considered spontaneous or only indirectly related to exposure. These observations are paralleled in the human exposures where effects in organs other than the lung are either not prominent or cannot unequivocally be associated with radon-daughter exposures alone (i.e., in the absence of associated pollutants typically found in the mine environment, such as ore dust, silica, diesel exhaust, and cigarette smoke). The major health effects in the experimental studies that simulate exposures in the mine environment are pulmonary emphysema, pulmonary fibrosis (pneumoconiosis), lung cancer, and lifespan shortening. In general, pulmonary fibrosis, emphysema, and lifespan shortening are not produced to any significant extent until radon-daughter exposures exceed about 5,000 WLM. However, lung cancer is produced in these studies using rats exposed to radon down to levels of 20 WLM, which are typical average human lifetime environmental exposure levels. Respiratory carcinoma, therefore, is the most prominent health effect associated with radon-daughter exposures (DOE 1987).

Human Carcinogenicity - The EPA has withdrawn its carcinogen assessment for radon and its daughters in IRIS following further review. A new carcinogen summary is in preparation by the CRAVE Work Group (IRIS 1990).

In most of the large epidemiological studies conducted to date, miners with cumulative radon-daughter exposures somewhat below about 100 WLM indicate excess lung cancer mortality. There are four major studies where a dose response can be inferred (Lundin et al. 1971; National Academy of Sciences 1980; Muller et al. 1983, 1985; Sevc et al. 1976; Radford and Renard 1984, all as cited in DOE 1987). These studies (followed since 1950) include 3,362 U.S. underground uranium miners whose exposures range from 60 to 7000 WLM (average, 800); 15,984 Canadian uranium miners with upper-estimate exposures ranging

from 5 to 510 WLM (average, 74); 2,400 Czechoslovakian miners followed since 1948 with an exposure range from 72 to 716 WLM (average, 200); and 1,415 Swedish iron miners born between 1880 and 1919 who were alive in 1930 and exposed from 27 to 218 WLM (average, 80). To date, from 3% to 8% of the miners in the studies have developed lung cancer, mostly bronchogenic, attributable to radon-daughter exposures (i.e., above that expected from smoking or other causes alone) (DOE 1987).

The cell type of bronchogenic carcinoma does not clearly define the lung cancer etiology. Small-cell or oat-cell carcinoma is the earliest to appear, but all forms are increased by radon-daughter exposure. In underground miners with the longest latent intervals, epidermoid carcinoma appeared dominant. The tumor cell type has been shown to vary with many parameters, including smoking quantity, age at first underground exposure, and latent interval. The percentage of small-cell carcinoma decreased, and the percentage of epidermoid carcinoma increased with latent interval (Saccomanno et al. 1982, as cited in DOE 1987). In view of the numerous cell types involved, documenting tumor etiology by type seems unlikely (DOE 1987).

Quantitative Estimates of Carcinogen Risk - Respiratory-cancer risk projection has generally followed either an absolute or a relative risk model (NAS 1980; Thomas and McNeill 1982; Whittemore and McMillan 1983; NCRP 1984a; ICRP 1985, all as cited in DOE 1987). Lung cancer rarely appears before age 40, regardless of age at exposure, and never before a minimum latent interval following exposure from 5 to 10 years. Most absolute models are modified to include these basic features and an average annual rate of appearance. In a relative risk model, lifetime risk from radon-daughter exposure is directly proportional to the natural occurrence of lung cancer. Nonsmokers have approximately one-tenth the lung-cancer rate of smokers, and nonsmoking women have a lower rate than nonsmoking men. Thus, radon-daughter-related lung cancer could ultimately be dependent on sex, lifespan (which leads to overall higher lifetime lung-cancer risk), and smoking history (DOE 1987).

Not enough is known concerning the prediction accuracy of the various projection models when applied to specific mining groups. It is also possible that neither absolute nor relative risk models will generally describe the

miners' risk. The various mining cohorts under study will not go to closure for about 20 more years; until then, the time course of lung-cancer development in humans for radon-daughter exposures will not be accurately known.

Underground miner data strictly allow the estimation of risk coefficients for radon-daughter exposures for adult males in the mine environment. These data can be extrapolated to population exposures on the assumptions that 1) lung cancer is proportional to lung dose, and 2) the influence of associated pollutant exposures in the mine environment is negligible or is not significantly different from the influence of associated pollutant exposures in indoor air. The uncertainties in this extrapolation include uncertainties in the following areas: 1) exposure levels of miners, 2) risk-projection, 3) radon-daughter dose to extrapolate adult-male data to populations (other age groups, females, etc.), and 4) influence of co-pollutant exposures. However, despite the uncertainties and assumptions, no better database exists for inferring population risks. The animal data support the concept of linearity with dose and the existence of elevated risk down to human-lifetime, background-exposure levels (DOE 1987).

Risk-projection models have been developed to estimate lifetime lung-cancer risk for exposure in underground miners and for environmental exposures. The range of lifetime risk coefficients for most models lies between 1 and 5 lung cancers per 10,000 persons exposed per WLM. A plausible range for environmental exposures at the 10- to 20-WLM lifetime exposure level is from 0 (if a threshold exists) to about 5 per 10,000 per WLM (if all environmental lung cancer in nonsmokers is radon-daughter related). When calculating an incremental risk from increased environmental exposure, the age at exposure should be considered. A person aged 60, if exposed to an elevated radon-daughter level for the remainder of life (an average of 24 years), will have a lower risk than an individual aged 30 exposed similarly for 24 years because of the potential for more years of risk expression. The NCRP has developed tables that allow age at exposure to be taken into account (NCRP 1984a, as cited in DOE 1987). In general, except for persons over age 60, the lifetime risk appears to be between 1 and 2 per 10,000 per WLM. Although this

is a small risk, the large number of persons exposed in the United States yields a significant number of lung cancers (DOE 1987).

The lifetime risk coefficient data developed by the NCRP for environmental exposures are 9.1E-3/WLM/year and 3.6E-3/pCi radon/L for exposure from infancy to death. The equivalent values for exposures of populations having an age distribution equal to that in the United States in 1975 are 5.6E-3 and 2.1E-3, respectively. The values for populations are somewhat smaller because the number of years at risk following radon exposure are reduced compared to exposures starting at infancy (DOE 1987).

The ICRP draft report on environmental exposures (ICRP 1985, as cited in DOE 1987) recommends a lifetime individual-risk coefficient of E-2/WLM/year. This is in very good agreement with the 9.1E-3/WLM/year recommended by the NCRP (NCRP 1984a, as cited in DOE 1987).

Toxicant Interactions - The data are not yet fully consistent nor developed, but most indicate that tobacco smoke in conjunction with radon exposure acts mainly as a cancer promoter. The U.S. uranium-miner data indicate that smokers have a shorter induction-latent period and a higher incidence of lung cancer than nonsmokers. However, follow-up is relatively short in comparison to other mining groups, so the ultimate relationship is yet to be developed. Data from Swedish base-metal miners is quite different. These miners also show a shorter induction-latent period if they smoke; however, one study found a greater incidence of lung cancer among nonsmokers than smokers, and other studies found their incidence to be approximately equal (Axleson and Sundell 1978; Radford and Renard 1984, as cited in DOE 1987).

The main difference in the U.S. and Swedish studies is in the length of follow-up and, thus, the portion of lifespan over which data on deaths are collected. It is possible to resolve, at least partially, these various data by postulating that radiation exposures induced approximately the same finite numbers of cancers in both smokers and nonsmokers. Because these appear earlier in smokers, one sees a larger excess in nonsmokers if one looks particularly late in the development, and perhaps an approximately equal number of lung cancers when follow-up is over the lifespan of the two groups. Less

certainty exists about the relationship among smoking, radon-daughter exposures and lung cancer at low environmental radon-daughter exposure levels (DOE 1987).

The animal lung carcinoma data are also inconsistent but partially explained by the temporal sequence of exposures. Smoke alternated the same day with radon daughters can be "protective;" cumulative radon-daughter exposures preceding smoke exposure produces synergism, while radon daughters following the cumulative exposure to smoke produces no net effect over radon daughters alone. The animal data, in general, support the concept that smoke acts mainly as a promoter. Under some circumstances, it may promote more mucus production and, therefore, shield sensitive cells from the radon-daughter alpha radiation (DOE 1987).

2.2.17 Styrene

Styrene is a colorless, refractive, oily liquid. It has a density of 0.9074 and a flash point of 88°F. Its molecular formula is C_8H_8 and its molecular weight is 104.16. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, is 50 ppm. The TLV, on a STEL basis, is 100 ppm (ACGIH 1988). Some of the common synonyms for styrene are vinylbenzene, cinnamene, cinnamenal, cinnamol, ethenylbenzene, phenylethylene, phenethylene, phyenylethylene, and styrene Monomer.

2.2.17.1 Summary

Styrene is irritating to eyes, the respiratory and gastrointestinal tracts, and skin. Central nervous system depression may occur. Peripheral neuropathies have been reported. "Styrene sickness" is common. Changes in psychoneurological functioning have been described with chronic exposure. Styrene is questionably mutagenic and teratogenic (HSDB 1990).

The RfDo for styrene is 2E-1 mg/kg/day, with the critical effect on red blood cells and the liver. The NOAEL is 200 mg/kg/day and the LOAEL is 400 mg/kg/day (IRIS 1990).

Styrene is among those substances evaluated by the EPA for evidence of human carcinogenic potential. This does not imply that this chemical is

necessarily a carcinogen. The evaluation for styrene is under review by an inter-office Agency work group (IRIS 1990).

An elevated incidence of hematopoietic and lymphatic cancer has been reported for workers in the styrene-butadiene rubber industry (HSDB 1990).

Styrene in concentrations of 100 ppm in air causes mild irritation of the eyes and throat in 20 minutes, but seems acceptable for working conditions. At 375 ppm, not all people feel significant eye irritations in 15 minutes, but all have nasal irritation. Concentrations of 400 and 500 ppm cause irritation of eyes and nose, but can be tolerated (HSDB 1990).

Styrene air concentrations of 10,000 ppm are dangerous to life within 20 to 30 minutes. Concentrations of 2,500 ppm are dangerous to life within 8 hours. Exposure to Styrene vapors above 800 ppm is immediately irritating. Eye damage can occur. High concentrations can have a toxic and anesthetic effect (1 hour at 1,000 ppm is severely toxic). One hour at 5,000 ppm produces unconsciousness; 10,000 ppm for 30 minutes has caused death. Repeated and prolonged contact of the liquid with the skin can cause defatting and dermatitis (HSDB 1990)

2.2.17.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for styrene is 2E-1 mg/kg/day, with the critical effect on red blood cells and the liver. The NOAEL is 200 mg/kg/day and the LOAEL is 400 mg/kg/day (IRIS 1990).

Four beagle dogs per sex were gavaged with doses of 0, 200, 400, or 600 mg styrene/kg bw/day in peanut oil for 560 days. No adverse effects were observed for dogs administered styrene at 200 mg/kg/day. Effects in the higher dose groups were increased numbers of Heinz bodies in the red blood cells, decreased packed cell volume and sporadic decreases in hemoglobin and red blood cell counts, and increased iron deposits and elevated numbers of

Heinz bodies in the livers. Marked individual variations in blood cell parameters were noted for animals at the same dose level. Other parameters examined were body weight, organ weights, urinalyses, and clinical chemistry (IRIS 1990).

Long-term studies (120 weeks) in rats and mice (Ponomarkow and Tomatis 1978, as cited in IRIS 1990) showed liver, kidney, and stomach lesions for rats (dosed weekly with styrene at 500 mg/kg) and no significant effects for mice (dosed weekly with 300 mg/kg). Rats receiving an average daily oral dose of 95 mg of styrene/kw bw for 185 days showed no adverse effect, while those receiving 285 or 475 mg/kg/day showed reduced growth and increased liver and kidney weights (Wolf et al. 1956, as cited in IRIS 1990). Other subchronic rat feeding studies found LOAELs in the 350-500 mg/kg/day range and NOAELs in the range of 100-400 mg/kg/day (IRIS 1990).

The lifetime studies in rats and mice (Ponomarkov and Tomatis 1978, as cited in IRIS 1990) are not appropriate for risk assessment of chronic toxicity because of the dosing schedule employed. The Wolf et al. study (1956), as cited in IRIS (1990), is of insufficient duration to be considered chronic (IRIS 1990).

The confidence in the RfDo is medium. The principal study is well done and the effect levels seem reasonable, but the small number of animals per sex prevents a higher confidence at this time. The database offers strong support, but lacks a bona fide fullterm chronic study; thus, it is also considered to have a medium confidence. Thus, the medium confidence in the RfDo follows. The risk assessment for the RfDi is under review by an EPA work group (IRIS 1990).

Styrene is irritating to the eyes, the respiratory and GI tracts, and skin. Central nervous system depression may occur. Peripheral neuropathies have been reported. "Styrene sickness" is common. Changes in psychoneurological functioning have been described with chronic exposure. Styrene is questionably mutagenic and teratogenic (HSDB 1990).

Workers in a factory producing polystyrene resins, where concentrations reached 200 ppm, revealed itching dermatitis in one case and erythematous papular dermatitis of forearms in two other cases (HSDB 1990).

Ten men aged 20-41 years old, who were occupationally exposed to styrene, showed increases in the rate of chromosomal aberrations in cultured lymphocytes for peripheral blood (11-26% compared with 3% or less among 5 non-exposed controls). Decondensation of chromatic and increased numbers of micronuclei and nuclear bridges were also observed (HSDB 1990).

In a case where 449 workers exposed to styrene were examined, prenarcotic symptoms, such as light-headedness, eye irritation and irritation of mucous membranes were significantly more frequent in a "high" exposure group than in a "low" exposure group. A distal hypesthesia of the legs occurred in 8.5% of the cases. The conduction velocities of both radial and peroneal nerves were less than normal in 18.8% and 16.4% of the workers, respectively. There was consistent decrement in peroneal nerve conduction velocity as the exposure to styrene continued, but no such relationship was observed for radial nerve conduction velocities (HSDB 1990).

Effects on the liver (e.g., increased serum bile acid and enhanced activity of plasma enzymes) and reproductive system (e.g., decreased frequency of births and increased frequency of spontaneous abortions in female workers) have been reported (HSDB 1990).

The main pathological findings of exposure to styrene are edema of the brain and lungs, epithelial necrosis of the renal tubules and hepatic dystrophy (HSDB 1990).

Human Carcinogenicity - Styrene is among those substances evaluated by the EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for styrene is under review by an inter-office Agency work group (IRIS 1990).

An elevated incidence of hematopoietic and lymphatic cancer has been reported for workers in the styrene-butadiene rubber industry. The researcher examined the 10-year mortality history of 6,678 male rubber workers. The age-related mortality rate due to lymphatic and hematopoietic cancer was reported

to be 4.4 times higher for workers with 2 years of experience and 5.6 times higher for workers with 5 years of experience compared to the general study population. For lymphatic leukemia, the age-adjusted mortality rate in synthetics plant workers was 2.9 times higher for workers with 2 years of experience and 3.7 times higher for workers with 5 years of experience, compared to the general study population (HSDB 1990).

Toxicity Ranges - Styrene in concentrations of 100 ppm in air causes mild irritation of the eyes and throat in 20 minutes, but seems acceptable for working conditions. At 375 ppm, not all people feel significant eye irritations in 15 minutes, but all have nasal irritation. Concentrations of 400 and 500 ppm cause irritation of eyes and nose, but can be tolerated (HSDB 1990).

Styrene air concentrations of 10,000 ppm are dangerous to life within 20 to 30 minutes. Concentrations of 2,500 ppm are dangerous to life within 8 hours. Exposure to styrene vapors above 800 ppm is immediately irritating. Eye damage can occur. High concentrations can have a toxic and anesthetic effect (1 hour at 1,000 ppm is severely toxic). One hour at 5,000 ppm produces unconsciousness; 10,000 ppm for 30 minutes has caused death. Repeated and prolonged contact of the liquid with the skin can cause defatting and dermatitis (HSDB 1990).

Symptoms and General Effects - "Styrene sickness" is not uncommon in industry after exposure to vapors or mists. Characteristic signs and symptoms include headache, fatigue, weakness, depression, and unsteadiness or feeling of drunkenness, and an abnormal EEG (HSDB 1990).

An acute ingestion or inhalation of styrene can have the following symptoms: 1) ingestion causes a burning sensation in the mouth and stomach, and causes nausea, vomiting and salivation; hematemesis may occur; 2) substernal pain, cough and hoarseness are described; 3) aspiration into the tracheobronchial tree, either during ingestion or subsequent to vomiting or eructation, is likely to produce a severe hemorrhagic pneumonitis; 4) in vapor exposures, a transient euphoria is sometimes observed; 5) headache, giddiness, vertigo, ataxia and tinnitus occur; 6) confusion, stupefaction and coma occur; 7) often associated with this coma are tremors, motor restlessness, hypertonus and hyperactive reflexes; 8) death occurs from respiratory failure or from

sudden ventricular fibrillation; 9) skin contact with liquid may cause erythema and even blisters if the contact is prolonged. Hemorrhagic inflammatory lesions develop on mucous membranes in contact with liquid (HSDB 1990).

A chronic or repeated inhalation of styrene can have the following symptoms. Severe muscle weakness leads to limb paralysis, associated with hypokalemia from renal tubular acidosis. Cardiac arrhythmias often accompany the hypokalemia. Sensory function and tendon reflexes are not impaired. Gastrointestinal complaints, including abdominal pain, nausea, vomiting and hematemesis, occur but there are no significant abdominal tenderness or palpable abdominal masses (HSDB 1990).

2.2.18 Tetrachloroethylene

Tetrachloroethylene is a colorless liquid with a chloroform-like odor. It has a density of 1.6311 and no registered flash point. Its molecular formula is C_2Cl_4 and its molecular weight is 165.82. Tetrachloroethylene has a vapor pressure of 15.8 mm at 22°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, is 50 ppm. The TLV, on a STEL basis, is 200 ppm (ACGIH 1988). The most common synonym is perchloroethylene, with carbonbichloride, carbordichloride, PCE, PER, PERC, perchlor, PERK, 1,1,2,2-tetrachloroethylene, and tetrachloroethane the common synonyms.

2.2.18.1 Summary

Tetrachloroethylene is toxic by ingestion, inhalation, or dermal exposure. Vasodilation and malaise ("degreasers' flush") occur in workers who drink ethanol after exposure to trichloroethylene. Inhalation abuse of typewriter correction fluid has been reported (HSDB 1990).

The RfDo for terachloroethylene is 1E-2 mg/kg/day, with the critical effect on hepatotoxicity in mice, weight gain. The NOAEL is 20 mg/kg/day and the LOAEL is 100 mg/kg/day (IRIS 1990).

Excessive exposure to tetrachloroethylene has resulted in effects on the central nervous system, mucous membranes, eyes and skin, and to a lesser extent, to the lungs, liver, and kidneys. The effects most frequently noted have been on the nervous system. Unconsciousness, dizziness, headache,

vertigo or light central nervous system depression have occurred in many instances after occupational exposures (HSDB 1990).

Several studies of the effects of prolonged exposure to perchloroethylene vapors on human volunteers are available. Prolonged exposure to 200 ppm results in early signs of central nervous system depression, while there was no response in men or women reportedly exposed to 100 ppm for 7 h/day. Clinical studies indicate no liver or kidney effects at these levels, but massive exposure to concentrations causing unconsciousness have resulted in proteinuria and hematuria (HSDB 1990).

2.2.18.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for terachloroethylene is 1E-2 mg/kg/day, with the critical effect on hepatotoxicity in mice, weight gain. The NOAEL is 20 mg/kg/day and the LOAEL is 100 mg/kg/day (IRIS 1990).

Buben and O'Flaherty (1985), as cited in IRIS (1990), exposed Swiss-Cox mice to tetrachloroethylene in corn oil by gavage at doses of 0, 20, 100, 200, 500, 1500, and 2000 mg/kg at 5 day/wk for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight/body weight, hepatic triglyceride concentration, DNA content, histopathological evaluation, and serum enzyme levels. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly higher than controls for animals treated with 100 mg/kg. At higher doses, hepatotoxic effects included decreased DNA content, increased SGPT, decreased levels of glucose-6-phosphate (G6P) and hepatocellular necrosis, degeneration and polyploidy (IRIS 1990).

A NOEL of 14 mg/kg/day was established in a second study as well (Hayes et al. 1986; as cited in IRIS 1990). Groups of 20 Sprague-Dawley rats of both sexes were administered doses of 14, 400, or 1400 mg/kg/day in drinking water.

Males in the high-dose group and females in the two highest groups exhibited depressed body weights. Equivocal evidence of hepatotoxicity (increased liver and kidney weight/body weight ratios) were also observed at higher doses (IRIS 1990).

Other data support the findings of the principal studies. Exposure of mice and rats to tetrachloroethylene by gavage for 11 days caused hepatotoxicity (centrilobular swelling) at doses as low as 100 mg/kg/day in mice (Schaum et al. 1980, as cited in IRIS 1990). Mice were more sensitive to the effects of tetrachloroethylene exposure than were rats. Increased liver weight was observed in mice at 250 mg/kg, but rats did not exhibit these effects until doses of 1000 mg/kg/day were reached. Relative sensitivity to humans cannot be readily established, but the RfD of 1E-2 mg/kg/day is protective of the most mild effects observed in humans [diminished odor perception/modified Romberg test scores in volunteers exposed to 100 ppm for 7 hours; roughly equivalent to 20 mg/kg/day (Stewart et al. 1961, as cited in IRIS 1990)].

The principal studies are of short duration. Inhalation studies have been performed that indicate that the uncertainty factor of 10 is sufficient for extrapolation of the subchronic effect to its chronic equivalent. Liver enlargement and vacuolation of hepatocyte were found to be reversible lesions for mice exposed to low concentrations of tetrachloroethylene (Kjellstrand et al. 1984, as cited in IRIS 1990). In addition, elevated liver weight/body weight ratios observed in animals exposed to tetrachloroethylene for 30 days were similar to those in animals exposed for 120 days. Several chronic inhalation studies have also been performed (Carpenter 1937; NTP 1985; Rowe et al. 1952, as cited in IRIS 1990). None are inconsistent with a NOAEL of 14 mg/kg/day for tetrachloroethylene observed by Buben and O'Flaherty (1985) and Hayes et al. (1986), both as cited in IRIS (1990).

The confidence in the RfDo is medium. No one study combines the features desired for deriving an RfD: oral exposure, larger number of animals, multiple dose groups, testing in both sexes and chronic exposure. Confidence in the principal studies is low mainly because of the lack of complete histopathological examination at the NOAEL in the mouse study. The database is

relatively complete but lacks studies of reproductive and teratology endpoints subsequent to oral exposure; thus, it receives a medium confidence rating, with the medium confidence rating for the RfDo following (IRIS 1990).

An RfDi is not available at this time.

Excessive exposure to tetrachloroethylene has resulted in effects on the central nervous system, mucous membranes, eyes and skin, and to a lesser extent, to the lungs, liver, and kidneys. The effects most frequently noted have been on the nervous system. Unconsciousness, dizziness, headache, vertigo or light central nervous system depression have occurred in many instances after occupational exposures (HSDB 1990).

Several studies of the effects of prolonged exposure to tetrachloroethylene vapors on human volunteers are available. Prolonged exposure to 200 ppm results in early signs of central nervous system depression, but there was no response in men or women reportedly exposed to 100 ppm for 7 h/day. Clinical studies indicate no liver or kidney effects at these levels, but massive exposure to concentrations causing unconsciousness have resulted in proteinuria and hematuria (HSDB 1990).

A 6-wk-old breast-fed infant had obstructive jaundice and hepatomegaly. Tetrachloroethylene was detected in the milk and blood. After discontinuance of breast-feeding, rapid clinical and biochemical improvement were noted (HSDB 1990).

After ingestion of 12-16 g of tetrachloroethylene, a 6-yr-old boy was admitted to the clinic in coma. In view of the high initial tetrachloroethylene blood level, hyperventilation therapy was performed. Under this therapeutic regimen, the clinical condition of the patient improved considerably. The tetrachloroethylene blood level profile that was determined under hyperventilation therapy could be computer-fitted to a two-compartment model. Elimination of tetrachloroethylene from the blood compartment occurred via a rapid and a slow process with half-lives of 30 minutes and 35 hours, respectively. These values compared favorably with the half-lives of 160 minutes and 33 hours under normal respiratory conditions. During hyperventilation therapy, the relative contribution to the fast elimination process increased

from 70% for physiological minute volume to 99.9%. A minor fraction of the ingested dose was excreted with the urine (integral of 1% during the first 3 days). In contrast to previous results, trace amounts of unchanged tetrachloroethylene were detected in the urine in addition to Trichloracetic acid and trichloroethanol (HSDB 1990).

Alterations in liver function in persons exposed to unknown concentrations of tetrachloroethylene over extended (chronic) periods have been reported by a number of investigators (Coler and Rossmiller 1953; Franke and Eggeling 1969; Hughes 1954; Trense and Zimmerman 1969; Meckler and Phelps 1966; Larsen et al. 1977; Moeschlin 1965; Dumortier et al. 1964, all as cited in EPA 1985). Liver function parameters that have been altered as a result of excessive tetrachloroethylene exposure include sulfobromophthalein retention time, thymol turbidity, serum bilirubin, serum protein patterns, cephalin-cholesterol flocculation, serum alkaline phosphatase, SGOT, and serum lactic acid dehydrogenase (LDH). However, these parameters may result from other causes that are completely dissociated with tetrachloroethylene (EPA 1985).

Absorption - Studies have shown that absorption of tetrachloroethylene through the skin, from vapor exposure or from partial body immersion, is minimal in comparison to oral and inhalation routes of exposure. Tetrachloroethylene is rapidly and completely absorbed into the body from the GI tract, presumably because of its high lipid solubility. tetrachloroethylene in vapor form in air is readily absorbed through the lungs into blood by first-order diffusion processes. Pulmonary uptake of a volatile compound like tetrachloroethylene during inhalation exposure is largely determined by the ventilation rate (about 4 to 8 L/min for humans at rest), duration of exposure at a given air concentration, solubility in blood and other body tissues, and its metabolism. When body tissue concentrations (body burden) are at steady-state with inspired air concentration, the rate of uptake is equal to the rate of metabolism plus nonpulmonary excretion of tetrachloroethylene. Because there are no known significant routes of excretion of tetrachloroethylene except pulmonary and metabolism, the steady-state uptake rate approximates the metabolism rate (EPA 1985).

Human Carcinogenicity - Tetrachloroethylene is among the chemicals evaluated by the EPA for evidence of human carcinogenic potential. This does not imply that it is necessarily a carcinogen. The evaluation for tetrachloroethylene is under review by an inter-office Agency work group. A risk assessment summary will be included in IRIS when the review is completed (IRIS 1990).

Toxicity Ranges - The estimated dose in humans to cause death is reported to be 3 to 5 ml/kg. An oral toxic dose for Tetrachloroethylene has not been established. The TLV for both is 50 ppm (HSDB 1990).

Toxicant Interactions - Stewart et al. (1977), as cited in EPA (1985), conjectured that repeated tetrachloroethylene exposure effects might be exacerbated by simultaneous administration of either alcohol or Diazepam. While both alcohol and Diazepam produced decrements in the various objective tests, the effects were no worse when these substances were combined with tetrachloroethylene exposure. It would appear that repeated 100 ppm tetrachloroethylene exposure is not close to the threshold for objective test effects (EPA 1985).

2.2.19 Toluene

Toluene is a colorless liquid with a benzol-like odor. It has a density of 0,866 and a flash point of 40°F. Its molecular formula is C_7H_8 and its molecular weight is 92.15. Toluene has a vapor pressure of 36.7 mm at 30°C (Sax and Lewis 1989). The TLV, on a TWA basis, is 100 ppm. The TLV, on a STEL basis, is 150 ppm (ACGIH 1988). Common synonyms for toluene are methylbenzene, methacide, methylbonzol, phenylmethane, and toluol.

2.2.19.1 Summary

The RfDo for toluene is 3E-1 mg/kg/day, with the critical effect on clinical chemistry and hematological parameters. It should be noted that the RfDo for toluene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Workgroup of EPA. The NOAEL for toluene is 300 ppm. There is no LOAEL listed for toluene. (IRIS 1990).

The weight-of-evidence classification is "D; not classified." The basis for this classification is no human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays (IRIS 1990).

2.2.19.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for toluene is 3E-1 mg/kg/day, with the critical effect on clinical chemistry and hematological parameters. It should be noted that the RfDo for toluene may change in the near future pending the outcome of a further review being conducted by the Oral RfD Workgroup of EPA. The NOAEL for toluene is 300 ppm. There is no LOAEL listed for toluene. (IRIS 1990).

Toluene is most likely a potential source of respiratory hazard. The only chronic toxicity study on toluene was conducted for 24 months in male and female F344 rats (CIIT 1980, as cited in IRIS 1990). Toluene was administered by inhalation at 30, 100, or 300 ppm to 120 male and 120 female F344 rats for 6 h/day, 5 day/wk. The same number of animals (120 males and 120 females) was used as a control. Clinical chemistry, hematology and urinalysis testing was conducted at 18 and 24 months. All parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene. Based on these findings, a NOAEL of 300 ppm was derived. An oral RfD of 20 mg/day can be derived using route-to-route extrapolation. This was done by expanding the exposure from 6 h/day, 5 day/wk to continuous exposure and multiplying by 20 m^3/day and 0.5 to reflect a 50% absorption factor (IRIS 1990).

Subchronic inhalation and subchronic oral studies in both mice and rats support the chosen NOAEL (NTP 1981, 1982, as cited in IRIS 1990). Furthermore, an oral study (Wolf et al. 1956, as cited in IRIS 1990) contains

subchronic data in which no adverse effects of toluene were reported at the highest dose tested (590 mg/kd/day).

The confidence in the RfDo is medium. Confidence in the principal study is high because a large number of animals per sex were tested in each of three dose groups and many parameters were studied. Interim kills were performed. The database is rated medium because several studies support the chosen effect level. The confidence of the RfDo is no higher than medium because the critical study was by the inhalation route (IRIS 1990).

Human Carcinogenicity - The weight-of-evidence classification is "D; not classified." The basis for this classification is no human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays (IRIS 1990).

Animal Carcinogenicity - A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT 1980, as cited in IRIS 1990). A total of 960 rats were exposed by inhalation for 6 h/day, 5 day/wk to toluene at 0, 30, 100, or 300 ppm. Groups of 20981/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals (IRIS 1990).

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenic response (Poel 1963, as cited in IRIS 1990). One drop of toluene (about 6 ml) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al. 1973, as cited in IRIS 1990). No increase in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 ml/mouse, twice weekly for 56 weeks (Doak et al. 1976,

as cited in IRIS 1990). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16-20 μL per drop for 72 weeks (Lijinsky and Garcia 1972, as cited in IRIS 1990). It is not reported whether evaporation of toluene from the skin was prevented during these studies (IRIS 1990).

Carcinogenicity Supporting Data - Toluene was found to be nonmutagenic in reverse mutation assays with S. typhimurium (Mortelmans and Riccio 1980; Nestmann et al. 1980; Bos et al. 1981; Litton Bionetics, Inc. 1981; Snow et al. 1981, as cited in IRIS 1990) and E. coli (Mortelmans and Riccio 1980, as cited in IRIS 1990), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc. 1981; Mortelmans and Riccio 1980, as cited in IRIS 1990) or mitotic crossing over (Mortelmans and Riccio 1980, as cited in IRIS 1990) in S. cerevisiae. Although Litton Bionetics, Inc. (1981), as cited in IRIS (1990), reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhtov 1972; Lyapkalo 1973, as cited in IRIS 1990) report toluene was effective in causing chromosal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations of blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al. 1980; Forni et al. 1971, as cited in IRIS 1990), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al. 1971; Funes-Craviota et al. 1977, as cited in IRIS 1990). This is supported by studies of cultured human lymphocytes exposed to toluene in vitro. No elevation of chromosomal aberrations or sister chromatic exchanges was observed (Gerner-Smidt and Friedrich 1978, as cited in IRIS 1990).

Quantitative Estimate of Carcinogen Risk - No estimate of the carcinogenic risk of toluene is available.

2.2.20 1,1,1-Trichloroethane

1,1,1-trichloroethane is a colorless liquid with a density of 1.3376 and no listed flash point. Its molecular formula is $C_2H_3Cl_3$ and its molecular weight is 133.40. 1,1,1-trichloroethane has a vapor pressure of 100 mm at 20.0°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA

basis, is 350 ppm. The TLV, on a STEL basis, is 450 ppm (ACGIH 1988). The most common synonym for 1,1,1-trichloroethane is methylchloroform, with aerothene TT, chlorothene, inhibisol, methyltrichloromethane, strobane, alpha-T, 1,1,1-TCE, and alpha-trichloroethane other common synonyms.

2.2.20.1 Summary

1,1,1-trichloroethane is one of the least toxic of the chlorinated hydrocarbons used as a solvent. Trichloroethane is a central nervous system and respiratory depressant and a skin and mucous membrane irritant (HSDB 1990).

The RfDo for 1,1,1-trichloroethane is 9E-2 mg/kg/day, with no critical adverse effects listed. The NOAEL is 500 ppm (air), and the LOAEL is 650 ppm (air) (IRIS 1990).

Men exposed to 900 to 1000 ppm of 1,1,1-trichloroethane experienced transient mild irritation and minimal impairment of coordination. Above 1700 ppm, this magnitude may induce headache and lassitude. Prolonged or repeated contact with skin results in transient erythema and slight irritation from the defatting action of the solvent. Some cases have also been observed in which repeated skin contact will cause a serious dermatitis characterized by skin cracking and infection from the defatting action of the solvent (HSDB 1990).

Four groups of workers (total number = 196) exposed for at least 5 years to average concentrations of 4, 25, 28 and 53 ppm methylchloroform were evaluated for adverse effects. Routine laboratory examinations, including peripheral hemograms, blood specific gravity and urinalysis, plus the sense-of-vibration test, were used. No consistent dose-related adverse effects were observed (HSDB 1990).

The estimated dose-response relationship for acute effects of single, short-term exposures, for concentrations above 5000 ppm, is the onset of central nervous system depression. Concentrations above 7,500 ppm, are possibly life threatening. A concentration of 2650-1900 ppm produces light-headedness and irritation of the throat. A concentration of 1000 ppm produces disturbance of equilibrium. Concentrations of 500 to 350 ppm produce slight

changes in perception and obvious odor. A concentration of 100 ppm is the apparent odor threshold. It should be noted that these approximations are crude estimates and contain several areas of uncertainty (HSDB 1990).

2.2.20.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for 1,1,1-trichloroethane is 9E-2 mg/kg/day, with no critical adverse effects listed. The NOAEL is 500 ppm (air) and the LOAEL is 650 ppm (air) (IRIS 1990).

Torkelson et al. (1958), as cited in (IRIS) 1990, exposed groups of rats, rabbits, guinea pigs and monkeys to 1,1,1-trichloroethane vapor at concentrations of 500, 1000, 2000, or 10,000 ppm. From these studies, it was determined that the female guinea pig was the most sensitive of the animals tested. At 500 ppm, groups of eight male and eight female guinea pigs showed no evidence of adverse effects compared with unexposed and air-exposed controls after exposure for 7 h/day, 5 day/wk for 6 months. Groups of five female guinea pigs exposed to 1,000 ppm 1,1,1-trichloroethane vapor 3 h/day, 5 day/wk for 3 months had fatty changes in the liver and statistically significant increased liver weights. Thus, this study defined a NOAEL of 500 ppm in guinea pigs (IRIS 1990).

Adams et al. (1950), as cited in IRIS (1990), subjected groups of 6-10 male and female guinea pigs to 650 ppm 1,1,1-trichloroethane vapor 7 h/day, 5 day/wk for 2 to 3 months. These animals exhibited a slight depression in weight gain compared with both air-exposed and unexposed controls, thereby establishing a LOAEL of 650 ppm in guinea pigs (IRIS 1990).

The 1,1,1-trichloroethane samples used by Torkelson et al. (1958), as cited in IRIS (1990), were found to be 94-97% pure while the samples used by Adams et al. (1950), as cited in IRIS (1990), had a purity of greater than or equal to 99% (IRIS 1990).

In addition, the effects of 1,1,1-trichloroethane vapor have been investigated in mice (Quast et al. 1984; McNutt et al. 1975, as cited in IRIS 1990), rats (Quast et al. 1978, as cited in IRIS 1990), and rabbits and dogs (Pendergast et al. 1967, as cited in IRIS 1990). The only chronic oral exposure study was conducted by NCI (1977), as cited in IRIS (1990), in rats. The observations from these studies and from Torkelson et al. (1958), as cited in IRIS (1990), and Adams et al. (1950), as cited in IRIS (1990), are somewhat inconsistent, thus making it difficult to draw conclusions about the dose levels of 1,1,1-trichloroethane that result in adverse effects. For example, inhalation exposure to 650 ppm by Adams et al. (1950), as cited in IRIS (1990), was associated with slight growth retardation in guinea pigs. Further review of this study indicates that 1500 ppm exposure also caused slight growth retardation without causing any organ-specific adverse effects following 1 to 3 months exposure. These observations are in contrast with those of Torkelson et al. (1958), as cited in IRIS (1990), who observed adverse effects in the liver and lungs of guinea pigs exposed to 1,000 ppm for 90 days (IRIS 1990).

When published, the results and technical evaluation of recent inhalation studies in mice (Quast et al. 1984, as cited in IRIS 1990) and rats conducted by Dow Chemical may be of greater value for the overall RfD consideration for 1,1,1-trichloroethane (IRIS 1990).

The confidence in the RfDo is medium. Although studies by Adams et al. (1950), as cited in IRIS (1990), and Torkelson et al. (1958), as cited in IRIS (1990), used both sexes of several species, the number of animals at each dose level was limited, the length of exposure varied with different dose levels and few toxic endpoints were examined. Confidence in these studies is thus considered low. The database is fairly comprehensive; however, results from these studies are somewhat inconsistent and some of the more recent studies have yet to be critically evaluated. Confidence in the database is, therefore, rated medium. Confidence in the RfDo can be considered medium to low (IRIS 1990).

Men exposed to 900 to 1000 ppm of 1,1,1-trichloroethane experienced transient mild irritation and minimal impairment of coordination. Above

1700 ppm, this magnitude may induce headaches and lassitude. Prolonged or repeated contact with skin results in transient erythema and slight irritation from the defatting action of the solvent. Some cases have also been observed in which repeated skin contact causes serious dermatitis characterized by skin cracking and infection from the defatting action of the solvent (HSDB 1990).

The effect of the solvent methylchloroform on psychophysiological functions, such as reaction time, perceptual speed and manual dexterity, was studied in 12 healthy male subjects. Each subject was tested during exposure to 250 ppm, 350 ppm, 450 ppm and 550 ppm of methylchloroform in inspiratory air and under control conditions with exposure to pure air. A linear relationship was noted between the concentration in alveolar air and arterial blood. Subject reaction time, perceptual speed and manual dexterity were all impaired during exposure. Analyses on the results strongly suggest that psychophysiological functions in humans are unfavorably affected by an exposure to an average concentration of 359 ppm (HSDB 1990).

Four groups of workers (total number = 196) exposed for at least 5 years to average concentrations of 4, 25, 28 and 53 ppm methylchloroform were evaluated for adverse effects. Routine laboratory examinations, including peripheral hemograms, blood-specific gravity and urinalysis, plus sense-of-vibration test were used. No consistent dose-related adverse effects were observed (HSDB 1990).

To determine whether unchanged solvent urinary concentration could be used as a biological exposure index, workers occupationally exposed to various solvents were studied. Nine unrelated groups working in plastic boat, chemical, plastic button, paint, and shoe factories were studied. A total 659 males were monitored. Urine samples were collected at the beginning of the workshift and at the end of the first half of the shift. A close relationship (correlation coefficient always above 0.85) between the average environmental solvent concentration measured in the breathing zone and the urinary concentration of unchanged solvent was observed. The proposed Biological Equivalent Exposure Limit (805 μg/L) corresponded to the environmental Threshold Limit Value (860 μg/L) for 1,1,1-trichloroethane. Biological

exposure data for urine collected over 4 hours during random sampling for at least 1 year could be used to evaluate long-term exposure for individuals or groups of workers (HSDB 1990).

Human Carcinogenicity - The weight-of-evidence classification for 1,1,1-trichloroethane is "D; not classifiable as to human carcinogenicity." The basis for this classification is there are no reported human data and animal studies (one lifetime gavage, one intermediate-term inhalation) that have not demonstrated carcinogenicity. Technical-grade 1,1,1-trichloroethane has been shown to be weakly mutagenic, although the contaminant, 1,4-dioxane, a known animal carcinogen, may be responsible for this response (IRIS 1990).

Animal Carcinogenicity - The animal carcinogenicity data are considered inadequate. The NCI (1977), as cited in IRIS 1990, treated 50 male and 50 female Osborne-Mendal rats with 750 or 15000 mg/kg technical-grade 1,1,1-trichloroethane 5 times/wk for 78 weeks by gavage. The rats were observed for an additional 32 weeks. Twenty rats of each sex served as untreated controls. Low survival of both male and female treated rats (3%) may have precluded significant development of tumors late in life. Although a variety of neoplasms was observed in both treated and matched control rats, they were common to aged rats and were not significantly related to dosage. Similar results were obtained when the NCI (1977), as cited in IRIS 1990, treated B6C3F1 hybrid mice with the time-weighted average doses of 2807 or 5615 mg/kg 1,1,1,-trichloroethane by gavage 5 day/wk for 78 weeks. The mice were observed for an additional 12 weeks. The control and treated groups had 20 and 50 animals of each sex, respectively. Only 25% to 45% of those treated survived until the time of terminal sacrifice. A variety of neoplasms were observed in treated groups but with an incidence not statistically different from matched controls (IRIS 1990).

Quest et al. (1978), as cited in IRIS 1990, exposed 96 Sprauge-Oawley rats of both sexes to 875 or 1750 ppm 1,1,1-trichloroethane vapor for 6 h/day, 5 day/wk for 12 months, followed by an additional 19-month observation period. The only significant sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage. It was not evident that a MTD was used nor was a range-finding study conducted. No

significant dose-related neoplasms were reported, but these dose levels were below those used in the NCI study (IRIS 1990).

Carcinogenicity Supporting Data - Mutagenicity testing of 1,1,1-trichloroethane has produced positive results in S. typhimurium strain TA100 (Simmon et al. 1977; Fishbein 1979; Snow et al. 1979, all as cited in IRIS 1990) as well as some negative results (Henschler et al. 1977; Taylor 1978, as cited in IRIS 1990).

It was mutagenic for S. typhimurium strain TA1535 both with exogenous metabolic activation (Farber 1977, as cited in IRIS 1990) and without activation (Nestmann et al. 1980, as cited in IRIS 1990). 1,1,1-trichloroethane did not result in gene conversion or mitotic recombination in Saccharomyces cerevisiae (Farber 1977; Simmon et al. 1977, as cited in IRIS 1990) nor was it positive in a host-mediated forward mutation assay using Schizosaccharomyces pombe in mice. The chemical also failed to produce chromosomal aberrations in the bone marrow of cats (Rampy et al. 1977, as cited in IRIS 1990), but responded positively in a cell transformation test with rat embryo cells (Price et al. 1978, as cited in IRIS 1990).

An isomer, 1,1,2-trichloroethane, is carcinogenic in mice, inducing liver cancer and pheochromocytomas in both sexes. Dichloroethanes, tetrachloroethane and hexachloroethane also produced liver cancer in mice and other types of neoplasms in rats. It should be noted that 1,4-dioxane, a known animal carcinogen, is a contaminant of technical-grade 1,1,1-trichloroethane. It causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice (IRIS 1990).

Quantitative Estimate of Carcinogenic Risk - No quantitative estimate of carcinogenic risk for either oral or inhalation exposure exists.

Toxicity Ranges - The acute lethal dose to the human has been established at 500 to 5,000 mg/kg. The 1,1,1-trichloroethane has a TLV in air of 350 ppm as compared to the 10 ppm TLV of 1,1,2-trichloroethane (HSDB 1990).

From the available data, it can be estimated that a single exposure to concentrations of methylchloroform of less than 5,000 ppm is probably not

life-threatening to humans, though higher concentrations may produce central nervous system depression and possibly death (HSDB 1990).

A summary of the estimated dose-response relationships for acute effects of single short-term exposures is greater than 5000 ppm, which is the onset of central nervous system depression, and could be life threatening. A concentration of 2650-1900 ppm produces light-headedness and irritation of the throat. A concentration of 1000 ppm produces disturbance of equilibrium. Concentrations of 500 to 350 ppm produce slight changes in perception and obvious odor. A concentration of 100 ppm is the apparent odor threshold. It should be noted that these approximations are crude estimates and contain several areas of uncertainty (HSDB 1990).

2.2.21 Trichloroethylene

Trichloroethylene (TCE) is a mobile liquid with a characteristic odor of Chloroform. It has a density of 1.4649 and a flash point of 89.6°F. Its molecular formula is C_2HCl_3 and its molecular weight is 131.38. Trichloroethylene has a vapor pressure of 100 mm at 32°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, is 50 ppm. The TLV, on a STEL basis, is 200 ppm (ACGIH 1988). Some of the common synonyms for Trichloroethylene are acetylenetrichloride, benzinol, 1-chloro-2,2,-dichloroethylene, circosolv, 1,1-dichloro-2-chloroethylene, ethyinyltrichloride, ethylenetrichloride, lanadin, narcogen, TCE, TRI, triasol, trichlorethene, trichloroethene, 1,1,2-trichloroethylene, 1,2,2-trichloroethylene, tri-clene, triol, vitran, and westrosol.

2.2.21.1 Summary

Past health assessment information on TCE is under review by EPA. The past carcinogen assessment summary by EPA has been withdrawn and a new one is under development by the EPA CRAVE Work Group (IRIS 1990). A risk assessment for TCE is underreview by an EPA work group (IRIS 1990). Thus, past assessment information may be considerably modified in the future.

Trichloroethylene is a probable human carcinogen (EPA Group B2) and, according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant (4.1 cancer cases per year and maximum

lifetime individual risks of 9.4E-5). Thus, EPA indicated that it will consider adding TCE to the list of hazardous air pollutants for which it will establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add TCE to the list only after studying possible techniques that might be used to control emissions and further assessing the public health risks. The EPA will add TCE to the list if emissions standards are warranted (IRIS 1990).

Exposures to TCE vapors causes irritation of the mucous membranes with resultant conjunctivitis and rhinitis. Skin contact produces severe erythema and vesiculation followed by exfoliation. Ingestion causes a burning sensation in the mouth, nausea, vomiting and abdominal pain. Chronic exposure, as in solvent abusers, can produce weight loss, nausea, fatigue, visual impairment, dermatitis, and rarely jaundice (HSDB 1990).

Workers exposed at concentrations averaging about 10 ppm complained of headache, dizziness and sleepiness (HSDB 1990).

Prolonged occupational exposure to TCE has been associated with impairment of peripheral nervous system function, persistent neuritis and temporary loss of tactile sense, and paralysis of the fingers after direct contact with the solvent (HSDB 1990).

The Nuclear Regulatory Commission (NRC) in their Drinking Water and Health Volume 5 1983 report, as cited in HSDB (1990), estimated a human lifetime carcinogenic risk of 3.77E-7 for males and 6.84E-8 for females, assuming a daily consumption of 1 L of water containing trichloroethylene in a concentration of 1 μg/L.

2.2.21.2 Health Effects

Past health assessment information on TCE is under review by EPA. The past carcinogen assessment summary of EPA has been withdrawn and a new one is currently under development. Thus, a potential exists for considerable modification to past assessment information. The EPA published the Health Assessment Document for Trichloroethylene. Final Report in July 1985, EPA/600/8-82/006F (EPA 1985); and a Draft Addendum to the report, SAB-EHC-88-012, in March 1988 (EPA 1988). However, these reports were not used in this

health effects assessment report, but are cited here for reference purposes. These EPA documents were not used because EPA is currently redoing their health assessment of trichloroethylene and will likely make considerable change to some of the positions reflected in these documents.

Noncarcinogenic Effects - A risk assessment for TCE is under review by an EPA work group (IRIS 1990).

Exposures to its vapors causes irritation of the mucous membranes with resultant conjunctivitis and rhinitis. Skin contact produces severe erythema and vesiculation followed by exfoliation. Ingestion causes a burning sensation in the mouth, nausea, vomiting and abdominal pain. Chronic exposure, as in solvent abusers, can produce weight loss, nausea, fatigue, visual impairment, dermatitis, and rarely jaundice (HSDB 1990).

Workers exposed at concentrations averaging about 10 ppm complained of headache, dizziness and sleepiness (HSDB 1990).

Prolonged occupational exposure to trichloroethylene has been associated with impairment of peripheral nervous system function, persistent neuritis and temporary loss of tactile sensem, and paralysis of the fingers after direct contact with the solvent (HSDB 1990).

Following chronic and acute overexposure of trichloroethylene during operation of a dry-cleaning unit, symptoms included symmetrical bilateral V)IIth cranial nerve deafness as well as cerebral cortical dysrhythmia and alterations in the electroencephalogram (EEG). The patient recovered after the exposure stopped (HSDB 1990).

The behavioral effects of exposure to TCE indicate that laboratory and work-place exposure to 540 or 1030 mg/m^3 for 70 minutes has no effect on reaction time or short-term memory (HSDB 1990).

Evoked trigeminal potentials were studies in 104 subjects occupationally exposed to TCE. Subjects had an average exposure time of 8.23 years and an average daily exposure of 7 hours (exposure levels were not given). Controls were 52 healthy nonexposed subjects. Symptoms suffered by 49 of the exposed subjects included dizziness, headache, asthenia, insomnia, mood perturbation, and sexual problems. Eighteen subjects had trigeminal nerve symptoms. These

subjects were significantly older (P,0.001) than asymptomatic subjects. Forty subjects had a pathological trigeminal somatosensory evoked potential (TSEP). Of these, 28 had a normal trigeminal examination and 12 an abnormal one. For those with trigeminal symptoms, an abnormal TSEP was observed in subjects who had the longest and most intense exposure periods (HSDB 1990).

Human Carcinogenicity - The carcinogen assessment summary for TCE has been withdrawn following further review. A new carcinogen summary is in preparation by the EPA CRAVE Work Group (IRIS 1990).

Trichloroethylene is a probable human carcinogen (EPA Group B2) and, according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant (4.1 cancer cases per year and maximum lifetime individual risks of 9.4E-5). Thus, EPA indicated that it will consider adding TCE to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add TCE to the list only after studying possible techniques that might be used to control emissions and further assessing the public health risks. The EPA will add TCE to the list if emissions standards are warranted (IRIS 1990).

An epidemiology study on the hepatic tumor incidence in subjects working with TCE failed to show a correlation between liver cancer and occupational exposure. Another study, which looked at the mortality of 2117 workers exposed to TCE, found no correlation between cancer and occupational exposure (HSDB 1990).

Major consideration must be given to cumulative effects of trichloroethylene in long-term feeding studies carried out by the National Cancer Institute. Mice (both sexes, at both low and high dose levels) experienced a highly significant increase in hepatocellular carcinomas. Mikiskova and mikiska (1966), as cited in HSDB (1990), demonstrated that TCE had a pronounced depressant effect on the central nervous system (HSDB 1990).

The Carcinogen Assessment Group (CAG), Office of Health and Environmental Assessment in EPA's Research and Development Office, has prepared a list of chemical substances for which substantial or strong evidence exists showing

that exposure to these chemicals, under certain conditions, causes cancer in humans, or can cause cancer in animal species that makes them potentially carcinogenic in humans. Substances are placed on the CAG list only if they have been demonstrated to 1) induce malignant tumors in one or more animal species, or 2) induce benign tumors that are generally recognized as early stages of malignancies, and/or positive epidemiologic studies indicated they were carcinogenic. Trichloroethylene is on the CAG list (HSDB 1990).

Quantitative Estimate of Carcinogen Risk - The NRC in their Drinking Water and Health Volume 5 1983 report, as cited in HSDB (1990), estimated human lifetime carcinogenic risk of 3.77E-7 for males and 6.84E-8 for females, assuming a daily consumption of 1 L of water containing TCE in a concentration of 1 μg/L.

Toxicity Ranges - The estimated dose in humans to cause death is reported to be 3 to 5 ml/kg. Eye irritation is reported at 160 ppm. The lowest concentration producing unconsciousness in adult humans is 16 mg/L; the equivalent oral dose is 40-150 ml (HSDB 1990)

Toxicant Interactions - Vasodilation and malaise ("degreasers' flush") occurs in workers who drink ethanol after exposure to Trichloroethylene (HSDB 1990).

2.2.22 1,2,4-Trimethylbenzene

1,2,4-trimethylbenzene is a liquid with a density of 0.888 and a flash point of 130°F. Its molecular formula is C_9H_{12} and its molecular weight is 120.21 (Sax and Lewis 1989). The TLV, on a TWA basis, is 25 ppm (ACGIH 1988). Some common synonyms are psi-cumene, pseudocumene, pseudocumol, 1,2,5-trimethylbenzene, and trimethylbenzene.

2.2.22.1 Summary

Trimethylbenzene is irritating to skin, eyes, and mucous membranes. It can cause central nervous system depression and thrombocytopenia. Asthmatic bronchitis may be provoked by exposure to trimethylbenzene. Chemical pneumonitis or pulmonary edema may develop, as well as headache, fatigue, nausea, and anxiety may be noted with exposures to trimethylbenzene.

Pertinent data regarding carcinogenicity of trimethylbenzenes to humans from oral or inhalation exposure could not be located by EPA in the available literature. Thus, trimethylbenzenes are best classified in EPA "Group D; Not classified" (EPA 1987).

There are no adequate subchronic or chronic inhalation or oral data that define dose-specific adverse effects. Therefore, no RfDs are available for trimethylbenzene.

The rat inhalation LC50 is 18 g/m^3/4 hours. The guinea pig intraperitoneal LDLo is 1788 mg/kg; the rat intraperitoneal LDLo is 1752 mg/kg (RTECS 1987).

2.2.22.2 Health Effects

Noncarcinogenic Toxicity - Bernshtein (1972), as cited in EPA (1987), reported that phagocytic activity of leukocytes was inhibited in rats after inhalation of a mixture of trimethylbenzenes (1 mg/L, 1000 mg/m^3) 4 h/day, 6 day/wk for 6 months (EPA 1987).

Wiglusz et al. (1975a,b), as cited in EPA (1987), reported "slight" alteration in differential white blood cell count and elevated SGOT in male rats that had been exposed to 1,3,5-trimethylbenzene (3 mg/L, 3000 mg/m^3) 6 h/day, 6 day/wk for 5 weeks (EPA 1987).

Battig et al. (1957), as cited in EPA 1987, reported symptoms of nervousness, tension, anxiety and asthmatic bronchitis in a "significant number" of 27 people who worked for several years with a solvent containing 30% 1,3,5-Trimethylbenzene and 50% 1,2,4-trimethylbenzene. Tendencies toward hyperchromic anemia and blood coagulation were also observed among these individuals. Concentrations ranges for hydrocarbon vapor ranged from 10-60 ppm. Gerarde (1960), as cited in EPA (1987), speculated that a small proportion of benzene in the hydrocarbon vapor was probably responsible for the hematologic effects (EPA 1987).

In cases where paint thinner was used that contained more than 60% of mesitylene and pseudocumene, there were symptoms of disturbance of blood coagulation and a tendency to hematoma formation with low levels of

thrombocytes and erythrocytes. Bronchitis, headache, fatigue and drowsiness was experienced by 70% of workers exposed to high concentrations (HSDB 1990).

Human Carcinogenicity - Pertinent data regarding carcinogenicity of trimethylbenzenes to humans from oral or inhalation exposure could not be located by EPA in the available literature. Thus, trimethylbenzenes are best classified in EPA "Group D; Not classified" (EPA 1987).

IARC has not evaluated the weight of evidence for carcinogenicity to humans of trimethylbenzenes. Because data are inadequate, an IRAC classification of Group 3 is most appropriate. According to the EPA guidelines for evaluating the weight of evidence, and EPA classification of Group D (not classified) best reflects the lack of carcinogenicity test data (EPA 1987).

Quantitative Estimate of Carcinogen Risk - There are no adequate subchronic or chronic inhalation or oral data that define dose-specific adverse effects. Therefore, no RfDs are available for trimethylbenzene.

Animal Toxicity - The rat inhalation LC50 is 18 g/m^3/4 hours. The guinea pig intraperitoneal LDLo is 1788 mg/kg, the rat intraperitoneal LDLo is 1752 mg/kg (RTECS 1987).

Toxicant Interactions - Benzene and its methyl derivatives are metabolized to derivatives of phenol and hippurate. Oral administration of benzene along with either 1,2,3- or 1,3,5-trimethylbenzene resulted in a higher concentration of phenol in the blood than when benzene was administered alone. Hippuric acid levels in the blood were also elevated when benzene was administered together with 1,2,3-trichlorobenzene, but were decreased when benzene was administered with 1,3,5-trimethylbenzene (Mikulski et al. 1979, as cited in EPA 1987).

2.2.23 Undecane

Undecane is a colorless liquid with a density of 0.7402 and a flash point of 149°F. Its molecular formula is $C_{11}H_{24}$ and its molecular weight is 156.35. It has a Hazard Rating of 2 (Sax and Lewis 1989). Common synonyms for undecane are hendecane and n-undecane.

2.2.23.1 Summary

The amount of information regarding toxicological effects of undecane is very limited. No studies of human toxicology were found.

The only health effect related limit found was the intravenous LD50 in mice of 517 mg/kg.

2.2.23.2 Health Effects

The amount of information regarding toxicological effects of undecane is very limited. No studies of human toxicology were found.

General Toxicity - The direct aspiration into the lungs of paraffins with carbon numbers C_6 to C_{16} may cause chemical pneumonitis, pulmonary edema and hemorrahaging (HSDB 1990).

An intravenous LD50 in mouse is 517 mg/kg, with a statement that the toxic effects have not yet been reviewed (RTECS 1987).

Sax and Lewis (1989) make a statement that undecane is moderately toxic by the intravenous route, and they give undecane a Hazard Rating of 2.

2.2.24 Xylene

Xylene is a clear liquid with a density of 0.864 and a flash point of 100°F. It has a molecular formula of C_8H_{10} and it has a molecular weight of 106.18. Xylene has a vapor pressure of 6.72 mm at 21°C. It has a Hazard Rating of 3 (Sax and Lewis 1989). The TLV, on a TWA basis, is 100 ppm. The TLV, on a STEL basis, is 150 ppm. These TLVs are for the o-, m-, and p-isomers of xylene (ACGIH 1988). Common synonyms for xylene are dimethylbenzene, 1,2-dimethylbenzene, 1,3-dimethylbenzene, 1,4-dimethylbenzene, m-xylene, meta-xylene, o-xylene, ortho-xylene, p-xylene, and para-xylene.

2.2.24.1 Summary

The RfDo for xylene is 2E+0 mg/kg/day, with the critical effect being hyperactivity, and decreased body weight. The NOAEL for xylene is 250 mg/kg/day, and the FEL is 500 mg/kg/day (IRIS 1990).

Xylene is a central nervous system depressant that produces lightheadedness, nausea, headache, and ataxia at low doses and confusion, respiratory

depression, and coma at high doses. Above 200 ppm, xylene causes conjunctivitis, nasal irritation, and sore throats. It is a potent respiratory irritant at high concentrations (HSDB 1990).

Central nervous system defects were more common in children of mothers exposed to organic solvents and dusts during pregnancy. Hydranencephaly occurred in children whose mothers had been exposed to the solvents toluene, xylene, and White Spirit during manufacture of rubber products (HSDB 1990).

Women exposed to xylene are liable to suffer from menstrual disorders (menorrhagia, metrorrhagia). It has been reported that female workers exposed to xylene in concentrations that periodically exceed the exposure limits were also affected by pathological pregnancy conditions (toxicosis, danger of miscarriage, hemorrhage during childbirth) and infertility (HSDB 1990).

The weight-of-evidence classification for xylene is "D; not classifiable as to human carcinogenicity." The basis for this classification is the orally administered technical xylene mixtures did not result in significant increases in incidences in tumor responses in rats or mice of both sexes (IRIS 1990).

2.2.24.2 Health Effects

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for xylene is 2E+0 mg/kg/day, with the critical effect being hyperactivity, and decreased body weight. The NOAEL for xylene is 250 mg/kg/day, and the FEL is 500 mg/kg/day (IRIS 1990).

Groups of 50 male and 50 female Fischer 344 rats and 50 male and 50 female B6C3F1 mice were given gavage doses of 0, 250, or 500 mg/kg/day (rats) and 0, 500, or 1000 mg/kg/day (mice) for 5 day/wk for 103 weeks. The animals were observed for clinical signs of toxicity, body weight gain, and mortality. All animals that died or were killed at sacrifice were given gross necropsy and comprehensive histological examinations. There was a dose-related increased mortality in male rats, and the increase was significantly

greater in the high-dose group compared with controls. Although increased mortality was observed at 250 mg/kg/day, the increase was not significant. Although many of the early deaths were caused by gavage error, NTP (1986), as cited in IRIS (1990), did not rule out the possibility that the rats were resisting gavage dosing because of the behavioral effects of xylene. Mice given the high dose exhibited hyperactivity, a manifestation of central nervous system toxicity. There were no compound-related histopathologic lesions in any of the treated rats or mice. Therefore, the high dose is a FEL and the low dose a NOAEL (IRIS 1990).

EPA (1984), as cited in IRIS (1990), reported an RfD of 0.01 mg/kg/day, based on a rat dietary NOAEL of 200 ppm or 10 mg/kg/day as defined by Bowers er al. (1982), as cited in IRIS (1990), in a 6-month study. This NOAEL was divided by an uncertainty factor of 1,000. EPA (1985, 1986), as cited in IRIS (1990), noted that this study used aged rats, loss of xylene from volatilization was not controlled, only one exposure level was used, and histopathologic examination was incomplete. An RfD of 4.31 mg/day (about 0.06 mg/kg/day) based on an inhalation study (Jenkins et al. 1970, as cited in IRIS 1990) using rats, guinea pigs, monkeys, and dogs exposed to o-Xylene at 3358 mg/m^3, 8 h/day, 5 day/wk for 6 weeks or at 337 mg/m^3 continuously for 90 days was derived by DOE (1985), as cited in IRIS (1990). Deaths in rats and monkeys, and tremors in dogs, occurred at the highest dose, whereas no effects were observed in the 337 mg/m^3 continuous exposure group. The RfD based on the NTP study (1986), as cited in IRIS (1990), is preferable because it is based on a chronic exposure in two species by a relevant route of administration, and comprehensive histology was performed. Xylene is fetotoxic and teratogenic in mice at high oral doses (Nawrot and Staples 1981; Marks et al. 1982, as cited in IRIS 1990), but the RfD as calculated should be protective of these effects (IRIS 1990).

The confidence in the RfDo for xylene is medium. The NTP study (1986), as cited in IRIS (1990), was given a medium confidence level because it was a well-designed study in which adequately sized groups of two species were tested over a substantial portion of their lifespan, comprehensive histology was performed, and a NOAEL was defined; but clinical chemistries, blood

enzymes, and urinalysis were not performed. The database was given a medium confidence level because, although supporting data exist for mice and teratogenicity and fetotoxicity data are available with positive results at high oral doses, a LOAEL for chronic oral exposures has not been defined. The medium confidence in the RfDo follows (IRIS 1990).

Xylene is a central nervous system depressant that produces lightheadedness, nausea, headache, and ataxia at low doses and confusion, respiratory depression, and coma at high doses. Above 200 ppm, xylene causes conjunctivitis, nasal irritation, and sore throats. It is a potent respiratory irritant at high concentrations (HSDB 1990).

Transient mildly elevated hepatic aminotransferase levels and reversible renal failure were reported in an estimated 10,000 ppm xylene exposure occurring during the painting of a poorly ventilated ship compartment. Two men were comatose and one was dead on arrival after prolonged exposure over 18 hours. The survivors developed no long-term sequelae. The contributions of hypoxia and a toluene solvent could not be quantitated (HSDB 1990).

Six volunteers were able to detect odor of mixed xylenes at concentrations of 60 mg/m^3 in a 15-minute exposure period. The only common sign of discomfort at 2,000 mg/m^3 was eye irritation. Some olfactory fatigue occurred with recovery in 10 minutes (HSDB 1990).

In workers exposed to organic solvents (acetone, benzene, toluene, ethyl acetate, butyl acetate, xylene, gasoline, and turpentine), the incidence of chronic bronchitis was higher and the volume of expiratory air was lower than in normal control subjects. In smokers, the incidence was higher than nonsmokers of exposed and nonexposed groups. Smoking increases risk of chronic bronchitis in subjects exposed to organic solvents (HSDB 1990).

Central nervous system defects were more common in children of mothers exposed to organic solvents and dusts during pregnancy. Hydranencephaly occurred in children whose mothers had been exposed to the solvents toluene, xylene, and White Spirit during manufacture of rubber products (HSDB 1990).

Exposed women are liable to suffer from menstrual disorders (menorrhagia, metrorrhagia). It has been reported that female workers exposed to

xylene in concentrations that periodically exceed the exposure limits were also affected by pathological pregnancy conditions (toxicosis, danger of miscarriage, hemorrhage during child birth) and infertility (HSDB 1990).

Human Carcinogenicity - The weight-of-evidence classification for xylene is "D; not classifiable as to human carcinogenicity." The basis for this classification is the orally administered technical xylene mixtures did not result in significant increases in incidences in tumor responses in rats or mice of both sexes (IRIS 1990).

Animal Carcinogenicity - The animal carcinogenicity data are considered inadequate. In an NTP study (1986), as cited in IRIS (1990), 50 male and 50 female F344/n rats were treated by gavage with mixed xylenes in corn oil (60% m-xylene, 14% p-xylene, 9% o-xylene and 17% ethylbenzene) at dosages of 0, 250 or 1000 mg/kg/day. Animals were killed and examined histologically when moribund or after 104-105 weeks. An apparent dose-related increased mortality was observed in male rats, but this difference was statistically significant for the high dose group only. No other differences in survival between dosage groups of either sex were observed. Interstitial cell tumors of the testes could not be attributed to administration of the test compound observed in male rats (43/50 control, 38/50 low-dose and 41/40 high-dose). NTP (1986), as cited in IRIS (1990), reported no significant changes in the incidence of neoplastic or nonneoplastic lesions in the rats or mice that could be considered related to the mixed Xylene treatment, and concluded that under conditions of these 2-year gavage studies, there was "no evidence of carcinogenicity" of xylene (mixed) for rats or mice of either sex at any dosage tested (IRIS 1990).

Maltoni et al. (1985), as cited in IRIS (1990), in a limited study, reported higher incidences (compared with controls) of malignant tumors in male and female Sprague-Dawley rats treated by gavage with xylene in olive oil at 500 mg/kg/day, 4 or 5 day/wk for 104 weeks. This study did not report survival rates or specific tumor types; therefore, the results cannot be interpreted (IRIS 1990).

Berenblum (1941), as cited in IRIS (1990), reported that undiluted xylene applied at weekly intervals produced one tumor-bearing animal out of

40 after 25 weeks in skin-painting experiments in mice. No control groups were described. Pound (1970), as cited in IRIS (1990), reported negative results in initiation-promotion experiments with xylene as the initiator and cronton oil as the promotor.

Carcinogenicity Supporting Data - The frequency of sister chromatid exchanges and chromosomal aberrations were nearly identical between a group of 17 plant industry workers exposed to xylene and their respective referents (Haglund et al. 1980, as cited in IRIS 1990). In vitro, xylene caused no increase in the number of sister chromatid exchanges in human lymphocytes (Gerner-Smidt and Friedrich 1978, as cited in IRIS 1990). Studies indicate that xylene isomers, technical grade xylene or mixed xylene are not mutagenic in tests with Salmonella typhimurium (Florin et al. 1980; NTP 1986; Bos et al. 1981, all as cited in IRIS 1990) nor in mutant reversion assays with Escherichia coli (McCarrol et al. 1981, as cited in IRIS 1990). Technical grade xylene, but not o- and m-xylene, was weakly mutagenic in Drosophila recessive lethal tests. Chromosomal aberrations were not increased in bone marrow cells of rats exposed to xylenes by inhalation (Donner et al. 1980, as cited in IRIS 1990).

Quantitative Estimate of Carcinogen Risk - There are no quantitative estimates of risk for either the oral or the inhalation routes.

2.2.25 Additional Calk-Associated Compounds

The following three compounds are additional contaminants found in caulking material. In the reviewed public building measurement studies, these contaminants were not specifically reported as being found, but they are included here for completeness. It is suspected that if these contaminants are detected in building caulking material, they are very likely to be released to the indoor air of a public building.

2.2.25.1 Carbitol

Carbitol is a colorless liquid with a mild pleasant odor. It has a density of 0.9902 and a flash point of 201°F. Its molecular formula is $C_6H_{14}O_3$ and its molecular weight is 134.2. It has a Hazard Rating of 2 (Sax and Lewis 1989). The most common synonym for carbitol is carbitol cellosolve,

with carbitol solvent, diethylene glycol ethyl ether, dioxitol, diglycol monoethyl ether, ethoxy diglycol, 2-(2-ethoxyethoxy)ethanol, ethylcarbitol, ethyldiethyleneglycol, poly-solv, and solvsol other common synonyms.

2.2.25.1.1 Summary. The amount of information regarding toxicological effects of carbitol is very limited. No studies of human toxicology were found.

2.2.25.1.2 Health Effects. The amount of information regarding toxicological effects of carbitol is very limited. No studies of human toxicology were found.

General Toxicity - Carbitol is moderately toxic by ingestion, intravenous, intraperitoneal and possibly other routes. It is mildly toxic by skin contact, and it is a skin and eye irritant. Experimental reproductive effects have been associated with it (Sax and Lewis 1989).

Skin and eye irritation levels are shown in RTECS at 112 mg/3 days with mild effects for human skin. A rabbit skin level of 500 mg with mild irritation is provided. A rabbit eye irritation level of 50 mg with mild irritation is listed (RTECS 1987).

A reproductive effects level for rats, administered orally, is provided showing an LDLo of 50 mg/kg resulting in specific developmental abnormalities (musculoskeletal system) (RTECS 1987).

Three values of tumorigenic data for rats, administered orally, are provided. These levels are 1) oral rat TDLo of 890 gm/kg/53 weeks, 2) oral rat TD of 1752 gm/kg/2 years, and 3) oral rat TD of 584 gm/kg/2 years. The tumors developed were in the kidney, ureter and bladder (RTECS 1987).

Toxicity data are also provided in RTECS. A mouse inhalation LCLo of 130 mg/m^3/2 hours with toxic effects not yet reviewed is provided. A rat intramuscular LDLo value of 7826 mg/kg with no toxic effects is listed. A rabbit intramuscular LDLo value of 4472 mg/kg with no toxic effects noted is listed. The following is provided: a mouse intraperitoneal LD50 of 9719 mg/kg with lungs, thorax or respiration (chronic pulmonary edema or congestion); kidney, ureter and bladder (changes in both tubules and glomeruli); and blood (changes in spleen) affected. A rat intravenous LD50 of 6565 mg/kg with toxic

effects not yet reviewed is listed. Also, a rabbit intravenous LDLo of 2236 mg/kg with no toxic effects noted is listed. A mouse subcutaneous LDLo of 5 gm/kg with toxic effects not yet reviewed is listed. A rat subcutaneous LDLo of 16770 mg/kg with no toxic effects noted is listed. A rabbit skin LD50 of 11890 mg/kg with no toxic effects noted is provided (RTECS 1987).

2.2.25.2 Ethylene Glycol

Ethylene glycol is a colorless, sweet-tasting, hygroscopic liquid. It has a density of 1.113 and a flash point of 232°F. Its molecular formula is $C_2H_6O_2$ and its molecular weight is 62.08. Ethylene glycol has a vapor pressure of 0.05 mm at 20°C (Sax and Lewis 1989). The TLV, on a TWA basis, is 50 ppm (ACGIH 1988). Common synonyms for ethylene glycol are 1,2-dihydroxyethane, 1,2-ethanediol, ethylene alcohol, ethylene dihydrate, glycol, glycol alcohol, MEG, monoethylene glycol, norkool, and tescol.

2.2.25.2.1 Summary. The amount of toxicological information available for ethylene glycol is somewhat limited.

The RfDo for ethylene glycol is 2E+0 mg/kg/day, with kidney toxicity listed as the critical effect. The NOAEL is 200 mg/kg/day, and the LOAEL is 1,000 mg/kg/day (IRIS 1990).

The RfDi is not available at this time.

Ethylene glycol is in the same range of toxicity as methylethylketone, propylenedichloride, and TCE, but its hazards are believed to be less because its vapor pressure is substantially lower (HSDB 1990).

Ethylene glycol has not been evaluated by the EPA for evidence of human carcinogenic potential.

2.2.25.2.2 Health Effects.

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis, but may not exist for other toxic effects, such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for ethylene glycol is 2E+0

mg/kg/day, with kidney toxicity listed as the critical effect. The NOAEL is 200 mg/kg/day, and the LOAEL is 1,000 mg/kg/day (IRIS 1990).

DePass et al. (1986a); as cited in IRIS (1990), conducted 2-year studies using groups of approximately 30 rats per sex and 20 mice per sex that were fed diets providing ethylene glycol dosages of 0, 40, 200, or 1,000 mg/kg/day. High-dose rats had increased mortality, neutrophil count, water intake, kidney hemoglobin and hematocrit, and chronic nephrities. Female rats exposed to 1,000 mg/kg/day had mild fatty changes in the liver. No adverse effects occurred at other doses in rats or at any dose in mice (IRIS 1990).

Groups of Sprauge-Dawley rats (16/sex/group) were fed diets containing 0, 0.1, 0.2, 0.5, 1.0, or 4.0% ethylene glycol for 2 years (Bolld 1965, as cited in IRIS 1990). Male rats at 1.0 and 4.0% and females at 4.0% had increased mortality, decreased growth, increased water consumption, proteinuria, and renal calculi. There was an increased incidence of cytoplasmic crystal deposition in renal tubular epithelium at 0.5 and 1.0%. There were no effects on organ weights or hematologic parameters. The authors concluded that 0.2% (2,000 ppm) was a NOAEL for rats; the LOAEL was 0.5% (5,000 ppm). Assuming that a rat consumes food equivalent to 5% of its body weight/day, the NOAEL and the LOAEL are equivalent to 100 mg/kg/day and 250 mg/kg/day, respectively (IRIS 1990).

The choice of the DePass et al. study (1986a), as cited in IRIS (1990), over the Blood study (1965), as cited in IRIS (1990), as the basis of the Rfd reflects the greater confidence in the former study because of the greater number of animals tested and effects considered. The magnitude of the RfD in either case is similar (IRIS 1990).

Bolld et al. (1962), as cited in IRIS (1990), fed a diet containing 0.2 or 0.5% ethylene glycol to rhesus monkeys for 3 years. No treatment-related toxic effects on histologic appearance of kidneys or other major organs were found.

In a teratogenicity study, Maronpot et al. (1983), as cited in IRIS (1990), found increased preimplantation loss and increased incidence of poorly ossified vertebral centra in offspring of rats treated at 1,000 mg/kg in the

diet on days 6-15 of gestation. No effects occurred at 40 or 200 mg/kg. Lamb et al. (1985), as cited in IRIS (1990), reported that exposure of male and female mice to 1.0% ethylene glycol in drinking water for 14 weeks resulted in significantly fewer litters, decreased mean live pup weight, and decreased number of live pups per litter. DePas et al. (1986a), as cited in IRIS (1990), conducted a three-generation study in which rats were treated with 0, 40, 200, or 1,000 mg/kg/day and mice with 0, 750, 1500, or 3000 mg/kg/day on days 6-15 of gestation. The percentage of litters with malformed fetuses increased in a dose-related manner in both species at all doses. There was a dose-related increase in postimplantation losses per litter in both species, but it was significant only in high-dose rats. Maternal body weight gain was decreased at all doses in rats and at the two higher doses in mice (IRIS 1990).

The confidence in the RfDo is high. Confidence in the DePass et al. study (1986a), as cited in IRIS (1990), is rated high because it was a well-conducted lifetime study in two species by a relevant route and defined a NOAEL and LOAEL. Confidence in the database is also high because it contains another chronic rat study and a monkey study that support the NOAEL and LOAEL from the DePass et al. study (1986a), as cited in IRIS (1990). It also contains data that indicate that the RfDo is protective of teratogenic and reproductive effects. Therefore, confidence in the RfDo is also high (IRIS 1990).

The RfDi is not available at this time.

Ethylene glycol is in the same range of toxicity as methylethylketone, propylenedichloride, and TCE, but its hazards are believed to be less because its vapor pressure is substantially lower (HSDB 1990).

Human Carcinogenicity - Ethylene glycol has not been evaluated by the EPA for evidence of human carcinogenic potential.

2.2.25.3 Octene

Octene was not found in Sax and Lewis (1989), IRIS (1990), HSDB (1990), RTECS (1987), or in the various bibliographic databases searched. Thus, it was concluded that no toxicological information is available on octene at this time.

2.3 COMBUSTION PRODUCTS

Pollutant emissions from indoor combustion vary considerably as a function of the type of fuel, the type and condition of the appliance, and the conditions under which combustion takes place. The major combustion products are CO_2 and water vapor. Major combustion by-products are CO, nitrogen dioxide, sulfur dioxide, aldehydes and other organic compounds, and particulate matter. Tobacco smoking, gas-fired appliances, wood stoves, fireplaces, and kerosene heaters are some of the major sources of indoor-air contaminating combustion by-products.

Metabolic activity is responsible for most of the indoor CO_2 concentration in the indoor environment. Gas and kerosene heaters also emit appreciable quantities of CO_2. Carbon monoxide is a product of incomplete combustion. Emissions from vehicles in attached or underground garages or from outside traffic, with emissions being brought in through the ventilation systems, also contribute indoor air contaminants. Oxides of nitrogen are formed when combustion takes place at high temperatures. Sulfur oxides are combustion products of sources burning sulfur containing fuels (e.g., kerosene and coal). In general, sulfur oxides are usually more of a concern with outdoor ambient air quality.

Among the aldehydes and other organic compounds associated with combustion products, formaldehyde and benzo(a)pyrene are the sources of greatest concern. Formaldehyde was discussed earlier in Section 2.2.11. Wood combustion and tobacco smoke are the main sources of the normally fairly low levels of benzo(a)pyrene found in the indoor environment.

2.3.1 Benzo(a)pyrene

Benzo(a)pyrene [B(a)P] in its pure form is yellow crystals that are insoluble in water but soluble in benzene, toluene, and xylene. The American Conference of Governmental Industrial Hygienists do not list any TLVs for B(a)P. Instead, they note that it is a "Suspected human carcinogen and exposures to carcinogens must be kept to a minimum." B(a)P has a Hazard Ratng of 3 (Sax and Lewis 1989).

2.3.1.1 Summary

The weight-of-evidence classification for B(a)P is "B2; probable human carcinogen." Human data specifically linking B(a)P to a carcinogenic effect are lacking. However, there are multiple animal studies in rodent and non-rodent species demonstrating B(a)P to be carcinogenic following administration by oral, intratracheal, inhalation and dermal routes. B(a)P has produced positive results in several vitro bacterial and mammalian genetic toxicology assays (IRIS 1990).

The carcinogenicity observed in association with B(a)P is believed to come from its metabolic derivatives rather than the compound itself. The review of data on B(a)P as a pure compound shows that those derivatives can range from noncarcinogenic to extremely carcinogenic. Not only does carcinogenic response vary from metabolite to metabolite, but the response to B(a)P and/or its metabolites may vary from one species to another, one variety to another, and even among individuals within a variety. In light of this information, the use of an single dose-response relationship in a model for predicting cancer risk, even if it is based on extensive comparisons of actual populations of smoking and nonsmoking humans, is open to question (DOE 1987).

Recent animal studies on the carcinogenicity of complex mixtures such as coal liquids have demonstrated that the carcinogenicity of the mixture does not vary directly with its B(a)P content (DOE 1987).

B(a)P is a ubiquitous poly aromatic hydrocarbon (PAH) produced during the combustion of materials such as coal, wood, tobacco, diesel fuel, and tar, and in some commercial processes. It has been extensively studied and shown to be a potent carcinogen in experimental animals and in human tissues. As a

PAH, B(a)P is not chemically reactive with cellular components of living organisms. Rather, it is a procarciongen that is metabolized by living cells into carcinogenic derivatives capable of reacting directly with the macromolecules of animal and human cells (Kramer et al. 1983, as cited in DOE 1987). B(a)P has been widely used as a reference compound for estimating human health effects for emissions and effluent suspected of posing a carcinogenic risk to human populations (DOE 1987).

2.3.1.2 Health Effects - Pure B(a)P

Human Carcinogenicity - The weight-of-evidence classification for B(a)P is "B2; probable human carcinogen." Human data specifically linking B(a)P to a carcinogenic effect are lacking. However, there are multiple animal studies in rodent and nonrodent species demonstrating B(a)P to be carcinogenic following administration by oral, intratracheal, inhalation and dermal routes. B(a)P has produced positive results in several vitro bacterial and mammalian genetic toxicology assays (IRIS 1990).

Human carcinogenicity data are inadequate. Lung cancer has been shown to be induced in humans by various mixtures of polycyclic aromatic hydrocarbons known to contain B(a)P including cigarette smoke, roofing tar and coke oven emissions. It is not possible, however, to conclude from this information that B(a)P is the responsible agent (IRIS 1990).

No dose-response information on the experimental or occupational exposure of humans to pure B(a)P appears to exist. However, there have been a number of studies on the exposure of human organs, cells, and microsomal fractions cultured in vitro. The most significant finding of these studies has been that comparisons of limited human data with the more extensive animal data suggest basically similar effects of B(a)P (Kramer et al. 1983, as cited in DOE 1987). At the same time, differences in the reactions of different human organs have been demonstrated. For example, the urinary bladder appears to be most sensitive, followed by the skin, bronchus, esophagus, and colon. Moreover, there are significant variations in the susceptibility of tissues taken from different individuals, some of which appear to be associated with genetic differences (DOE 1987).

B(a)P is well known as a complete carcinogen when applied to the skin of mice, rats and rabbits (IARC 1973, as cited in IRIS 1990). Suscutaneous or intramuscular B(a)P injection has been shown to result in local tumors in mice, rats, guinea pigs, monkeys and hamsters (IARC 1973, as cited in IRIS 1990). Intratracheal instillation of B(a)P produced increased incidences of respiratory tract neoplasms in both male and female Syrian hamsters (Feron et al. 1973; Kobayashi 1975, as cited in IRIS 1990).

B(a)P administered orally to rats and hamsters produces stomach tumors. Neal and Rigdon (1967), as cited in IRIS (1990), administered dietary B(a)P at concentrations of 0, 1 10, 20, 30, 40, 45, 50, 100, and 250 ppm to male and female CFW-Swiss mice. The control group numbered 289; treatment groups varied in number from 9 to 73 animals and treatment time from 1 to 197 days. Stomach tumors were observed in mice consuming 20 or more ppm B(a)P. Incidence was apparently related both to the dose amount and the number of administered doses. Apparent increased incidences of leukemia and lung adenomas were reported in the mice on high B(a)P diets (250 and 1000 ppm) (Ridgon and Neal 1966; 1969, as cited in Iris 1990.

Tyssen et al. (1981), as cited in IRIS (1990), exposed groups of 24 hamsters by inhalation of B(a)P at concentrations of 2.2, 9.5, or 45 mg/m^3 for 4.5 h/day for 10 weeks followed by 3 h/day (7 day/wk) for up to 675 days. No animals in the lowest treatment group developed respiratory tumors. Those hamsters exposed to 9.5 mg/m^3 developed tumors of the nasal cavity, larynx, trachea, and pharynx. In addition to respirator tract tumors, animals in the highest dose group were seen to have neoplasms of the upper digestive tract (IRIS 1990).

B(a)P is among the best-studied agents producing genetic toxicological effects. It is metabolized to reactive electrophiles capable of binding to DNA. In vitro assays in which B(a)P has produced positive results include the following: bacterial DNA repair, bacteriophage induction, point mutations at multiple loci in several bacterial species and strains, mutations in Drosophila melanogaster, sister-chromatid-exchange, chromosomal aberrations and mutation and transformation of cultured mammalian cells. In vivo exposure

of mammalian species to B(a)P has produced the following results: sister-chromatid-exchange, chromosomal aberrations, sperm abnormalities, and positive results in the mouse specific locus (spot) test (IARC 1973; 1983; Santodonato et al. 1981, all as cited in IRIS 1990).

Quantitative Estimate of Carcinogen Risk - No quantitative estimate of carcinogenic risk from oral or inhalation exposure is available at this time.

2.3.1.3 Health Effects - B(a)P in Complex Mixtures

Although studies of the effects of B(a)P on animals and on human tissues are useful in demonstrating the metabolic derivatives responsible for mutagenic/carcinogenic activity, or for determining differences between animals and humans, or among humans to different exposure scenarios, they have serious limitations in extrapolating to the environmental exposure of humans. One important limitation is that B(a)P is not normally encountered in the environment (either ambient or indoor) as a pure compound. Rather, it occurs with many other organics in what are commonly referred to as complex mixtures. For example, B(a)P is encountered in cigarette smoke along with about 1000 other compounds and in coal-derived products with as many as 2500 other compounds (DOE 1987).

Risk assessments performed in the 1970s and early 1980s tended to estimate the carcinogenic potential of these mixtures on the basis of their B(a)P content (Mahlum et al. 1984, as cited in DOE 1987). This practice continues. In a recent international symposium, it was concluded that for each individual type of polycyclic organic matter (POM) source, "both Benzo (A) Pyrene and total POM provide excellent indicators of hazard..." (Milliken et al. 1984, as cited in DOE 1987). As a result of this emphasis, many people regard B(a)P as the determinant carcinogen in many complex mixture pollutants, whether or not there is experimental evidence on which to base this assumption (DOE 1987).

Human Health Effect Studies - The evidence most cited for the carcinogenicity of B(a)P in humans comes from epidemiological studies of workers who have been occupationally exposed to this substance as a component of complex mixtures encountered. For example, EPA developed estimates of cancer risk for worker populations exposed to coke-oven emissions (EPA 1981, updated in EPA

1984b, as cited in DOE 1987). The EPA scientists developed a unit risk factor (the lifetime probability of dying from lung cancer as a result of exposure to coke-oven emissions) based on the benzene-soluble organic fraction of emissions, of which B(a)P is a component. Based on the rate of lung cancer among coke-oven workers, and assuming that there is no level of exposure that does not have some risk associated with it, the estimated lifetime risk of dying from lung cancer from continuous exposure to 1 μg of benzene-soluble organic per cubic meter of air has been estimated at 9.25E-4 (DOE 1987).

More commonly, humans are exposed to B(a)P as a component of cigarette smoke (NRC 1981, as cited in DOE 1987). Estimates of risk from B(a)P in the indoor environment given in The Expanded Weatherization Final Environmental Impact Statement (DOE 1984) are based on a model developed from the risk of lung cancer among cigarette smokers and tested using data from occupational populations exposed to coke-oven emissions. Again, the tendency is to attribute most or all of the carcinogenic activity of a complex mixture, this time cigarette smoke, to its B(a)P content. Evidence exists from both human and animal studies that this assumption is not reliable (DOE 1987).

A pilot study in four Indian villages of women exposed to total suspended particulates (TSP) and particulate B(a)P from cooking on simple stoves has been reported by Smith et al. (1983), as cited in DOE (1987). Stove fuels were traditional biomass fuels that resulted in TSP exposures averaging 7 mg/m^3 and approximately 4000 ng/m^3 B(a)P during the cooking period. A comparison of resulting exposure levels with smokers revealed that village cooks received more than a factor of 10 greater nominal doses to B(a)P. Yet, these women did not show incidences of lung or other cancers proportional to their B(a)P exposure (DOE 1987).

Nonhuman Studies - Pure B(a)P adsorbed to fine particles has a longer lung retention time (1 day for 90% clearance) than a pure B(a)P aerosol (4 hours for 90% clearance). A further increase in lung clearance time to about 60 days was shown in experiments with B(a)P plus diesel particles (complex mixture) (Sun et al. 1982, as cited in DOE 1987). Therefore, B(a)P associated with complex mixtures is retained in the lungs longer than pure B(a)P, whether bound to a fine particle or as an aerosol (DOE 1987).

Several studies conducted at the Pacific Northwest Laboratory (PNL) with coal liquids have suggested that the mutagenic and carcinogenic activities of B(a)P were inhibited when the B(a)P was contained in a complex mixture. Pelroy (1984), as cited in DOE 1987, using the Ames Salmonella histidine reversion assay (used as a screening test for potential carcinogenicity) showed that the mutagenic activities of the neutral PAH fractions of high boiling coal distillates were very low relative to their B(a)P content. Moreover, the addition of small amount of coal distillate to the assay system substantially inhibited the mutagenic activity of exogenous B(a)P (DOE 1987).

Studies using the mouse skin tumor initiaton-promotion assay were performed to directly determine the carcinogenicity of a number of coal-derived liquids. From these studies, we have obtained numerous lines of evidence that the carcinogenic activity of B(a)P is substantially reduced when administered in a complex mixture (DOE 1987).

One line of evidence came from comparing the carcinogenicity of coal liquids from two different coal liquefraction processes, the heavy distillate (HD) from the solvent refined coal-II (SRC-II) process, and the finer feed from the Integrated Two-Stage Liquefaction (ITSL) process. Although the HD contained 300 ppm B(a)P and the finer feed 30,000 ppm B(a)P, the carcinogenic potencies of the two liquids were almost identical (DOE 1987).

A second line of evidence was obtained when the carcinogenic activities of two SRC-II distillates were compared. Distillates boiling from 800°F to 850°F and more than 859°F each contained about 1800 ppm B(a)P. In addition, analysis showed that the 800° to 850° distillate contained numerous other known carcinogens. Yet the greater than 850° distillate was 3 to 5 times more carcinogenic than the 800°to 850° one. Chronic skin painting assay results also demonstrate a higher activity for the greater than 850° distillate (DOE 1987).

Assay of PAH fractions from these two distillates resulted in similar differences in carcinogenic activity, even though they contained the same quantities of B(a)P. This provides additional evidence that B(a)P activity is inhibited in complex mixtures. Further evidence was obtained when the PAH fraction for the greater than 850° distillate was further fractionated using

high-performance liquid chromatography. This technique resulted in a fraction greatly enriched in B(a)P and greatly reduced in the number of PAH. Assay of this B(a)P-enriched fraction showed that its carcinogenic activity was greater than that of the parent PAH fraction and approached that of pure B(a)P (DOE 1987).

Because the results of the various studies indicated that the carcinogenic activity of many complex mixtures was not correlated with B(a)P levels and that the activity of B(a)P was inhibited when tested as a part of a complex mixture, Mahlum et al. 1984, as cited in DOE (1987), directly tested the influence of coal liquids on the skin tumor-initiating activity of B(a)P. In the first experiment, the carcinogenic activity of B(a)P in acetone was compared with that of B(a)P administered in a broad boiling range (300 to 850°F) liquid. Initiating doses of either 10 or 50 μg of B(a)P were used. With both doses, the activity of B(a)P was significantly lower when applied in the coal liquid. These results clearly demonstrated the inhibiting effect of the mixture on B(a)P tumorigenic activity (DOE 1987).

Scientists at PNL recently completed an experiment to determine if the inhibition of B(a)P activity was associated with materials having specific boiling ranges. Mahlum et al. 1984, as cited in DOE (1987), tested the effect of discrete boiling point cuts prepared from the 300 to 850°F liquid noted above, on the expression of B(a)P activity by applying a 25-μg dose of B(a)P to mouse skin in acetone:methylene chloride vehicle or in acetone:methylene chloride containing 5 μg of the distillate of interest. The results of this experiment indicated that a distillate boiling from 300 to 700°F had little effect on B(a)P expression. However, all distillates with boiling ranges of 700, 750 to 800, 800 to 850, and more than 850°F markedly reduced the carcinogenic activity of B(a)P, probably as a result of altered metabolism (DOE 1987).

In other PNL experiments, the influence of complex mixtures on metabolism and DNA binding of B(a)P was examined. The results of these experiments are consistent with the skin tumor experiments in that both the rate of metabolism and the extent of binding of B(a)P to DNA are inhibited by the high boiling coal distillates. These results demonstrate unequivocally that the

B(a)P content of mixtures is not well correlated with carcinogenic activity (or microbial mutagenic activity). Further, PNL data suggest that the failure of B(a)P levels to correlate with carcinogenic activity is caused by an inhibition of expression of B(a)P activity by other components of the mixture (DOE 1987).

2.3.2 Carbon Dioxide

Carbon dioxide is a colorless, odorless gas. Its molecular formula is CO_2 and its molecular weight is 44.01. It has a Hazard Rating of 1 (Sax and Lewis 1989). The TLV, on a TWA basis, is 5,000 ppm. The TLV, on a STEL basis, is 30,000 ppm (ACGIH 1988). Common synonyms for carbon dioxide are carbonic acid gas and carbonic anhydride.

2.3.2.1 Summary

Carbon dioxide is one of the two major products of combustion (i.e., CO_2 and H_2O vapor). Human metabolic activity accounts for most of the indoor CO_2 concentrations.

It is recognized that repeated daily exposure at 0.5 to 1.5% inspired carbon dioxide at 1 atmosphere pressure is well tolerated by normal individuals (HSDB 1990).

Two percent carbon dioxide in inhaled air increases pulmonary ventilation 50%. Dizziness, headache, confusion and dyspnea occur at 5% concentration carbon dioxide. Eight to ten percent causes severe headache, sweating, dimness of vision and tremor; consciousness is lost after 5 to 10 minutes (HSDB 1990).

2.3.2.2 Health Effects

Carbon dioxide is one of the two major products of combustion (i.e., CO_2 and H_2O vapor). Human metabolic activity accounts for most of the indoor CO_2 concentrations.

General Health Effects - It is recognized that repeated daily exposure at 0.5 to 1.5% inspired carbon dioxide at 1 atmosphere pressure is well tolerated by normal individuals (HSDB 1990).

Two percent carbon dioxide in inhaled air increases pulmonary ventilation by 50%. Dizziness, headache, confusion and dyspnea occur at 5% concentration of carbon dioxide. Eight to ten percent causes severe headache, sweating, dimness of vision and tremor; consciousness is lost after 5 to 10 minutes (HSDB 1990).

In a normal person, inhalation of 1.6% carbon dioxide air approximately doubles the respiratory minute volume and at 5% almost triples it. A concentration of 10% produces unbearable dyspnea after a few minutes, and continued exposure results in vomiting, disorientation and hypertension (HSDB 1990).

Adding 1% carbon dioxide to air increased the human pulmonary ventilation rate by 37 and 7% on the ground and under a pressure simulating a 5000-m altitude, respectively. Blood flow to the brain increased at 3 but not 1% carbon dioxide. Carbon dioxide at 0.5% or 1% stimulated hyperventilation to a degree which prevented a decrease in the psychomotor performance at a simulated 5800-m, but not at 5000-m, altitude (HSDB 1990).

Long-term exposure to levels between 0.5 and 1%, as may occur in submarines, is likely to involve increased calcium deposition in body tissues, including the kidney (HSDB 1990).

2.3.3 Carbon Monoxide

Carbon monoxide (CO) is a colorless and odorless gas. Its molecular formula is CO and its molecular weight is 28.01. It has a Hazard Rating of 3 (Sax and Lewis 1989). Common synonyms for carbon monoxide are carbonic oxide, and carbon oxide.

2.3.3.1 Summary

Carbon monoxide causes hypoxia (oxygen starvation) and, at sufficiently high concentrations, asphyxiation. By binding to hemoglobin (Hb) in the red blood cells and forming COHb, CO displaces oxygen at the binding sites of the Hb molecule that normally serves as the main carrier for transporting oxygen to the cells in the body. The ability of the blood to carry oxygen is thus reduced. Relatively low atmospheric concentrations of CO can result in significant oxygen deprivation, as reflected by high COHb levels, because CO

has an approximately 220-fold higher affinity to Hb than oxygen. A CO concentration of 550 ppm, for example, can lead to COHb levels of 20% within 1 hour.

The central nervous system, the cardiovascular system, and the liver are tissues most sensitive to CO-induced hypoxia. Manifestations of central nervous system hypoxia become apparent at COHb concentrations of 2 to 5%. They include loss of alertness; impaired perception and judgement; loss of coordination; reduced performance, vigilance, and concentration; drowsiness; confusion; and, at sufficiently high concentrations and sufficiently long exposures, coma and death (DOE 1987).

Cardiovascular hypoxia manifests itself at COHb levels as low as 3%. It causes a decrease in exercise time to produce angina pectoris, increased incidence of myocardosis (degeneration of heart muscle), and increased probability of heart failure in susceptible patients (DOE 1987).

2.3.3.2 Health Effects

General Health Effects - Carbon monoxide causes hypoxia (oxygen starvation) and, at sufficiently high concentrations, asphyxiation. By binding to hemoglobin (Hb) in the red blood cells and forming COHb, CO displaces oxygen at the binding sites of the Hb molecule that normally serves as the main carrier for transporting oxygen to the cells in the body. The ability of the blood to carry oxygen is thus reduced. Relatively low atmospheric concentrations of CO can result in significant oxygen deprivation, as reflected by high COHb levels, because CO has an approximately 220-fold higher affinity to Hb than oxygen. A CO concentration of 550 ppm, for example, can lead to COHb levels of 20% within 1 hour. By comparison, normal physiological values for nonsmokers range from 0.3 to 0.7% (Coburn et al. 1963; as cited in OOE 1987). Cardiovascular patients can experience aggravation of their symptoms at COHb levels of 2.5 to 4%. A 1-hour exposure to 1,500 ppm is potentially lethal for healthy persons. Chronic exposure to lower concentrations, as experienced by smokers and traffic-regulating policemen, stimulates the body to compensate somewhat by producing more red blood cells (erythrocytes) and more Hb. A threshold might exist at a COHb concentration at which adaptation can no longer compensate (NRC 1977, as cited in DOE 1987).

The central nervous system, the cardiovascular system, and the liver are tissues most sensitive to CO-induced hypoxia. Manifestations of central nervous system hypoxia become apparent at COHb concentrations of 2 to 5%. They include loss of alertness; impaired perception and judgement; loss of coordination; reduced performance, vigilance, and concentration; drowsiness; confusion; and, at sufficiently high concentrations and sufficiently long exposures, coma and death (DOE 1987).

Cardiovascular hypoxia manifests itself at COHb levels as low as 3%. It causes a decrease in exercise time to produce angina pectoris, increased incidence of myocardosis (degeneration of heart muscle), and increased probability of heart failure in susceptible patients (DOE 1987).

Populations at special risk include fetuses; patients with certain health problems, such as cardiovascular or chronic respiratory (bronchitis, emphysema, or asthma) diseases; individuals under the influence of drugs or alcohol; the elderly; and persons not adapted to high altitude who are exposed to CO at high altitudes. A combination of any two or more risk factors increases the risk accordingly. Table 2.11 shows threshold COHb concentrations (DOE 1987).

It is expected that individuals with predisposing illnesses or physiological conditions that limit pulmonary gas exchange or oxygen transport to body tissues would be more susceptible to the hypoxia effects of CO. People with angina pectoris, peripheral vascular disease, and other cardiovascular diseases appear to be at greatest risk from low-level exposures to CO (EPA 1984c, as cited in DOE 1987). Anderson et al. (1973, as cited in DOE (1987), observed that angina pectoris patients can be affected by COHb levels from 2.9 to 4.5%. Aronow et al. (1974), as cited in DOE (1987), suggest that patients with peripheral vascular disease can be at risk from low-level CO exposures.

Infants born to women who have survived acute exposure to high concentrations of carbon monoxide while pregnant often display neurological sequelae and there may be gross damage to the brain. Persistent low levels of carboxyhemoglobin in fetuses of women who smoke may also reduce the infants' mental abilities (HSDB 1990).

TABLE 2.11. Threshold COHb Concentrations

Category	Threshold COHb %	Effects
A	0.3 to 0.7	Physiological norm for nonsmokers
B	2.5 to 3.0	Cardiac function decrements in impaired individuals; blood flow alterations; and, after extended exposure, changes in red blood cell concentration
C	4.0 to 6.0	Visual impairments, vigilance decrements, reduced maximal work capacity. Norm for smokers
D	10.0 to 20.0	Slight headache, lassitude, breathlessness from exertion, dilation of blood cells in the skin, abnormal vision, potential damage to fetuses
E	20.0 to 30.0	Severe headaches, nausea, abnormal manual dexterity
F	30.0 to 40.0	Weak muscles, nausea, vomiting, dimness of vision, severe headaches, irritability, and impaired judgement
G	50.0 to 60.0	Fainting, convulsions, coma
H	60.0 to 70.0	Coma, depressed cardiac activity and respiration, sometimes fatal

2.3.4 Environmental Tobacco Smoke

Tobacco smoke, with about 38000 constituents (EPRI 1985, as cited in DOE 1987), can contribute substantially to indoor air pollution under conditions of heavy smoking and poor ventilation. Constituents of the gas phase of tobacco smoke include CO, CO_2, oxides of nitrogen, ammonia, volatile N-nitrosamines, hydrogen cyanide and cyanogen, volatile hydrocarbons, volatile alcohols, and volatile aldehydes and ketones. The particulate phase comprises nicotine, water and "tar." The term "tar" refers to nonvolatile N-nitrosamines, aromatic amines, alkanes, alkenes, tobacco isoprenoids, benzenes, and naphthalenes, poly aromatic hydrocarbons, N-heterocyclic hydrocarbons (aza-arenes), phenols, carboxylic acids, metallic constituents, radioactive substances, agricultural chemicals, and tobacco additives. Many of these chemicals have been found to be toxic or carcinogenic in humans and/or laboratory animals (DOE 1987). Environmental tobacco smoke has a Hazard Rating of "D" (Sax and Lewis 1989).

2.3.4.1 Summary

The harmful effects of smoking on the smoker are well known and documented. However, health effects of chronic involuntary exposure of nonsmokers to environmental tobacco smoke (ETS) at concentrations that generally are well below recommended TLVs for the individual chemicals, are still controversial. Acute effects on susceptible individuals, mainly temporary irritation of the eyes and mucous membranes of the upper respiratory tract, and headaches, are generally recognized. In contrast, results of epidemiological studies linking involuntary exposure of ETS to an increased incidence of 1) cancer in nonsmoking spouses, 2) morbidity (especially respiratory diseases) in infants and children of smoking parents (especially smoking mothers), and 3) aggravation of symptoms in patients with cardiovascular and chronic obstructive lung diseases (COLD) are still heatedly debated. Even within the biomedical community, opinions vary widely.

In view of the difficulties of 1) making meaningful concentration measurements, 2) developing standards for normalizing exposures occurring under widely varying conditions, 3) conducting "perfect" epidemiological studies, 4) developing a consensus regarding the interpretation of results of

such studies, and 5) resolving the existing disagreements and controversy in the biomedical community regarding these issues, no meaningful risk assessments for ETS exposures and quantifications of health effects can be made at this time (DOE 1987).

Several of the studies that have been conducted to address this controversial problem are discussed in Section 2.3.4.2, "Health Effects". Against the evidence from these and some other epidemiological studies stands criticism of the methods, statistics, and data interpretation. Also there are several other studies with ambiguous or negative studies. Several of these other studies are listed in DOE (1987).

Over the past several months, the EPA has been reviewing the effects of ETS. In the past, the EPA has used previous estimates by private researchers on the damage caused by ETS. Such estimates have ranged from 12 to 5,200 lung cancer deaths annually in the United States and as many as 46,000 deaths overall, if illnesses such as heart disease and respiratory ailments are included. The findings of the EPA's review are in draft form, which have yet to be reviewed by the EPA's Scientific Advisory Board.

2.3.4.2 Health Effects

General Health Effects - The harmful effects of smoking on the smoker are well known and documented. However, health effects of chronic involuntary exposure of nonsmokers to ETS at concentrations that generally are well below recommended TLVs for the individual chemicals, are still controversial. Acute effects on susceptible individuals, mainly temporary irritation of the eyes and mucous membranes of the upper respiratory tract, and headaches, are generally recognized. In contrast, results of epidemiological studies linking involuntary exposure of ETS to an increased incidence of 1) cancer in nonsmoking spouses, 2) morbidity (especially respiratory diseases) in infants and children of smoking parents (especially smoking mothers), and 3) aggravation of symptoms in patients with cardiovascular diseases and COLD, are still heatedly debated. Even within the biomedical community, opinions vary widely. Based on statements from experts at recent workshops, the position of the majority of investigators in this field appears to be that the available evidence for significant health effects of involuntary chronic exposure to ETS

is ambiguous and incomplete. ETS health effects are considered minor and negligible, but this opinion is not universally shared. Almost all investigators do agree on the need for further studies, particularly in defining passive smoke exposure conditions (DOE 1987).

Quantitative Risk Estimates - In view of the difficulties of 1) making meaningful concentration measurements B(a)P standards for normalizing exposures occurring under widely varying conditions, 3) conducting "perfect" epidemiological studies, 4) developing a consensus regarding the interpretation of results of such studies, and 5) resolving the existing disagreements and controversy in the biomedical community regarding these issues, no meaningful risk assessments for ETS exposures and quantifications of health effects can be made at this time (DOE 1987).

Acute Health Effects - Many deleterious effects of tobacco smoke on the health of smokers have long been established beyond reasonable doubt and are generally recognized by the scientific and medical communities. However, considerable differences exist between active and passive exposure to tobacco smoke (exposure conditions and duration, quality and quantity of inhaled combustion products). Therefore, unqualified extrapolation from the health effects of active smoking to those of passive smoking would not be a valid scientific approach. The extrapolation would also be very tenuous when it is realized that those most heavily exposed to ETS are the smokers themselves (DOE 1987).

Measurable quantities of physiologically active smoke components (e.g., CO, nicotine and its metabolite cotinine) are absorbed by involuntary smokers. Many nonsmokers are bothered by tobacco smoke (National Clearinghouse for Smoking and Health 1975, as cited in DOE 1987) and/or experience irritation of the eyes and of the nasopharyngeal mucosa, headache, and cough (Speer 1968; Barad 1979; Weber et al. 1976 1979; Hugod et al. 1978; Johansson 1976; Johansson and Ronge 1965, all as cited in DOE 1987). Age and sensitivity to tobacco smoke components may affect the acute reaction(s) of nonsmokers in addition to exposure conditions.

Several investigators reported acute physiological effects in the form of increased heart rate and blood pressure in healthy subjects exposed to cigarette smoke (Luquette et al. 1970; Rummel et al. 1975, as cited in DOE 1987), and small decreased in maximal aerobic capacity, exercise time to exhaustion, and maximal oxygen consumption (Aronow and Cassidy 1975; Gliner et al. 1975; Raven et al. 1974, all as cited in DOE 1987). However, these effects were minor and transitory and, therefore, probably inconsequential. There were no effects on ventilatory lung functions such as lung volume, maximal expiratory flow volume, single-breath nitrogen washout, submaximal exercise (Pimm et al. 1978; Gliner et al. 1975, as cited in DOE/BPA 1978) and on lung functions during intermittent bicycle ergometer performance (Shephard et al. 1979, as cited in DOE 1987).

Chronic Health Effects - Of greater concern than the nuisance and/or transient acute effects are the potentially more serious chronic health effects of passive smoke exposure. Observations in recent years have focused concern mainly on three areas (DOE 1987):

- effects of chronic exposure to ETS on respiratory functions in infants and children
- effects of chronic exposure to ETS on patients with predisposing diseases
- effects of chronic exposure to ETS on the development of malignant tumors

Effects on Respiratory Functions of Infants and Children - Colley (1974), as cited in DOE (1987), observed a higher incidence of respiratory illness in children with smoking parents. However, this might have been an indirect effect of ETS because of an even stronger relationship between cough and mucus production in the smoking parents, resulting in greater disease-spreading capacity of these parents, and respiratory infections in their children. Bland et al. (1978), as cited in DOE (1987), described similar findings. In another study, Colley et al. (1974) and Leader et al. (1976), as cited in DOE (1987), investigated the incidence of bronchitis and pneumonia in 2,205 children during the first 5 years of life. The authors found a cause-effect relationship between these incidences and parental smoking habits

(number of parents smoking; number of cigarettes smoked), but only for the first year of life. However, in a different paper, Cederlof and Colley (1974), as cited in DOE (1987), pointed out that, "when parents' respiratory symptoms were taken into account, exposure of the child to cigarette smoke generated by the parents' smoking had little if any effect upon the child's respiratory symptoms." Lebowitz and Burrows (1976) and Schilling et al. (1977), as cited in DOE (1987), also came to the conclusion that the effects of parental smoking on children were insignificant when parental symptoms were taken into account.

On the other hand, Rentakallio (1978a,b), as cited in DOE (1987), in a study with 12,000 Finnish children, found a significantly ($P<0.001$) higher morbidity, and increased ($P<0.001$) and longer hospitalization, mostly from respiratory diseases, in children of smoking mothers. This increased morbidity manifested itself during the first 5 years of life and was most pronounced during the first year of life. Harlap and Davies (1974), as cited in DOE (1987), reported a dose-response relationship between maternal smoking and hospital admissions of infants for bronchitis and pneumonia, but only between the sixth and ninth months of life. Tager et al. (1976, 1979, 1983), as cited in DOE (1987), described a decline in expiratory flow rates in children as a function of the number of parents smoking and the number of cigarettes smoked. Weiss et al. (1980), as cited in DOE (1987), observed a significant linear relationship between parental smoking and persistent wheezing and decreased mean forced midexpiratory flow. Ware et al. (1984), as cited in DOE (1987), found that maternal cigarette smoking was associated with increases of 20 to 35% in the incidences of eight respiratory illnesses and symptoms investigated at two successive annual examinations of 10,106 white children living in six cities. Paternal smoking was associated with smaller but still substantial increases. Illness and symptom incidences were linearly related to the number of cigarettes smoked by the child's mother, and were higher for children of current smokers than for children of ex-smokers. The association between maternal smoking status and childhood respiratory illnesses and symptoms wee reduced, but not eliminated, by adjustment for parental illness history. Levels of forced expiratory volume in 1 second (FEV_1) were significantly lower for children of current smokers that for

children of nonsmokers at both examinations, and highest for children of ex-smokers. Levels of forced vital capacity (FVC) were lower for children of nonsmokers than for children of current smokers at both examinations, but the difference was statistically significant only at the first examination. Both the increase in mean FVC and the decrease in mean FEV_1 among children of current smokers were linearly related to daily cigarette consumption. None of the respiratory illnesses and symptoms studies were significantly associated with exposure to gas cooking in the child's home. The results suggest a causal effect of sidestream cigarette smoke on increased respiratory illness and reduced FEV_1 values in preadolescent children (DOE 1987).

Gardner et al. (1984), as cited in DOE (1987), monitored 131 infants from birth through the first year of life to investigate effects of social and familial factors on respiratory diseases. The authors found a significant relationship between pneumonia and parental smoking, especially smoking by mothers at home. Analysis of questionnaire data and lung function tests by Tashkin et al. (1984), as cited in DOE (1987), on children revealed that passive exposure to maternal smoking affected airways of boys aged 7 to 11. A total of 971 white, non-hispanic, nonsmoking, nonasthmatic children were divided into three categories related to parental smoking status: 1) at least mother smokes, 2) only father smokes, and 3) neither parent smokes. Prediction equations for several indices of forced expired volume and flow were derived separately for boys and girls 7 to 17 years of age. Analysis of variance was performed separately on younger (aged 7 to 11) and older (12 to 17) children of each sex. Among younger male children, residual values were significantly lower in the maternal smoking category than in the other two household categories for maximal flow after exhalation of 25% of FVC; no differences were noted between the paternal smoking only and nonsmoking household categories. The differences between maternal and paternal smoking effects are probably explained by the longer daily exposure of children of nonemployed smoking mothers. A trend toward similar results was found in older male children. Among females, forced expiratory flow during the middle half of the FVC and maximal flow after exhalation of 75% of FVC were significantly lower in relation to maternal smoking in older children only. Analysis of Variance (ANOVA) revealed no decrement in lung function in

relation to passive smoking among children with asthma or bronchitis (n=138). Chi-square analysis showed no differences in the frequency of respiratory symptoms among children in the different passive exposure categories. The authors noted that the apparent effect on lung function of heavy exposed older girls is more likely to be confounded by selective under-reporting of active smoking (DOE 1987).

A review by Weiss et al. (1983); as cited in DOE 1987, reflects the current state of knowledge on the effects of chronic exposure to ETS in infants and children and in patients with predisposing diseases. The authors point to the relatively large body of data relating parental (particularly maternal) cigarette smoking to the occurrence of both acute respiratory illnesses and chronic respiratory symptoms in children. The effect appears to be greatest early in life and cannot be separated from in utero exposure. While data liking parental smoking to lower levels of pulmonary function are all cross-sectional and less conclusive, the magnitude of the direct effect of passive smoke exposure is likely to be relatively small (from 1 to 5% reduction in maximally obtained lung-function level in exposed children). The important effects of passive smoke exposure in childhood are twofold: the slight reduction n pulmonary function may predispose an individual to increased risks from environmental agents later in life; and having a parent who smokes substantially increased the likelihood that a child will become a smoker. Involuntary smokers are exposed to a quantitatively smaller and qualitatively different (but not necessarily less hazardous) smoke exposure than active smokers. Quantitation of exposure is particularly difficult in physiological and epidemiological studies. Acute physiological studies have documented minimal physiological changes in healthy subjects. However, individuals with heart or lung disease may be affected more. Data on adults are insufficient to allow a quantitative estimate of effects. The authors state, as many others have done, that further research is needed to confirm findings on passive smoking (DOE 1987).

Reviewing the link between parental smoking habits and respiratory symptoms in offspring, Holt and Turner (1984), as cited in DOE (1987), conclude that infants whose parents smoke experience a greater frequency of

respiratory infections, particularly in the first year of life. Increased wheezing, exacerbation of asthma, and reduced lung function in older children have also been reported. These effects appear to be more strongly related to maternal than to paternal smoking, especially when infants are involved (DOE 1987).

According to Bake (1984), as cited in DOE (1987), data strongly suggest an association between exposure to ETS in the home and a small reduction in ventilatory lung function in adults exposed more than 15 to 20 years. However, the potential magnitude of ETS exposure is uncertain because no study has considered the combined effects of various related elements. Bake sees indications that, all other factors being equal, exposure to ETS would probably also affect lung function in children. However, a review of various studies show uncertainty regarding parental smoking effects and only minimal consequences in children (DOE 1987).

Effects on Patients with Predisposing Diseases - There is evidence that ETS-induced COHb levels can reduce the exercise duration required to provoke angina pectoris in patients with coronary artery disease (Aronow and Isbell 1973; Aronow et al. 1974a,b; Anderson et al. 1973, all as cited in DOE 1987).

Patients with COLD experienced a reduction in mean exercise time until onset of marked dyspnea from 219 to 147 seconds. However, expected effects on blood pressure, heart rate, arterial pO_2/pCO_2 or pH were not detected, thus leaving unresolved the mechanism of early dyspnea induction (Aronow et al. 1977, as cited in DOE 1987).

It is also evident that allergic individuals can be more sensitive to many environmental pollutants/irritants, including tobacco smoke, but it remains unresolved whether this constitutes a true allergy following a specific sensitization to cigarette smoke (Taylor 1974, as cited in DOE 1987). Parental smoking is also a significant exacerbating factor in childhood asthma (O'Connel and Logan 1974, as cited in DOE 1987).

Effect on Development of Malignant Tumors - Of greatest concern is the question of whether or not chronic exposure to ETS presents a (lung) cancer

risk to exposed nonsmokers. The most frequently cited and debated epidemiological studies are those of Hirayama (1981) and of Trichopoulos et al. (1981), as cited in DOE (1987).

From 1966 to 1979, Hirayama (1981), as cited in DOE (1987), investigated mortality records in 29 health center districts, studied 91,540 nonsmoking wives 40 years of age or older, and assessed standardized mortality rates for lung cancer according to the smoking habits of their husbands. He found that wives of former smokers and of smokers of fewer than 20 cigarettes per day had a relative risk factor, or risk ratio (RR), of 1.6. Wives of heavy (more than 20 cigarettes per day) smokers had a relative risk of 2.1. No significant effects on the incidence of other forms of cancer or other diseases were apparent at that time, but there was a statistically insignificant tendency toward a higher risk of developing emphysema and asthma in the nonsmoking wives of heavy smokers. Updating his findings 2 years later, Hirayama (1983), as cited in DOE (1987), noted that of 429 women who died from lung cancer during 16 years of follow-up (1966 to 1981), 303 had been nonsmokers; 200 of these deaths occurred among the 91540 nonsmoking married women whose husband's smoking habits were known. Standardized mortality ratios of lung cancer in nonsmoking women were 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were nonsmokers, ex-smokers, and daily smokers of more than less than 15, 15 - 19, and more than 19 cigarettes per day, respectively. Based on the extent of the husbands' smoking, trends of increased risk among nonsmoking women were similar for different age groups, occupational groups, and duration of observation. Smoking by the husband was the only factor found to increase the risk of lung cancer in nonsmoking wives. A significantly increased risk of cancer of the paranasal sinuses in nonsmoking wives, related to the amount of husbands' smoking, was also observed (DOE 1987).

Trichopoulos et al. (1981), as cited in DOE (1987), questioned 51 women on lung cancer and 163 other hospital patients in Greece on their and their husbands' smoking habits. Forty of the lung cancer patients and 149 of the other patients were nonsmokers. Among the nonsmoking women, there was a statistically significant difference between the cancer patients and the other patients with respect to their husband's smoking habits. The relative risk of

lung cancer associated with a smoking husband was 2.4 for smokers of less than 20 cigarettes per day and 3.4 for heavier smokers. The authors updated their findings 2 years later (Trichopoulos et al. 1983, as cited in DOE 1987). While they recognized that their study (1981) had been criticized for the small number of subjects, lack of histological confirmation, and hospital differences, the authors point out that there were twice the number of cases and 50% more controls at the conclusion of the study, with the results remaining substantially the same. For a total of 77 cases and 225 nonsmoking female controls, the RR of lung cancer for never-married women or those with husbands who were nonsmokers or ex-smokers for 5 to 20 years (24 cases, 109 controls) was 1.0; for spouses of men who were ex-smokers for less than 5 years (15 cases, 35 controls), the RR was 1.9; for spouses of men currently smoking for 1 to 20 cigarettes per day (24 cases, 56 controls), the RR was 2.4; and for women whose husbands currently smoked 21 or more cigarettes per day (14 cases, 25 controls), the RR was 3.4. The authors comment that the relatively low RR and the many potential sources of bias preclude any single study from providing conclusive evidence, but that the similarity of results from different studies in different populations will permit valid conclusions regarding effects of ETS on lung cancer incidence in nonsmokers (DOE 1987).

Correa et al. (1983), as cited in DOE (1987), investigated the smoking habits of parents and spouses in a case-control study involving 1,338 lung cancer patients and 1,393 control subjects in Louisiana. Nonsmokers married to heavy smokers had an increased risk of lung cancer, as did subjects who had mothers who smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables, which indicated active smoking. The authors state that it is not clear whether the results reflect a biological effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking (DOE 1987).

In a German Study (Knoth et al. 1983, as cited in DOE 1987) of 792 patients of both sexes with brochogenic carcinoma, there were 59 female patients, 39 of them nonsmokers. Of the nonsmoking female patients, 61.5% had lived with smokers, triple the number anticipated based on the smoking habits

of men in their respective age groups. Neither occupational exposure nor hereditary factors accounted for the excess. Hence, exposure to ETS may be the most obvious interpretation of the high percentage of nonsmokers among the female patients with bronchogenic carcinoma. In addition, the percentage of squamous cell and small-cell carcinoma, the typical smokers' carcinomas, among the nonsmoking wives (66.6%) was not significantly lower than that among the females who smoked (80%) (DOE 1987).

Gillis et al. (1984), as cited in DOE (1987), analyzed ETS exposure, smoking and mortality rates for 8,128 subjects who attended a multiphasic screening unit. The subjects were between 45 and 64 years of age, and 97% were male/female partnerships. The prevalence of infected mucus, persistent mucus, dyspnea, and hypersecretion was slightly higher in ETS-exposed nonsmokers than in controls (nonexposed nonsmokers). Male lung cancer mortality was 4/10,000 in controls, 13/10,000 for ETS-exposed nonsmokers, 22/10,000 in smokers, and 24/10,000 in ETS-exposed smokers. No such trend was noted among the women. Overall myocardial infarction mortality was slightly higher in the ETS-exposed group, but no other differences in smoking-related mortality were found (DOE 1987).

Preliminary results of a case-control study by Sandler et al. (1985); as cited in DOE 1987) indicate that the overall cancer risk for passive smokers rose steadily and significantly with the number of household members who smoked. These findings are based on 369 patients and 409 control subjects (DOE 1987).

Miller (1984a), as cited in DOE (1987), in an epidemiology study conducted from 1975 to 1976 in Erie County, Pennsylvania, observed a significantly increased cancer mortality in nonemployed wives chronically exposed to ETS compared to nonemployed wives with little or no ETS exposure. Several errors in Miller's first publication were subsequently corrected (Miller 1984b, as cited in DOE 1987). The corrections did not significantly change the originally reported results.

Lawrence and Paulson (1983), as cited in DOE (1987), voiced interesting thoughts on cancer risk from low concentrations of ETS. They state that one method for establishing safe dose levels for such low ETS exposure is via

extrapolation of data from high-dose experiments. A linear extrapolation technique was applied to data from a 1954 prospective epidemiological study on deaths from lung and bronchial cancer among 291,000 veterans. Most smokers had begun smoking before the age of 25. Mortality was observed for 8.5 years after questioning the participants of the study. To simulate conditions in animal experiments, the analysis was restricted to data on respondents who never quit smoking and smoked for most of their adult lives. The extrapolation yielded a practically safe dose of 0.005 cigarettes/day, a level of environmental exposure that was exceeded in nonsmokers in nearly all cases. The authors observed that there is a large discrepancy between the low levels to which involuntary exposure to other carcinogens are increasingly regulated and controlled, and levels of passive exposure to cigarette smoke apparently considered acceptable. Because there is no proof that mainstream smoke is more hazardous than sidestream smoke, the extrapolation may be questionable. Also, linear extrapolation may not be the most conservative method (DOE 1987).

Against the evidence from these and some other epidemiological studies stands criticism of their methods, statistics, and data interpretation. Also, there are several other studies with ambiguous or negative studies. Several of these other studies are listed in DOE (1987).

2.3.5 Nitrogen Oxides

Oxides of nitrogen technically include NO, NO_2, nitrous oxide (N_2O), nitrogen trioxide (OONO), dinitrogen trioxide (N_2O_3), dinitrogen tetraoxide (N_2O_4), and dinitrogen pentoxide (N_2O_5). All of these compounds, as well as their secondary reaction products (e.g., nitrate aerosols) can affect human health. However, only NO and NO_2 are of practical importance as indoor air pollutants. Both compounds are produced from atmospheric nitrogen and oxygen in the course of the combustion process. The biological effects of NO_2 have been extensively studied during the past 30 years (DOE 1987).

NO_2 Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of

deleterious effects during a lifetime. The RfDo for NO_2 is 1E+0 mg/kg/day, with methemoglobinemia as the critical effect. The NOAEL is 10 ppm of drinking water. The LOAEL is 11-20 ppm (IRIS 1990).

This is an epidemiologic study on the formation of methemoglobinemia in infants who routinely consumed milk prepared from water containing various levels of nitrate. The study analyzed all cases of infant methemoglobinemia occurring in 37 United States states irrespective of date of occurrence or type of water supply. Nitrate (nitrogen) content ranged from 10 ppm to > 100 ppm. No incidences of methemoglobinemia were found to occur in drinking water containing less than 10 ppm nitrate (nitrogen). Therefore, a NOAEL of 10 ppm was derived. Several more recent epidemiologic studies support Walton's (1951), as cited in IRIS (1990), threshold for infant methemoglobinemia (NAS 1977; Winton 1971; Calabrese 1978, as cited in IRIS (1990).

The confidence in the RfDo is high. Confidence in the study is high because the NOEL is determined in the known sensitive human population. The database contains several recent supporting epidemiologic studies for the critical effect in the sensitive population (infants); therefore, a high confidence rating is given to the database. High confidence in the RfDo follows (IRIS 1990).

Currently there is no RfDi for NO_2. A risk assessment for NO_2 is under review by an EPA work group.

General Health Effects - There are basically three mechanisms of NO_x toxicity (DOE 1985, as cited in DOE 1987):

- Formation of highly reactive free radicals by oxidation of unsaturated fatty acids such as lecithin, a major component of cell membranes. Free radicals can 1) interfere with the chemistry and physiology of these membranes; 2) change structural proteins (e.g., elastin and collagen), thereby affecting the structural and mechanical integrity of lung tissue; and 3) react with Hb to form methemoglobin, thereby reducing the O_2-carrying capacity of the blood.
- Formation of highly ionized acid in the respiratory tract, which probably accounts for the acute irritation.
- Formation of potentially carcinogenic nitrosamines in the respiratory tract and especially in the acid milieu of the stomach, which might also contribute to liver dysfunction.

Nitric oxide is relatively nontoxic at normally encountered concentrations, but persists longer indoors than outside and has a longer indoor half-life than NO_2. Therefore, it cannot be ignored as an indoor air pollutant. Nitrogen dioxide affects the respiratory system not unlike ozone (O_3), albeit to a lesser degree (DOE 1987).

Both NO and NO_2 bind to Hb to form methemoglobin at similar rates, thus reducing the O_2-carrying capacity of the blood. It can be assumed that NO at 3 ppm is physiologically similar to 10 to 15 ppm of CO (Case et al. 1979; as cited in DOE 1987). Nitric oxice and NO_2 can change heme by causing polycythemia. They can also cause leukocytosis and other hematological changes, and vascular membrane lesions that can result in edema (NRC 1977, as cited in DOE 1987). Nitrogen dioxide decreases the activity of acetylcholinesterase in erythrocyte membranes, increases the activity of glucose-6-phosphate dehydrogenase, increases peroxidized erythrocyte lipids, and causes significant decreases in Hb and hematocrit values (Posin et al. 1978, as cited in DOE 1987).

Oxides of nitrogen can cause acute and chronic changes in the small airways and lungs. A 4-hour exposure of rats to 2 ppm induced nonciliated cells of the small airways to differentiate into ciliated cells and mature Clara cells (Evans and Freeman 1980, as cited in DOE 1987). It also caused a proliferation of alveolar Type II cells while destroying epithelial Type I cells. Gardner et al. (1979); as cited in DOE 1987, observed significantly increased mortality in animals challenged with bacterial aerosols following NO_2 exposure to 1.5 ppm for 2 hours or to 0.5 ppm for 2 weeks.

In healthy humans, respiratory functions generally are not affected at levels of 1.5 ppm NO_2 or below. However, sensitive individuals can experience respiratory tract irritation at 0.5 ppm NO_2. An overview of effects of short-term NO_2 exposures (<3 hours) in healthy and sensitive individuals is provided in Figure 2.1.

Children and people with asthma, chronic bronchitis, and emphysema appear to be the most sensitive population groups (Table 2.12). People with

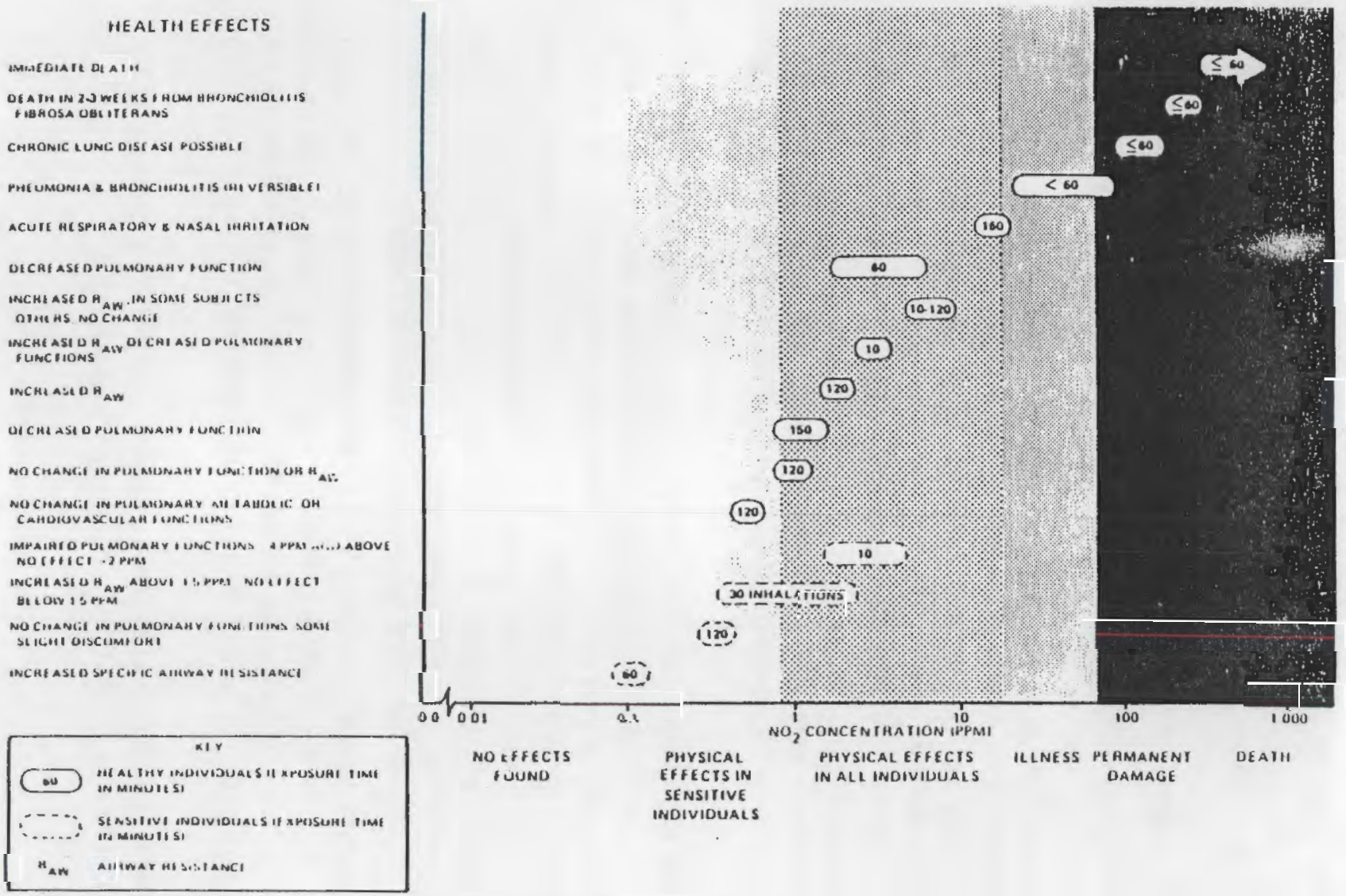

FIGURE 2.1. Effects of Short-Term Exposures to Nitrogen Dioxide in Healthy and Sensitive Humans
SOURCE: U.S. DOE (1985), pp. 2-5, as cited in DOE (01987)

TABLE 2.12. Population Groups Sensitive to NO_2

Sensitive Group:	Children
Supporting Evidence:	Children under age 2 exhibit increased prevalence of respiratory infection when living in homes with gas stoves. Children up to age 11 exhibited increased prevalence of respiratory infections when living in gas-stove homes.
Supporting References:	Speizer et al. 1980; Melia et al. 1979
Population Estimates:	Age 0-5, 17.2 million[(a)]; age 5-13, 36.6 million[(a)]
Sensitive Group:	Asthmatics
Supporting Evidence:	Asthmatics reacted to lower levels of NO_2 than normal subjects in controlled human exposure studies.
Supporting References:	Kerr et al. 1979; Orehek et al. 1976
Population Estimates:	6.0 million[(a)]
Sensitive Group:	Chronic bronchitics
Supporting Evidence:	Chronic bronchitics reacted to low levels of NO_2 in controlled human exposure studies.
Supporting References:	Kerr et al. 1979; Von Nieding et al. 1971, 1973
Population Estimates:	6.5 million[(a)]
Sensitive Group:	Emphysematics
Supporting Evidence:	Emphysematics have significantly impaired respiratory systems. Because studies have shown that NO_2 impairs respiration by increasing airway resistance, it is reasonable to assume that emphysematics may be sensitive to NO_2.
Supporting References:	Von Nieding et al. 1971; Beil and Ulmer 1976; Orehek et al. 1976
Population Estimates:	1.3 million[(a)]

TABLE 2.12. (contd)

Sensitive Group:	Persons with tuberculosis, pneumonia, pleurisy, hay fever or other allergies.
Supporting Evidence:	Studies have shown that NO_2 increases airway resistance. Persons who have or have had these conditions may be sufficiently impaired to be sensitive to low levels of NO_2.
Supporting References:	Von Nieding et al. 1971; Beil and Ulmer 1976; Orehek et al. 1976.
Population Estimates:	Unknown
Sensitive Group:	Persons with liver, blood or hormonal disorders.
Supporting Evidence:	NO_2 induces changes in liver drug metabolism, lung hormone metabolism, and blood biochemistry.
Supporting References:	Menzel 1980; Posin et al. 1978
Population Estimates:	Unknown

(a) 1970 U.S. Bureau of Census and 1970 U.S. National Health Survey. All subgroups listed are not necessarily sensitive to NO_2 exposure at low levels.

SOURCE: U.S. Environmental Protection Agency 1982a; as cited in DOE 1987. (Table by T. Namekata, Battelle Human Affairs Research Centers, Seattle, Washington)

hay fever, liver, hematological, or homonal disorders can also be affected by low levels of NO_2, but exposure data for the latter groups are too sparse for recommending specific exposure limits (DOE 1987).

There is no convincing evidence of potentiating effects of NO_2 exposure in the presence of other pollutants such as O_3, CO, or SO_2 (Table 2.13). Increased sensitivity to the bronchoconstrictor acetylcholine following exposure to a mixture of NO_2, O_2, and SO_2, as reported by Von Nieding et al. (1973), as cited in DOE (1987), is difficult to interpret because of 1) the

TABLE 2.13. Effects on Pulmonary Function in Subjects Exposed to NO_2 and Other Pollutants

Concentration (ppm):	0.05 NO_2 + 0.11 SO_2 + 0.025 O_3
Exposure Duration:	2 hours
Study Population:	11 healthy subjects
Reported Effects:	Increased sensitivity to bronchoconstrictor as shown by increases in R_{aw}. No effect on A_2DO_2 or R_{aw} without bronchoconstrictor.
References:	Von Nieding et al. 1973

Concentration (ppm):	0.50 O_3; 0.50 O_3 + 0.29 NO_2; 0.50 O_3 + 0.29 NO_2 + 30 CO
Exposure Duration:	4 hours
Study Population:	4 healthy male subjects
Reported Effects:	Minimal change in pulmonary function caused by O_3 alone. Effects not caused by NO_2 or CO.
References:	Hackney et al. 1975

Concentration (ppm):	0.25 O_3; 0.25 O_3 + 0.29 NO_2; 0.25 O_3 + 0.29 NO_2 + 30 CO
Exposure Duration:	2 hours
Study Population:	7 male subjects; some believed to be unusually reactive to irritants
Reported Effects:	Minimal change in pulmonary function caused by O_3 alone. Effects Not increased by NO_2 or CO.
References:	Hackney et al. 1975.

Concentration (ppm):	50 CO + 5 SO_2; 4.8 NO_2 + 50 CO + 5 SO_2
Exposure Duration:	---
Study Population:	3 subjects
Reported Effects:	Increased dust retention from 50 to 76% after NO_2 was added to air containing SO_2 and CO.
References:	Schlipkoter and Brockhaus 1963

TABLE 2.13. (contd)

Concentration (PPM):	0.5 $)_3$; 0.5 O_3 + 0.5 NO_2 under the following conditions: 1) 25°C, 45% relative humidity (RH); 2) 30°C, 85% RH: 3) 35°C, 40% RH; 4) 40°C, 50% RH.
Exposure Duration:	Rest, 60 minutes; exercise, 30 minutes, rest, 30 minutes
Study Population:	8 young adults
Reported Effects:	Response found only for O_3; no greater than additive effect or interaction between O_3 and NO_2 was observed.
References:	Horvath and Folinsbee 1979

(Table by T. Namekata, Battelle Human Affairs Research Centers, Seattle, Washington)

uncertain health significance of altered sensitivity to bronchoconstrictors in healthy or sensitive subjects, 2) uncertainties from methodological differences between their techniques and those used by other investigators, and 3) the lack of confirmation of the findings by other investigators (DOE 1987).

Community epidemiological studies of NO_2 are summarized in Table 2.14. Because of methodological problems (i.e., use of Jacob-Hochheiser method) with the studies performed by Shy et al. (1970a,b) and Pearlman et al. (1971), both as cited in DOE (1987), in Chattanooga, a quantitative assessment of the health effects reported to be associated with NO_2 levels from these investigators is not possible. In addition, it is difficult to distinguish between health effects caused by NO_2 and effects caused by other pollutants identified in the ambient air (e.g., O_3, particulates, SO_2) at the time of the studies. These problems limit the usefulness of these studies for standard-setting purposes (DOE 1987).

TABLE 2.14. Effects of NO_2 on Pulmonary Function in Community Epidemiological Studies

Concentration (ppm):	Median hourly 0.07 NO_2, 0.15 O_x; 0.35 NO_2. 0.02 O_x
Study Population:	205 office workers in L.A.; 439 office workers in San Francisco
Reported Effects:	No differences in most tests. Smokers in both cities showed greater changes in pulmonary function than nonsmokers.
References:	Linn et al. 1976.
Concentration (ppm):	High exposure area: 24-hour highs--0.055 and 0.035 NO_2; 1-hour mean--0.14 to 0.30 NO_2. Low exposure area: 1-hour mean--0.06 to 0.09 NO_2.
Study Population:	128 traffic policemen in urban Boston and 140 patrol officers in nearby suburbs
Reported Effects:	No difference in various pulmonary function tests
References:	Speizer and Ferris 1973; Burgess et al. 1973
Concentration (ppm):	High exposure group: estimates 1-hour maximum--0.25 to 0.51 NO_2. Annual mean 24-hour--0.051 NO_2. Low exposure group: estimated 1-hour maximum--0.12 to 0.23 NO_2. Annual mean 24-hour--0.01 NO_2.
Study Population:	Adult nonsmokers in L.A.
Reported Effects:	No differences found in several ventilatory measurements, including spirometry and flow-volume curves.
References:	Cohen et al. 1972
Concentration (ppm):	1-hour concentration at time of testing (1:00 p.m.) 0.02 to 0.19 NO_2
Study Population:	20 children 11 years of age

TABLE 2.14. (contd)

Reported Effects:	During warmer part of year, NO_2, SO_2, and TSP significantly correlated with $\dot{V}_{max}$ at 25 and 50% FVC specific airway conductance. Significant correlation between each of four pollutants (NO_2, NO, SO_2, and TSP) and $\dot{V}_{max}$ at 25 and 50% FVC; but no clear delineation of specific pollutant concentrations at which effects occur.
References:	Kagawa and Toyama 1975

(a) Table by T. Namekata, Battelle Human Affairs Research Centers, Seattle, Washington.

Though some pulmonary-function effects related to NO_2 concentrations are shown in the investigation by Kagawa and Toyama (1975), as cited in DOE (1987), the results suggest that these effects were caused by a complex mixture of pollutants. Inadequate characterization of exposure to NO_2 prevents firm conclusions about the relationship between NO_2 exposure and resulting health effects (DOE 1987).

The findings of Shy et al. (1970a,b), Pearlman et al. (1971), and Kagawa and Toyama (1975), all as cited in DOE (1987), are not inconsistent with the hypothesis that NO_2, in a complex mixture with other pollutants in the ambient air, adversely affects respiratory function and illness in children. However, these findings neither provide clear evidence for a positive association between health effects and exposure to ambient NO_2, nor do they refute such an association. Little or no evidence of health effects at ambient NO_2 concentrations is provided by other community epidemiological studies (DOE 1987).

The community epidemiological studies cited and discussed above did not take into account exposure to, and the effects of, indoor air pollutants, such as NO_2 generated by the use of gas stoves. Results of community studies on effects associated with indoor NO_2 exposure involving gas stoves are summarized in Table 2.15. Major uncertainties in the studies by Melia et al. (1977, 1979) and Speizer et al. (1980), both as cited in DOE (1987), are the

TABLE 2.15. Community Studies of NO_2 Involving Gas Stoves[a]

Concentration (ppm):	95th percentile of 24-hour average in activity room: 0.02 to 0.06 (gas); 0.01 to 0.05 (electric). Frequent peaks in one home of 0.4 to 0.6 (gas). Maximum peak--1.0 (gas).
Study Population:	9,120 children, ages 6 to 10, six different cities, data also collected on history of illness before age 2.
Reported Effects[b]:	Significant association between history of serious respiratory illness before age 2 and use of gas stoves (P 0.01). Also, small but statistically significant decreases in pulmonary function (FEV_1 and FVC) in children from gas-stove homes.
References:	Speizer et al. 1980
Concentration (ppm):	NO_2 concentrations not measured at time of study.
Study Population:	2,554 children from homes using gas to cook compared to 3,204 children from homes using electricity, ages 6 to 11.
Reported Effects[b]:	Proportion of children with one or more respiratory symptoms or disease (bronchitis, day or night cough, morning cough, cold going to chest, wheeze asthma) increased in homes with gas- versus electric-stove homes (girls, P 0.10; boys, not significant) after controlling for confounding factors.
References:	Melia et al. 1977
Concentration (ppm):	NO_2 concentrations not measured in some homes studied for health effects.
Study Population:	4,827 children, ages 5 to 10
Reported Effects[b]:	Higher incidence of respiratory symptoms and disease associated with gas stoves (boys, P 0.02; girls, P 0.15) for residences in urban but not rural areas, after controlling for confounding factors.
References:	Melia et al. 1979

TABLE 2.15. (contd)

Concentration (ppm):	Kitchens (weekly average): 0.005 to 0.317 (gas) and 0.006 to 0.168 (electric). Bedrooms (weekly average): 0.004 to 0.169 (gas) and 0.003 to 0.037 (electric).
Study Population:	808 children, ages 6 to 7
Reported Effects[b]:	Higher incidence of respiratory illness in gas-stove homes (P 0.10). Prevalence not related to kitchen NO_2 levels, but increased with NO_2 levels in bedrooms of children in gas-stove homes. Lung function not related to NO_2 levels in kitchen or bedroom.
References:	Florey et al. 1979; Goldstein et al. 1979 (both are companion papers to Melia et al. 1979)
Concentration (ppm):	Sample of households (24-hour average): 0.005 to 0.11 (gas), 0 to 0.6 (electric) and 0.015 to 0.05 (outdoors)
Study Population:	128 children, ages 0 to 5; 346 children, ages 6 to 10; 421 children, ages 11 to 15
Reported Effects:	No significant difference in reported respiratory illness between homes with gas and electric stoves in children from birth to 12 years.
References:	Mitchell et al. 1974. See also Keller et al. 1979.
Concentration (ppm):	Sample of households same as reported above, but no new monitoring reported.
Study Population:	174 children under 12 years of age
Reported Effects[b]:	No evidence that cooking mode is associated with the incidence of acute respiratory illness.
References:	Keller et al. 1979
Concentration (ppm):	See above for monitoring.
Study Population:	Housewives cooking with gas stoves, compared to those cooking with electric stoves. 146 households.

TABLE 2.15. (contd)

Reported Effects[(b)]:	No evidence that cooking with gas is associated with an increase in respiratory disease.
References:	Keller et al. 1979
Concentration (ppm):	See above for monitoring.
Study Population:	Members of 441 households.
Reported Effects(b):	No significant difference in reported respiratory illness among adults in gas- versus electric-cooking homes.
References:	Mitchell et al. 1974. See also Keller et al. 1979.
Concentration (ppm):	Preliminary measurements, peak hourly, 0.25 to 0.50, maximum 1.0.
Study Population:	Housewives cooking with gas stoves, compared to those cooking with electric stoves.
Reported Effects[(b)]:	No increased respiratory illness associated with gas stove usage.
References:	U.S. Environmental Protection Agency 1974.

(a) Exposures in gas stove homes were to NO_2 plus other gas combustion products.
(b) Effects reported in published references are summarized here. However, EPA (1974), as cited in DOE, 1987, warns that considerable caution should be used in drawing firm conclusions from these studies.

(Table contributed by T. Namekata, Battelle Human Affairs Research Centers, Seattle, Washington)

Note: NO_2 TLV-TWA = 3 ppm or 6 mg/m^3 (ACGIH 1983)
EPA - recommended 1-hour average outdoor NO_2 standards <0.5 ppm or at range of 0.15 to 0.30 ppm, or annual standard in the range of 0.05 to 0.08 ppm (EPA 1982); as cited in DOE, 1987.

identification of agent(s) causing the reported health effects and, if NO_2, the exposure conditions (concentrations, average exposure time, and frequency) associated with the reported effects. Possible confounding factors that might be related to the increased incidence of respiratory illness and symptoms observed in children in gas-stove homes include humidity, socioeconomic status, and pollutants other than NO_2, such as CO and hydrogen cyanide, that are emitted during gas combustion. However, there is no evidence that gas stoves generate harmful concentrations of CO and hydrogen cyanide (HCN), and that these pollutants cause an increased incidence of respiratory diseases at typical indoor concentrations. The contribution, if any, of increased humidity to increased incidence of respiratory symptoms or diseases in buildings with gas stoves requires further investigation (DOE 1987).

Other factors, such as outdoor pollution levels and exposure to parental smoking, might have contributed to overall effects observed by Melia et al. and Speizer et al., as cited in DOE (1987). There is, however, no evidence in their studies to suggest that these factors differ for children living in electric versus gas-stove buildings (DOE 1987).

While animal studies provide some evidence that NO_2 impairs respiratory defense mechanisms, this evidence comes from studies conducted at considerably higher NO_2 exposure levels than those experienced in buildings with gas stoves (DOE 1987).

Speizer et al. (1980), as cited in DOE (1987), hypothesized that repeated peak values are probably the most important factor causing the effects observed in buildings with gas stoves. Their opinion is based, in part, on two facts: 1) there are no intermittent short-term (1/2 to 2 hours) NO_2 peak concentrations in buildings with electric stoves, and 2) long-term (24 hours or longer) concentrations in buildings with gas stoves are not markedly higher than in buildings with electric stoves (DOE 1987).

Effects of acute exposure to high NO_2 concentrations in humans, as summarized by the National Research Council (1977), as cited in DOE (1987), are shown in Table 2.16. The data in this table suggest a fatality threshold between 50 and 150 ppm, but exposure durations are not listed. A National

TABLE 2.16. Human Effects of Acute Exposure to High NO_2 Concentrations[a]

NO_2 Concentration mg/m³	ppm	Clinical Effect	Time Between Exposure and Termination of Effect
940	500	Acute pulmonary edema (fatal)	Within 48 hours
564	300	Bronchopneumonia (fatal)	2 to 10 days
282	150	Bronchiolitis fibrosa obliterans (fatal)	3 to 5 weeks
94	50	Bronchiolitis, focal pneumonitis (recovery)	6 to 8 weeks
47	25	Bronchitis, bronchopneumonia (recovery)	6 to 8 weeks

SOURCE: National Research Council 1977b, p. 269; as cited in DOE, 1987.

Research Council summary (1977), as cited in DOE (1987), of human responses to short-term NO_2 exposures without the presence of other air pollutants is shown in Table 2.17. The results of controlled exposure of mice, guinea pigs, hamsters, cats, and humans to NO_x, as reported by several investigators, are shown in Table 2.18 (DOE 1987).

Based on the best available information, EPA (1982a), as cited in DOE (1987), has recommended the following ambient air quality standards for NO_2:

- A 1-hour average NO_2 standard at some level below 0.5 ppm, or at the range of 0.15 ppm to 0.30 ppm, which would have to be met for a specified number of days in the calendar year.
- An annual standard in the range of 0.05 to 0.08 ppm as an alternative to the short-term standard.

An annual standard in the range of 0.05 to 0.08 ppm would appear to provide adequate protection against the potential and uncertain health effects that may be associated with exposure to short-term NO_2 levels. Such a standard could be used as a surrogate for a short-term standard. In addition, an

TABLE 2.17. Summary of Human Responses to Short-Term NO_2 Exposures Alone[a]

Effect	NO_2 Concentration mg/m^3	ppm	Time to Effect
Odor threshold	0.23	0.12	Immediate
Threshold for dark adaptation	0.14	0.075	Not reported
	0.50	0.26	Not reported
Increased airway resistance	1.3 to 3.8	0.7 to 2.0	20 minutes[b]
	3.0 to 3.8	1.6 to 2.0	15 minutes
	2.8	1.5	45 minutes[c]
	3.8	2.0	45 minutes[d]
	5.6	3.0	45 minutes[e]
	7.5 to 9.4	4.0 to 5.0	40 minutes[f]
	9.4	5.0	15 minutes
	11.3 to 75.2	6.0 to 40.0	5 minutes
	13.2 to 31.8	7.0 to 17.0	10 minutes[g]
Decreased pulmonary diffusing capacity	7.5 to 9.4	4.0 to 5.0	15 minutes
Increased alveolar arterial pO_2	9.4	5.0	25 minutes[h]
No change in sputum histamine concentration	0.9 to 6.6	0.5 to 3.0	45 minutes

(a) Reprinted from National Research Council 1977; as cited in DOE, 1987.
(b) Exposure lasted 10 minutes. Effect on flow resistance was observed 10 minutes after termination of exposure.
(c) Effect was produced at this concentration when normal subjects and those with chronic respiratory disease exercised during exposure.
(d) Effect occurred at rest in subjects with chronic respiratory disease.
(e) Effect occurred at rest in normal subjects.
(f) Exposure lasted 10 minutes. Maximal effect on flow resistance was observed 30 minutes later.
(g) Also failed to find increased flow resistance over the range of NO_2 exposures from 5.1 to 30.1 mg/m^3 (2.7 to 16.0 ppm).
(h) Effect occurred 10 minutes after termination of 15-minute exposure.

Note: NO_2 TLV-TWA = 3 ppm or 6 mg/m^3; TLV-STEL = 5 ppm or 10 mg/m^3 (ACGIH 1983). EPA-recommended 1-hour average outdoor NO_2 standard <0.5 ppm or at the range of 0.15 to 0.30 ppm, or annual standard in the range of 0.05 to 0.08 ppm (EPA 1982).

TABLE 2.18. Controlled Exposure to NO_2

Species: Mouse (6- to 8-weeks old)
Exposure: NO_2, 10 ppm, 2 hours/day, 5 days/week up to 30 weeks

Health Effects Observed: Lung damage, suppressed immune function with chronic exposure, enhanced immune reactivity with shorter exposures.

References: Holt et al. 1979

Species: Mouse (6- to 8-weeks old)
Exposure: NO, 10 ppm

Health Effects Observed: Paraseptal emphysema, suppressed immune function with chronic exposure, enhanced immune reactivity with shorter exposures.

References: Holt et al. 1979

Species: Mouse
Exposure: NO_2, 0.5 to 28 ppm, 6 months to 1 year

Health Effects Observed: Mortality after Streptococcus pyogenes, challenge mortality increased with increasing dose and exposure time.

References: Larsen et al. 1979

Species: Guinea pig
Exposure: NO_x, 1 ppm, 6 months

Health Effects Observed: Disturbed glycolysis, enhanced catabolic processes in brain, inhibited respiration, decreased brain aminotransferase activity, morphologic alterations in blood vessels.

References: Kosmider et al. 1974

Species: Human (asthma, N = 13; bronchitis, N = 7)
Exposure: NO_2, 0.5 ppm

Health Effects Observed: Lightness in chest, burning of eyes, headache, or dyspnea; pulmonary-function changes; nasal discharge

References: Kerr et al. 1979

TABLE 2.18. (contd)

Species: Human (asthma, N = 20)
Exposure: NO_2, 0.1 to 0.2 ppm

Health Effects Observed: Increased bronchoconstriction[a]

References: Orehek et al. 1979

Species: Cat
Exposure: NO_2, 80 ppm, 3 hours

Health Effects Observed: Diffuse alveolar damage

References: Langloss et al. 1977

Species: Guinea pig
Exposure: NO_2, 0.506 ppm; NO, 0.05 ppm; 122 days

Health Effects Observed: In lungs: decreased phosphatidylethanolamine, sphingomyelin, phosphatidylserine, phosphatidic acid, phosphatidylglycerol 3-phosphate; increased lysophosphatidylethanolamine.

References: Trzeciak et al. 1977

Species: Mouse
Exposure: NO_2, 1.5 to 5.0 ppm, 3 hours

Health Effects Observed: Mortality in mice challenged with Streptococcus aerosol significantly increased at 2.0 ppm and above.

References: Ehrlich et al. 1977

Species: Mouse
Exposure: NO_2, 0.5 ppm; 10, 12, and 14 days

Health Effects Observed: Average protein content of lungs significantly higher.

References: Sherwin and Layfield 1976

TABLE 2.18. (contd)

Species: Hamster
Exposure: NO_2, 30 ppm, 3 weeks

Health Effects Observed: Loss of body weight, increased dry lung weight, decreased lung elastin and collagen[b]

References: Kleinerman and Ip 1979

(a) Carbachol provocation.
(b) Elastin and collagen later returned to normal.

SOURCE: National Research Council 1981, p. 358; as cited in DOE, 1987.

annual standard would provide some, although unquantifiable, protection against possible adverse health effects from long-term exposure (DOE 1987).

The lack of scientifically demonstrated health effects in humans from NO_2 exposure in concentrations below 0.5 ppm could be interpreted to mean that there is no need for an NO_2 National Ambient Air Quality Standards (NAAQS). However, such an interpretation would ignore the cumulative evidence from controlled animal and human exposure studies, and community indoor studies, that strongly suggest that NO_2 can cause adverse health effects in sensitive population groups exposed to NO_2 levels at or near existing ambient levels (DOE 1987).

2.4 FIBERS

Mineral fibers include naturally occurring fibers, predominantly asbestos, and synthetic fibers, predominantly fiberglass and mineral (rock) wool, together with several other lesser-known species. Asbestos is a generic term referring to hydrated magnesium (with the exception of crocidolite) silicate fibers characterized by flexibility, strength, and resistance to fire and chemicals. These desirable characteristics have resulted in numerous industrial applications of asbestos, predominantly chrysotile. These applications include, but are not restricted to, thermal and acoustic insulation in buildings and ships; additives to construction and building (sheets, pipes,

panels, cement, plaster, etc.), friction (brake linings and clutches), coating, roofing and flooring materials; filters and gaskets; and textiles (e.g., fire-resistant clothing). Table 2.19 lists several types of fibers potentially encountered in public buildings (DOE 1987).

TABLE 2.19. Types of Fibers Potentially Encountered in Public Buildings

- Naturally Occurring Fibers
  - Asbestos
    - Serpentine
      - (1) Chrysotile - $Mg_3(Si_2O_3)(OH)_4$
    - Amphiboles
      - (1) Actinolite - $Ca_2(Mg,Fe)_5(Si_8O_{22})(OH)_2$
      - (2) Amosite - $(Fe,Mg)_7(Si_8O_{22})(OH)_2$
      - (3) Anthophyllite - $(Mg,Fe)_7(Si_8O_{22})(OH)_2$
      - (4) Crocidolite - $Na_2FeII_3FeIII_2(Si_8O_{22})(OH)_2$
      - (5) Tremolite - $Ca_2Mg_5(Si_8O_{22})(OH)_2$
  - Nonasbestos Fibers
    - Attapulgite (palygorskite)
    - Sepiolite (including meerschaum)
    - Noncommercial natural mineral fibers
- Synthetic Fibers
  - Vitreous Fibers
    - (1) Fibrous glass
    - (2) Mineral wool (rock wool, slag wool)
    - (3) Ceramic fibers
  - Other Synthetic Fibers
    - (1) Carbon fibers
    - (2) Miscellaneous others

2.4.1 Asbestos

Asbestos is the name applied to a group of six different minerals that occur naturally in the environment. The most common mineral type is white, but others may be blue, gray or brown. These minerals are made up of long, thin fibers that are somewhat similar to fiberglass. Asbestos fibers are very strong and are resistant to heat and chemicals. Because the fibers are so resistent to chemicals, they are also very stable in the environment; they do not evaporate into air or dissolve in water, and they are not broken down over time. Asbestos has a Hazard Rating of 3 (Sax and Lewis 1989).

2.4.1.1 Summary

The present EPA carcinogen assessment summary for asbestos may change in the near future pending the outcome of further review now being conducted by the CRAVE Work Group. The weight-of-evidence classification for asbestos is "A; human carcinogen." The basis is observation of increased mortality and incidence of lung cancer, mesotheliomas and gastrointestinal cancer in exposed workers. Animals studies by inhalation in two strains of rats showed similar findings for lung cancer and mesotheliomas. Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., greater than 10 μm length, developed benign polyps), and epidemiological data in this regard are inadequate (IRIS 1990).

The Inhalation Slope Factor for asbestos is 2.3E-1/fibers/mL. The Inhalation Unit Risk estimate for asbestos is 2.3E-1/fibers/mL. The extrapolation method used was additive risk of lung cancer and mesothelioma, using relative risk model for lung cancer and absolute risk model for mesothelioma.

2.4.1.2 Health Effects

Human Carcinogen - The present EPA carcinogen assessment summary for asbestos may change in the near future pending the outcome of further review now being conducted by the CRAVE Work Group. The weight-of-evidence classification for asbestos is "A; human carcinogen." The basis is observation of increased mortality and incidence of lung cancer, mesotheliomas and gastrointestinal cancer in exposed workers. Animals studies by inhalation in two strains of rats showed similar findings for lung cancer and mesotheliomas.

Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., greater than 10 μm length, developed benign polyps), and epidemiological data in this regard are inadequate (IRIS 1990).

Human Carcinogenicity Data - The human carcinogenicity data are considered sufficient. Numerous epidemiologic studies have reported an increased incidence of deaths due to cancer, primarily lung cancer and mesotheliomas associated with exposure to inhaled asbestos. Among 170 asbestos insulation workers in North Ireland followed for up to 26 years, an increased incidence of death was seen from all cancers (SMR=390), cancers of the lower respiratory tract and pleura (SMR=1760) (Elmes and Simpson 1971, as cited in IRIS (1990) and mesothelioma (7 cases). Exposure was not quantified.

Selikoff (1976) reported 59 cases of lung cancer and 31 cases of mesothelioma among 1249 asbestos insulation workers followed prospectively for 11 years. Exposure was not quantified. A retrospective cohort mortality study (Selikoff et al. 1979, as cited in IRIS 1990) of 17,800 U.S. and Canadian asbestos insulation workers for a 10-year period using best available information (autopsy, surgical, clinical) reported an increased incidence of cancer at all sites (319.7 expected vs. 995 observed, SMR=311) and cancer of the lung (105.6 expected vs. 486 observed, SMR=460). A modest increase in deaths from gastrointestinal cancer was reported with 175 deaths from mesothelioma (none expected). Years of exposure ranged from less than 10 to greater than or equal to 45. Levels of exposure were not quantified. In other epidemiologic studies, the increase for lung and pleural cancers has ranged from a low of 1.9 times the expected rate, in asbestos factory workers in England (Peto et al. 1977; as cited in IRIS 1990), to a high of 28 times the expected rate, in female asbestos textile workers in England (Newhouse et al. 1972, as cited in IRIS 1990). Other occupational studies have demonstrated asbestos exposure-related increases in lung cancer and mesothelioma in several industries including textile manufacturing, friction products manufacture, asbestos cement products, and in the mining and milling of asbestos. The studies used for the inhalation quantitative estimate of risk are listed in Table 2.20.

TABLE 2.20. Asbestos Dose-Response Data for Carcinogenicity, Inhalation Exposure

Human Data Occupational Group	Fiber Type	Exposure (fiber yr/mL)	Reported Average % Increase in Cancer/ fiber-yr/mL	Reference (as cited in IRIS 1990)
Lung Cancer:				
Textile Prod.	Predominantly Chrysotile	44	2.8	Dement et al. (1983)
Textile Prod.	Chrysotile	31	2.5	McDonald et al. (1983A)
Textile Prod.	Chrysotile	200	1.1	Peto (1980)
Textile Prod.	Chrysotile	51	1.4	McDonald et al. (1983b)
Friction Prod.	Chrysotile	32	0.058	Berry and Newhouse (1983)
Friction Prod.	Chrysotile	31	0.010	McDonald et al. (1984)
Insulation Products	Amosite	67	4.3	Seidman (1984)
Insulation Workers	Mixed (Chrysotile Crocidolite and Amosite)	300	0.75	Selikoff et al. (1979)
Asbestos Products		374	0.49	Henderson and Enterline (1979)
Cement Products		89 112	0.53 6.7	Weill et al. (1979) Finkelstein (1983)
Mesothelioma:				
Insulation Workers	Mixed	375	1.5E-6	Selikof et al. (1979); Peto et al. (1982)
Insulation	Amosite	400	1.0E-6	Seidman et al. (1979)
Textile Prod. Manufacturer	Chrysotile	67	3.2E-6	Peto (1980); Peto et al. (1982)
Cement Prod.	Mixed	108	1.2E-5	Finkelstein (1983)

A case-control study (Newhouse and Thompson 1965, as cited in IRIS 1990) of 83 patients with mesothelioma reported 52.6% had occupational exposure to asbestos or lived with asbestos workers compared with 11.8% of the controls. Of the remaining subjects, 30.6% of the mesothelioma cases lived within one-half mile of an asbestos factory compared with 7.6% of the controls (IRIS 1990).

The occurrence of pleural mesothelioma has been associated with the presence of asbestos fibers in water, fields and streets in a region of Turkey with very high environmental levels of naturally-occurring asbestos (Baris et al. 1979, as cited in IRIS 1990).

Kanarek et al. (1980), as cited in IRIS (1990), conducted an ecologic study of cancer deaths in 722 census tracts in the San Francisco Bay area, using cancer incidence data from the period of 1969-1971. Chrysotile asbestos concentrations in drinking water ranged from nondeductible to 3.6E+7 fibers/L. Statistically significant dose-related trends were reported for lung and peritoneal cancer in white males and for gall bladder, pancreatic and peritoneal cancer in white females. Weaker correlations were reported between asbestos levels and female esophageal, pleural and kidney cancer, and stomach cancer in both sexes. In an extension of this study, Conforti et al. (1981), as cited in IRIS (1990), included cancer incidence data from the period of 1969-1974. Statistically significant positive associations were found between asbestos concentration and cancer of the digestive organs in white females, cancer of the digestive tract in white males and esophageal and pancreatic and stomach cancer in both sexes. These associations appeared to be independent of socioeconomic status and occupational exposure to asbestos (IRIS 1990).

Marsh (1983), as cited in IRIS (1990), reviewed eight independent ecologic studies of asbestos in drinking water carried out in five geographic areas. It was concluded that even though one or more studies found an association between asbestos in water and cancer mortality (or incidence) from neoplasms of various organs, no individual study or aggregation of studies exists that would establish risk levels from ingested asbestos. Factors confounding the results of these studies include the possible underestimates

of occupational exposure to asbestos and the possible misclassification of peritoneal mesothelioma as GI cancer (IRIS 1990).

Polissar et al. (1984), as cited in IRIS (1990), carried out a case-control study which included better control for confounding variables at the individual level. The authors concluded that there was no convincing evidence for increased cancer risk from asbestos ingestion. At the present time, an important limitation of both the case-control and the ecologic studies is the short follow-up time relative to the long latent period for the appearance of tumors from asbestos exposure (IRIS 1990).

Animal Carcinogenicity Data - The animal carcinogenicity data are considered sufficient. There have been about 20 animal asbestos bioassays. The results of some of the more significant of these bioassays are provided in IRIS (1990). However, because the human carcinogenicity data is also considered sufficient, that information is not presented in this report.

Quantitative Estimate of Carcinogenic Risk - The Inhalation Slope Factor for asbestos is 2.3E-1/fibers/mL. The Inhalation Unit Risk estimate for asbestos is 2.3E-1/fibers/mL. The extrapolation method used was additive risk of lung cancer and mesothelioma, using relative risk model for lung cancer and absolute risk model for mesothelioma. The air concentrations at specified risk levels are as follows:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-4 fibers/mL
E-5 (1 in 100,000)	4E-5 fibers/mL
E-6 (1 in 1,000,000)	4E-6 fibers/mL

Inhalation Carcinogenicity Exposure Comments - Risks have been calculated for males and females according to smoking habits for a variety of exposure scenarios (EPA 1986, as cited in IRIS 1990). The unit risk value is calculated for the additive combined risk of lung cancer and mesothelioma, and is calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard to mesothelioma. The unit risk value is based on risks calculated using U.S. general population cancer rates and mortality patterns without consideration

of smoking habits. The risks associated with occupational exposure were adjusted to continuous exposure by applying a factor of 140 m^3 per 50 m^3 based on the assumption of 20 m^3/day for total ventilation and 10 m^3/8-hour workday in the occupational setting (IRIS 1990).

The unit risk is based on fiber counts made by phase contrast microscopy (PCM) and should not be applied directly to measurements by other analytical techniques. The unit risk uses PCM fibers because the measurements made in the occupational environment use this method. Many environmental monitoring measurements are reported in terms of fiber counts or mass as determined by transmission electron microscopy (TEM). PCM detects only fibers longer than 5 μm and greater than 0.4 μm in diameter, but TEM can detect much smaller fibers. TEM mass units are derived from TEM fiber counts. The correlation between PCM fiber counts and TEM mass measurements is very poor. Six data sets that include both measurements show a conversion between TEM mass and PCM fiber count that range from 5-150 ($\mu g/m^3$)/fibers/mL). The geometric mean of these results, 30 ($\mu g/m^3$)/fibers/mL), was adopted as a conversion factor (EPA 1986, as cited in IRIS 1990), but it should be realized that this value is highly uncertain. Likewise, the correlation between PCM and TEM fiber counts is very uncertain and no generally applicable conversion factor exists for these two measurements (IRIS 1990).

In some cases, TEM results are reported as numbers of fibers less than 5 μm long and of fibers longer than 5 μm. Comparison of PCM fiber counts and TEM counts of fibers greater than 5 μm show that the fraction of fibers detected by TEM that are also greater than 0.4μm in diameter (and detectable by PCM) varies from 22-53% (EPA 1986, as cited in IRIS 1990).

It should be understood that while TEM can be specific for asbestos, PCM is a nonspecific technique and will measure any fibrous material. Measurements by PCM that are made in conditions where other types of fibers may be present may not be reliable (IRIS 1990).

Some evidence suggests that different types of asbestos fibers vary in carcinogenic potency relative to one another and site specificity. It appears, for example, that the risk of mesothelioma is greater with exposure to crocidolite than with amosite or chrysotile exposure alone. This evidence

is limited by the lack of information on fiber exposure by mineral type. Other data indicate that differences in fiber size distribution and other process differences may contribute at least as much to the observed variation in risk as does the fiber type itself (IRIS 1990).

The unit risk should not be used if the air concentration exceeds 4E-2 $\mu g/m^3$, because above this concentration the slope factor may differ from that stated (IRIS 1990).

A large number of studies of occupationally exposed workers have conclusively demonstrated the relationship between asbestos exposure and lung cancer or mesothelioma. These results have been corroborated by animal studies using adequate numbers of animals. The quantitative estimate is limited by uncertainty in the exposure estimates, which results from a lack of data on early exposure in the occupational studies and the uncertainty of conversions between various analytical measurements for asbestos (IRIS 1990).

2.4.2 Synthetic Fibers

Biological effects of synthetic fibers have been reviewed by Hill (1977), Wagner et al. (1980), and Boatman et al. (1983), all as cited in DOE (1987). Some, but not all, of the animal studies show that synthetic fibers can result in pulmonary disease (Hill 1977; Bayliss et al. 1976; Stanton et al. 1977; Wright and Kuschner 1977; Boatman et al. 1983, all as cited in DOE 1987). Bayliss et al. (1976), as cited in DOE (1987), noted a significant excess of nonmalignant respiratory diseases in workers exposed to glass fibers. However, the evidence is not considered conclusive because of the number of studies showing no effects in humans or animals (Boatman et al. 1983, as cited in DOE 1987).

No epidemiological evidence exists at this time to link any of the synthetic fiber substitutes for asbestos to lung cancer. However, the use of these materials is relatively new. If they are indeed carcinogenic, and if cancers resulting from such exposures had latency periods similar to those induced by asbestos, these cancers would not manifest themselves epidemiologically until after the turn of the century (DOE 1987).

Lack of convincing evidence and reliable information at present does not permit a meaningful risk assessment of exposure to synthetic fibers in enclosed spaces (DOE 1987).

2.5 BIOGENIC PARTICLES

Biogenic indoor air pollutants include viruses; bacteria; fungi; algae; pollens and other plant-derived materials; protozoa; helminths; arthropods (particularly mites) and insects, their excretions and body fragments; bird feathers; dander of dogs and cats; and human epidermal scales. The dust in public buildings contain varying proportions of these materials. Some of these biogenic air pollutants originate outdoors and invade the buildings from there (e.g., pollens). Others originally migrated from outdoors but subsequently established themselves in the indoor environment (e.g., bacteria, fungi, arthropods, insects). Still others of them are generated indoors (e.g., human and pet danders).

2.5.1 Summary

In contrast to most of the chemical air pollutants (which may be toxic, carcinogenic or both), biogenic air contaminants can cause infectious diseases (e.g., colds, influenza, measles, chicken pox, smallpox, tuberculosis, Legionnaires' disease, pneumonia and several fungal diseases of the lung such as histoplasmosis, and aspergillosis). Biogenic air contaminants can cause allergic reactions such as allergic or vasomotor rhinitis (hay fever), asthma, and hypersensitivity pneumonitis (extrinsic allergic bronchioloalveolitis). Tissue changes caused by acute allergic reactions are reversible. However, if exposure to the offending allergen turns chronic, reversibility diminishes and eventually irreversible lesions will develop, often in the form of pulmonary fibrosis (lung scarring) (DOE 1987).

Little is known about indoor air concentrations of biogenic particles in public buildings and the effect of environmental changes on those concentrations. Systematic standardized and coordinated measurements would be required to provide an essential information base for developing guidelines for exposures to biogenic indoor air pollutants. The problem is complicated by the fact that, owing to the great diversity in physicochemical and biological

characteristics of biogenic particles, no single sampling or sample processing technique can cover the entire spectrum of biogenic particles. Therefore, no meaningful risk assessment of exposure to biogenic indoor air pollutants in public buildings can be made at this time.

2.5.2 Health Effects

General Health Effects - While harmful chemical air contaminants are toxic/carcinogenic, biogenic air pollutants usually show very low, if any, toxic/carcinogenic effects. Instead, they can cause infections or allergic responses, or both.

Aerial transmission of pathogenic viruses indoors can cause diseases such as upper respiratory infections (colds, influenza), lung disease (e.g., psittacosis), rubella (measles), varicella (chicken pox), and variola (smallpox) (Leedom and Loosli 1979; Zeterberg 1973; McLean et al. 1967, all as cited in DOE 1987). Aerial transmission of pathogenic bacteria can result in bacterial upper respiratory infections and lung disease such as tuberculosis, Legionaires' disease, and pneumonia. Kelsen and McGuckin (1980), as cited in DOE (1987), for example, observed a statistically significant relationship between airborne microbial counts (CFP) and respiratory attack rates in patients with nosomial pneumonia. Several genera of fungi are pathogenic when inhaled by humans, among them the highly infectious Histoplasma and Coccidioides, as well as Aspergillus, Blastomyces, Cryptococcus, Candida albicans, and dermatophytes (EPA 1987).

Colds and influenza alone, mostly transmitted by airborne infectious agents in the indoor environment, cause an enormous burden for the national economy in terms of loss of productivity and exposures. They account for more than 50% of all acute conditions with an incidence of about one per person per year (DHEW 1975, as cited in DOE 1987). Afflicted patients are incapacitated or restricted in their activities for an average of 4.5 days. Respiratory conditions cause more loss of time from work or school than any other disease (DOE 1987).

Allergic reactions generally occur on the skin or in the mucous membranes of the respiratory tract. An allergic response to inhaled biogenic

agents manifests itself generally as a local inflammatory reaction at the site of particle impingement. An estimated 15% of Americans suffer from reactions to airborne allergens. If the reaction takes place mainly in the nasal area, where larger inhaled particles such as pollen grains are retained, the condition is referred to as allergic or vasomotor rhinitis, more popularly know as hay fever. Allergic rhinitis is characterized by edema, swelling, vasodilation of nasal mucosa, mucus hypersecretion, nasal discharge, and congestion of the nasal airways.

Asthma refers to a partial, temporary narrowing of the bronchi from spasm of the smooth bronchial muscles, edema of the bronchial mucosa, mucus accumulation, or a combination of these factors. The fungus Aspergillus fumigatus, when inhaled, can affect bronchi and the alveolar region by a relatively rare condition called allergic bronchopulmonary aspergillosis. The disease is characterized by recurrent episodes of temporary shadowing on chest X-rays and in increased eosinophilic blood cells, often associated with asthma attacks. Histologically, eosinophils accumulate in the alveolar spaces, often leading to consolidation. As the disease progresses, the reversibility of tissue changes decreases; eventually chronic bronchial stenosis, bronchiectasis, and pulmonary fibrosis might develop.

Hypersensitivity pneumonitis, also called extrinsic allergic bronchioloalveolitis, refers to an allergic reaction in the peripheral bronchioles and alveoli between inhaled biogenic agents and circulating antibodies and sensitized lymphocytes. In its acute stage, the disease is characterized by infiltration of mononuclear cells into, and thickening of, alveolar septa and bronchioles, often accompanied by the formation of epithelial and giant-cell granulomas; when the disease progresses from continued allergen exposure, fibrosis can develop. Reaction sites and allergic diseases of the respiratory system are summarized in Table 2.21 (DOE 1987).

While the mechanism of sensitization in allergic individuals is still unclear, it is well known that a single pollen can provoke a severe allergic reaction in sensitized persons. Allergens maintain their allergenic effects, independent of the viability of the microbe involved (if any), for considerable periods of time until the proteins of the allergen are denatured.

Rimington et al. (1947), as cited in DOE (1987), for example, reported that house dust remained allergenic until all amino acids had been hydrolyzed (DOE 1987).

Among the various indoor air pollutants, biogenic particles are probably the most complex and least investigated materials. Reliable measurements of airborne biogenic particle concentrations in residences are lacking and the effects of controlled variables on these concentrations is unknown. The scarce information presently available on this subject is insufficient for developing guidelines for human exposure to biogenic indoor air contaminants.

Hypersensitivity Pneumonitis and Humidifier Fever - Outbreaks of interstitial lung disease and febrile syndromes are among the best documented building-related diseases. In addition to outbreaks, our epidemiologic understanding has been supplemented by numerous case reports documenting illness resulting from exposure to allergens from home humidifiers, air coolers, car air conditioners, and saunas. Symptoms have varied, even within an outbreak, from acute recurrent pneumonias to insidious progression of

TABLE 2.21. Allergic Respiratory Diseases - Reaction Sites, Diseases, and Immunologic Mechanisms

Reaction Site	Disease	Immunologic Mechanism
Nose	Allergic rhinitis	IgE
Airways	Allergic rhinitis	IgE
Airways and alveolar spaces	Asthma with pulmonary eosinophilia, allergic bronchopulmonary aspergillosis	IgE, IgG, immune complexes
Alveolar walls peripheral bronchioles	Hypersensitivity pneumonitis (extrinsic allergic bronchioloalviolitis)	IgG, immune and complexes, sensitized T-lymphocytes

SOURCE: National Research Council (1981), p. 398, as cited in DOE (1987).

cough, shortness of breath, and fatigue that the patient does not attribute to indoor air exposure. In addition to the pulmonary diseases, recurrent outbreaks of fever, leukocytosis, chills, muscle aches, and malaise, without prominent pulmonary symptoms or signs, are part of this disease spectrum. Individual outbreaks have had unusual association symptoms such as polyuria, nausea, or headache, follicular conjunctivitis, and diarrhea, in addition to respiratory complaints. Five occupational outbreaks have had a pattern of recurrence on Monday evenings or on the evening of the first day back to work, reminiscent of byssinosis and metal fume fever. On the other hand, symptoms worsened toward the end of the work week in one case, and no association with day of the work week is common (Walsh et al. 1984).

Attack rates have varied from 1 to 71%. Various bacteria and fungi have been implicated in outbreaks and case reports, but pure strains of organisms found in humidifier water or other sources are sometimes ineffective in bronchial challenge testing or in precipitin tests with sera from affected individuals. Protozoa may play a role in some of these outbreaks and may require special methods for detection in environmental samples (Walsh et al. 1984).

Infections - Many infectious diseases can be transmitted via indoor air. These infectious diseases include Legionnaires' disease, Pontiac fever, and Q fever.

Legionnaires' disease, a bacterial pneumonia, was first described in the context of an epidemic of 182 cases (20 fatal) among Legionnaires attending a convention in 1976 at the Bellevue Stratford Hotel in Philadelphia. Since the identification of the bacterial agent, Legionella pneumophila, many building-associated epidemics have been recognized, both retrospectively and prospectively. The multisystem illness involves the GI tract, kidney, central nervous system, lungs. From 1% to 7% of persons exposed become ill after an average incubation period of 5 to 6 days. The case-fatality rate is approximately 15%. Epidemics have been associated with aerosols from cooling towers and evaporative condensers and with dusts from landscaping and construction requiring soil excavation. In addition, the organism has been cultured from shower heads in hospitals and hotels associated with cases of Legionnaires'

disease. An epidemic of seven cases associated with an inn with a whirlpool occurred over a 15-month period from May 1980 to August 1981. Outbreaks of Legionnaires' disease are no longer etiologic puzzles to public health investigators, although many questions remain concerning Legionella ecology and infectivity (Walsh et al. 1984).

Pontiac fever was first described as a building-related epidemic of 144 cases in a county health department in Pontiac, Michigan in 1968. The air conditioning system was contaminated with L. pneumophila and was the mode of dissemination. Two subsequent outbreaks have been reported: one among 10 men who spent 9 hours cleaning a steam turbine condenser with compressed air and one in an automobile assembly plant thought to be caused by an aerosol of a contaminated oil-based coolant. In contrast to Legionnaires' disease, Pontiac fever is a 2- to 5-day illness characterized by fever, chills, headache, and myalgia. Cough, sore throat, chest pain, nausea, and diarrhea may be present, but in lower prevalence. The attack rate among exposed persons is characteristically 95 to 100%, with a mean incubation period of about 36 hours (Walsh et al. 1984).

Although Pontiac fever outbreaks are diagnosed by finding L. pneumophila organisms in environmental samples and diagnostic rises in antibody titer to the organism in convalescent-phase sera, no consensus exists regarding why Legionellae cause outbreaks of two distinct clinical syndromes. No convincing evidence supports the importance of dose, toxin production, or vital status of the inhaled organism. Rowbotham, as cited in Walsh (1984), has suggested that Pontiac fever represents a hypersensitivity pneumonitis from amoebae with a limited infection by L. pneumophila in most cases. Free-living amoebae are hosts to and victims of Legionella infection, depending on number and strain of each, and temperature. Inhalation of amoebae or amoebic vesicles might deliver many more Legionellae to the human host. Humidifier fever-type sensitization of amoebal antigens may interfere with the establishment of Legionella infection, or amoebic digestion of Legionellae may reduce the dose below that effective for clinical pneumonia. The recent epidemic of Legionellosis in the inn with a whirlpool is the first report of a Legionella source associated with sporadic cases of Legionnaires' disease over a 15-month

period and an epidemic of 34 cases of Pontiac fever in March 1981. Three groups of Legionella were isolated from whirlpool water: L pneumophila, serogroup 1 and 6, and L. dumoffi. Studies for amoebae and other protozoa were not performed before the whirlpool was closed in August 1981 (Walsh et al. 1984).

Q fever, a rickettsial illness caused by Coxiella burnetii, has caused several building associated epidemics. Symptoms resemble influenza with abrupt onset of high fever, chills, headache, and myalgia. In some outbreaks, pneumonia has been a prominent manifestation, and cases of hepatitis and endocarditis occur rarely. The reservoir for infection is infected sheep, goats, and cattle, whose excreta and placental tissue can contaminate buildings in which these animals are housed. All of the outbreaks cited occurred in university hospitals or research laboratory buildings in which the organism was cultured; however, in each outbreak, people without direct contact with animals or the organism became ill as a result of airborne transmission in the building (Walsh et al. 1984).

2.6 OTHER POTENTIAL CONTAMINANTS

To assess health impacts from contaminants in the indoor air of public buildings, contaminants that may affect human health must first be identified. Hundreds of such biological and chemical contaminants exist. An EPA study indicated at least 500 different volatile organic compounds have been identified in the indoor air of buildings (EPA 1988b).

As stated in Section 1.4 in this report, we considered only contaminants that were measured in indoor air of public buildings or those measured in test situations that simulated indoor air quality situations, as reported in the literature examined as a basis for selecting contaminants to study (see Section 1.4 for list of literature references). Contaminants found in building materials, but not reported as being found in any of the indoor air studies reviewed, were not included in this study. Therefore, there are many other potential contaminants that may be of concern in assessing the risk to human health from a public building.

For example, some of the contaminants identified (in the literature reviewed) in building materials but not found in the building studies examined include cumene, chlorobenzene, nonane, iso-octane, iso-nonane, iso-decane, tetrachloroethane, mesitylene, n-hexane, 3-carene, propanol, 2-butanone, acetone, diethylbenzene, hexanol, d-limonene, vinyl chloride, butanol, n-heptane, n-heptene-1, 3-pentanol, and ethylacetate.

The additional and very complex problem of complex chemical mixtures must also be addressed to fully understand and predict the risk from chemicals found in the indoor environment of public buildings. Though the health effect studies of the individual chemical compounds found in indoor air is extremely useful in understanding and predicting the risks from these chemicals, there are serious limitations in extrapolating the results from single chemical studies to the actual environmental exposure of humans, which is that of complex mixtures of these various chemical compounds. The toxicological study of complex mixture sets representing actual exposure in typical public building situations should be performed to more accurately examine the combined or synergistic effect of the actual chemical mixture set to which the public is being exposed.

3.0 POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCBs) are a series of technical mixtures consisting of many isomers and compounds that vary from mobile oily liquids to white crystalline solids and hard noncrystalline resins. The technical products vary in composition, in the degree of chlorination and possibly according to batch. With a Hazard Rating of 3 (Sax and Lewis, 1989), the molecular weight of PCBs varies from 189-399 g/mole. They have a flash point of 200°C and a vapor pressure of 7.7E-5 mm Hg (ATSDR 1987).

3.1 SUMMARY

In humans exposed to PCBs, reported adverse effects include chloracne (a long-lasting, disfiguring skin disease), impairment of liver function, a variety of neurobehavioral and affective symptoms, menstrual disorders, minor birth abnormalities, and probably increased incidence of cancer. Animals experimentally exposed to PCBs have shown most of the same symptoms, as well as impaired reproduction; pathological changes in the liver, stomach, skin, and other organs; and suppression of immunological functions. PCBs are carcinogenic in rats and mice and, in appropriate circumstances, enhance the effects of other carcinogens. Reproductive and neurobiological effects of PCBs have been reported in rhesus monkeys at the lowest dose level tested, 11 g/kg body weight per day over a period of several months (ATSDR 1987).

The weight-of-evidence classification for PCBs is "B2; probable human carcinogen." The basis is hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate, yet suggestive, evidence of excess risk of liver cancer in humans by ingestion and inhalation or dermal contact (IRIS 1990).

The Oral Slope Factor for PCBs is 7.7/mg/kg/day. The Drinking Water Unit Risk is 2.2E-4/μg/L. The extrapolation method used was the linear multistage procedure with extra risk.

3.2 HEALTH EFFECTS

The health effects discussed for PCBs focus on the inhalation route because this is the primary pathway for exposure of an individual to PCBs via indoor air in a public building. However, dermal exposure could also occur. Therefore, dermal route toxicity summaries are also provided. Oral route risk factors for PCBs are provided because such factors are only available for the oral route.

Lethality and Decreased Longevity (Inhalation) - Data regarding inhalation exposure levels that produce death in humans were not available. Exposure to near-saturation vapor concentrations of heated Aroclor 1242 (a PCB) (8.6 mg/m^3) 7 h/day, 5 day/wk for 24 days was not lethal for cats, rats, mice, rabbits, or guinea pigs (Treon et al., 1956, as cited in ATSDR 1987). This concentration represents a NOAEL for lethality for intermediate inhalation exposures. Figures 3.1, 3.2, 3.3 and 3.4 show effects of PCB-inhalation exposure, PCB-oral exposure, PCB-dermal exposure and levels of significant exposure for PCBs-inhalation, respectively. No data were available regarding lethality/decreased longevity of animals due to acute or chronic inhalation exposure to PCBs (ATSDR 1987).

Systemic/Target Organ Toxicity (Inhalation) - Oral toxicity studies in animals have established that the liver and cutaneous tissues are primary target organs of PCBs with increased serum levels of liver-associated enzymes and dermatologic effects such as chloracne and skin rashes. The results of some of these studies are equivocal, and exposure levels were not reported or were inadequately characterized. Furthermore, although inhalation is considered a major route of exposure, the contribution of dermal exposure to total occupational exposure is also significant (ATSDR 1987).

Fischbein et al. (1979, 1982, 1985), as cited in ATSDR (1987), reported data suggesting associations between serum levels of PCBs and (serum glutamic oxaloacetic transaminase (SGOT) levels and dermatologic effects in workers who had been exposed to 8-hour, time-weighted, average concentrations of Aroclors, primarily 1242 and 1254, ranging from 0.007 to 11.0 mg/m^3. Because of limitations of this study, these effects could be regarded as inconclusive and cannot be associated with specific exposure concentrations.

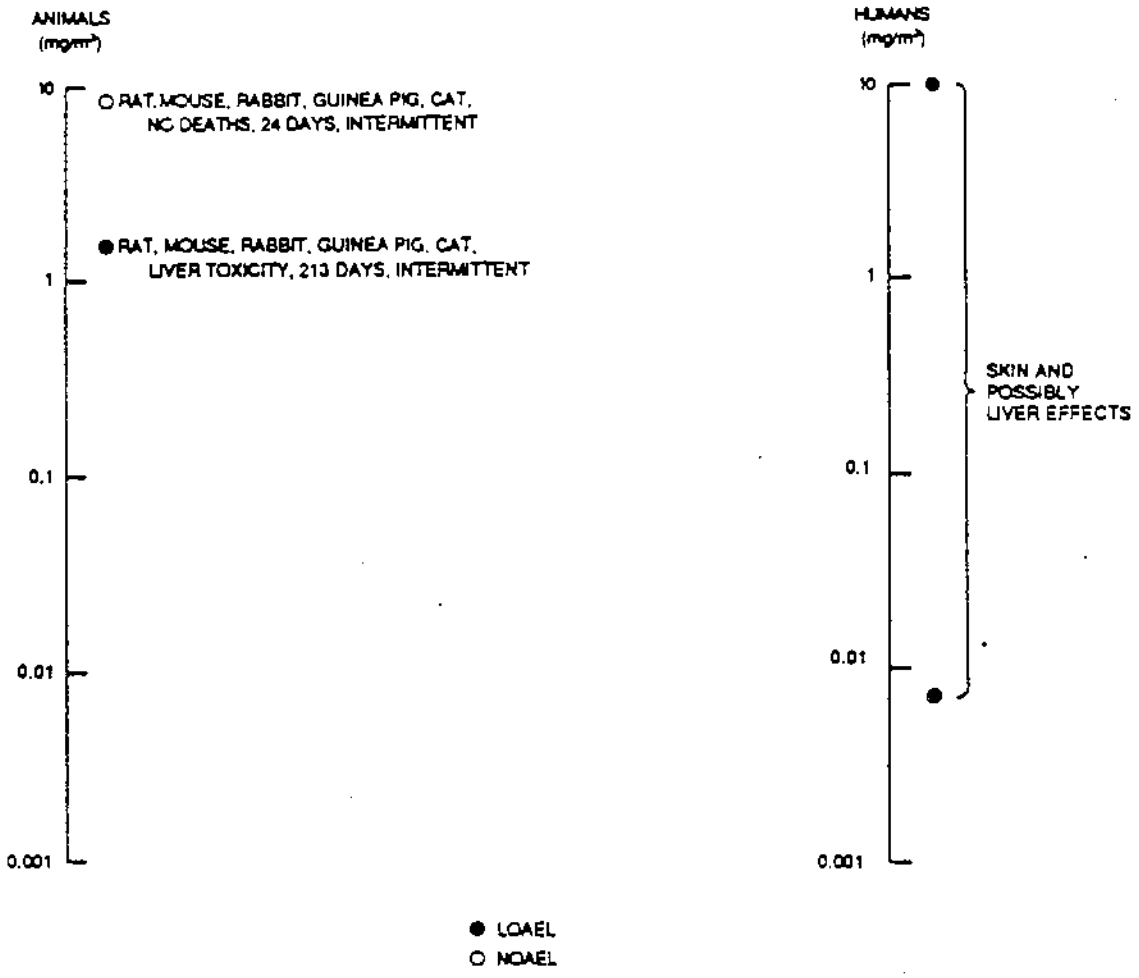

FIGURE 3.1. Effects of PCBs, Inhalation Exposure (ATSDR 1987)

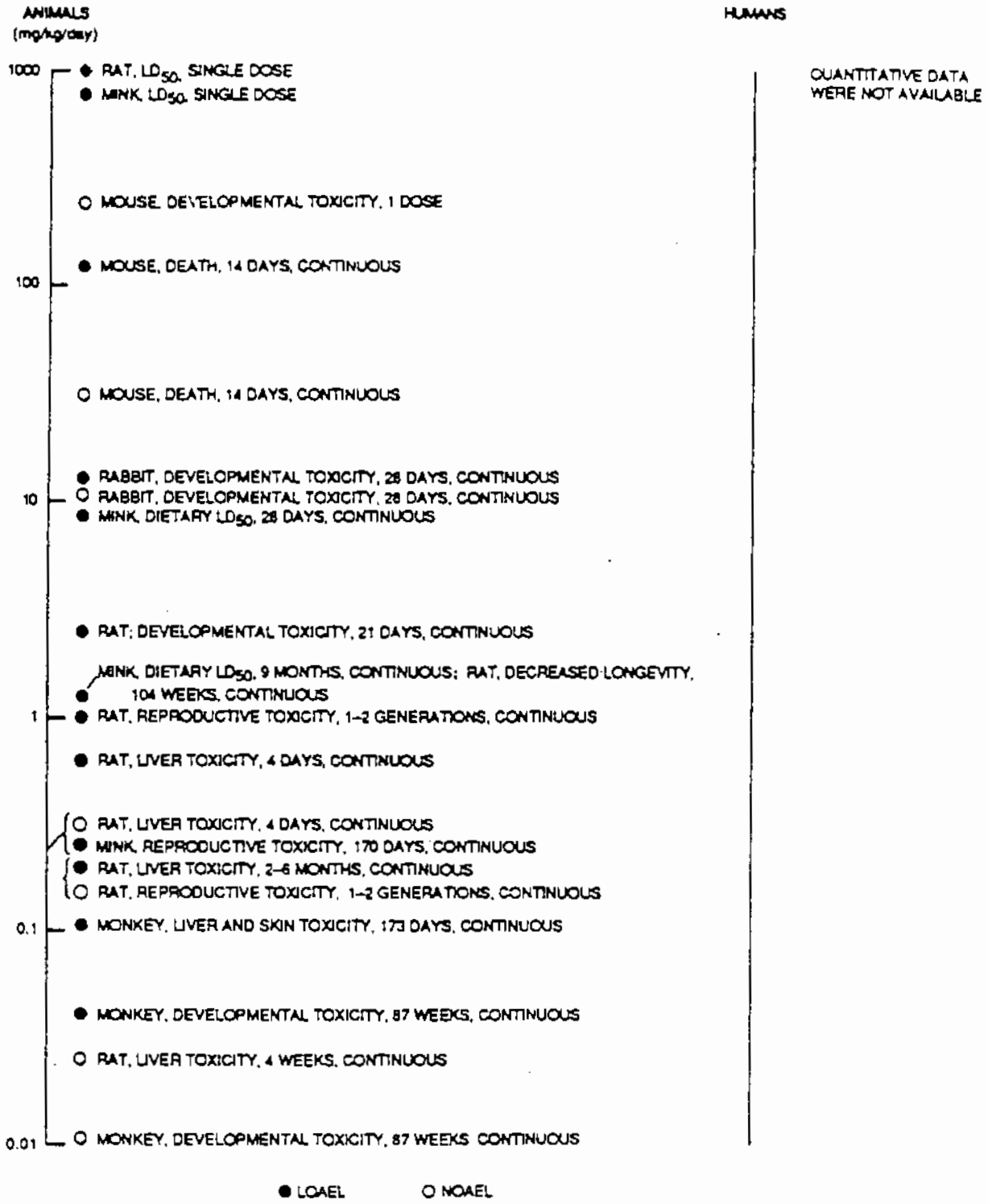

FIGURE 3.2. Effects of PCBs, Oral Exposure

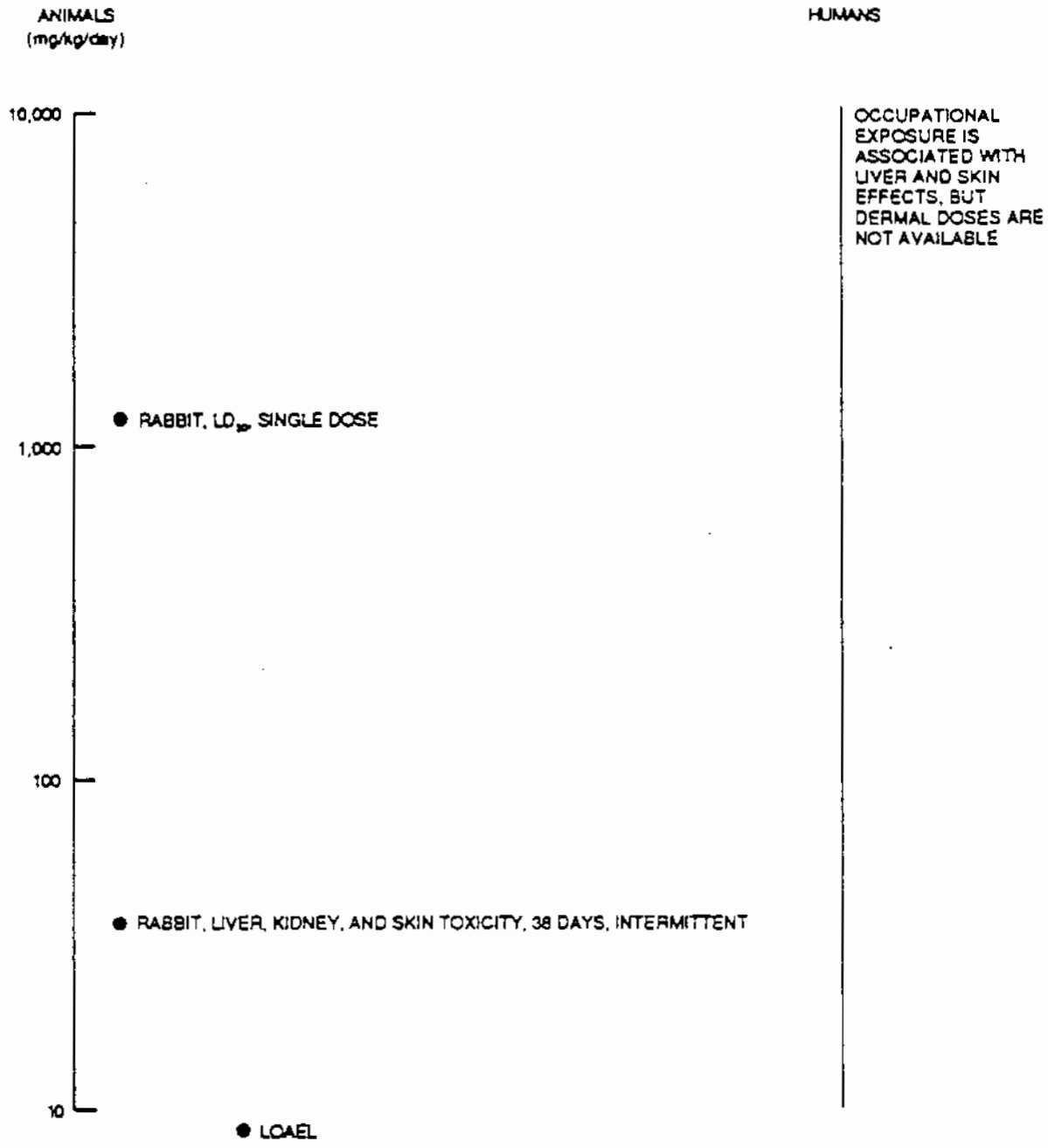

FIGURE 3.3. Effects of PCBs, Dermal Exposure

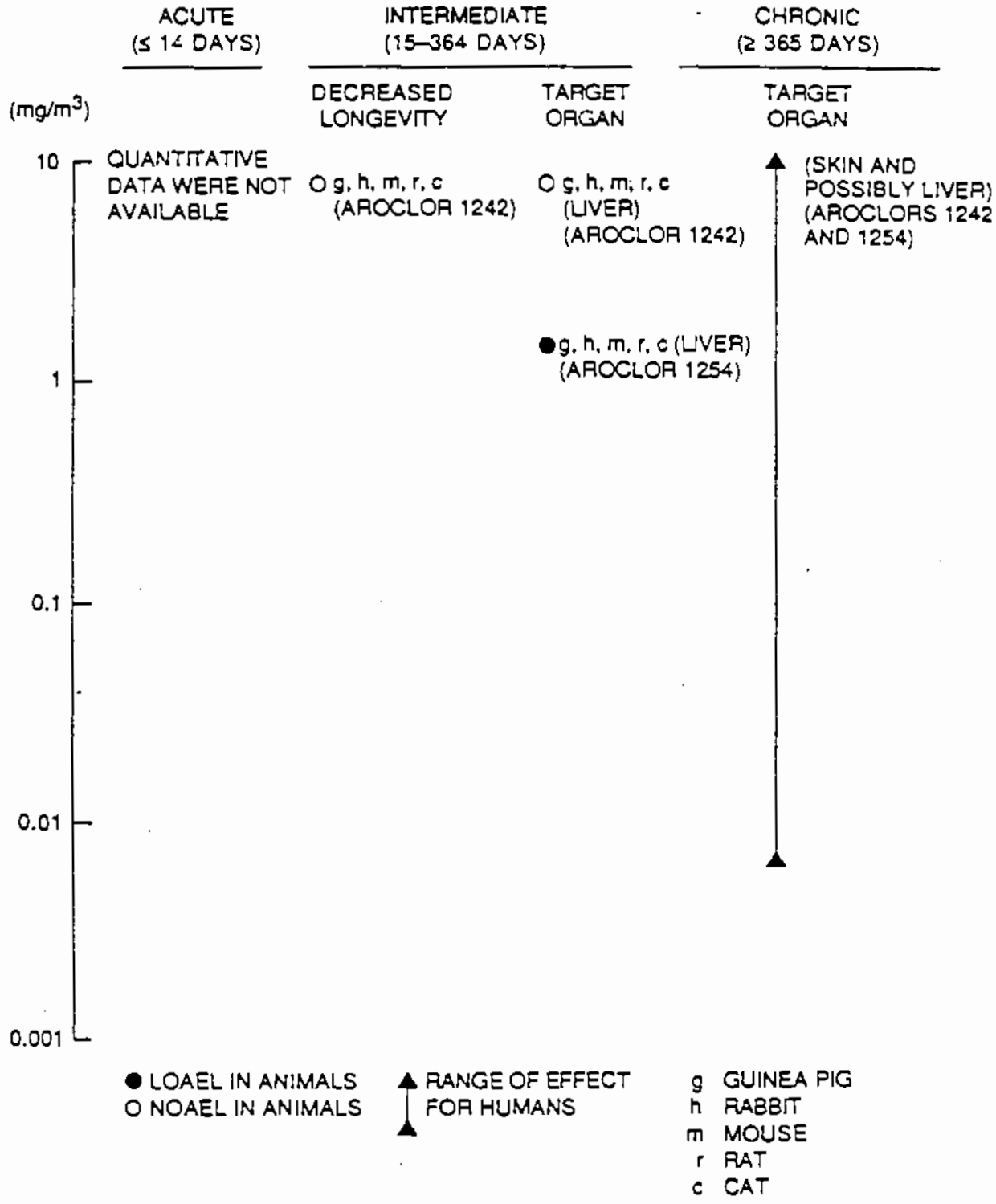

FIGURE 3.4. Levels of Significant Exposure for PCBs, Inhalation

It is, however, appropriate to plot the range of Aroclor concentrations from this study in Figures 3.1 and 3.4 because similar effects have been observed in other health surveys of PCB-exposed workers, information regarding human liver histopathology is lacking, and the liver and skin are unequivocal targets of PCB toxicity in animals. This concentration range is intended to approximate typical concentrations in occupational environments that may be associated with hepatic and dermatologic alterations (ATSDR 1987).

In only the animal inhalation study of PCBs, degenerative liver lesions, a frank effect, occurred in cats, rats, mice, rabbits, and guinea pigs that were exposed to 1.5 mg/m^3 Aroclor 1254 vapor for 7 h/day, 5 day/wk for 213 days (Treon et al., 1956, as cited in ATSDR 1987). This FEL is plotted on Figures 3.1 and 3.4. Histologic effects were not produced in those species exposed to Aroclor 1242 (1.9 mg/m^3, 7 h/day, 5 day/wk for 214 days; 8.6 mg/m^3, 7 h/day, 5 day/wk for 24 days). The higher NOAEL of 8.6 mg/m^3 for intermediate-duration inhalation exposure is plotted on Figure 3.4 since the FEL for Aroclor 1254 is lower than the NOAEL for Aroclor 1242, a minimal risk level cannot be derived for Aroclors as a class (ATSDR, 1987).

Developmental Toxicity (Inhalation) - Pertinent data regarding developmental effects of PCBs via inhalation exposure in animals were not located in the available literature. A report of slightly reduced birth weight and gestational age in infants born to mothers with occupational exposure to Aroclors (Taylor et al. 19B4, as cited in ATSDR 1987) is inconclusive and lacks monitoring data.

Reproductive Toxicity (Inhalation) - Pertinent data regarding reproductive effects of PCBs via inhalation exposure in humans or animals are not available (ATSDR 1987).

Genotoxicity (Inhalation) - The PCBs have produced generally negative results in in vivo and in vitro genotoxicity assays (ATSDR 1987).

Human Carcinogenicity (Inhalation) - Occupational studies (Brown 1986, Bertazzi et al. 1987, as cited in ATSDR 1987) provide inadequate but

suggestive evidence for carcinogenicity of PCBs by the inhalation route. Data regarding the carcinogenicity of inhaled PCBs in animals are not available (ATSDR 1987).

Lethality and Decreased Longevity (Dermal) - Human data are not available. Median lethal doses for single dermal applications of PCBs to rabbits ranged from less than 1,269 mg/kg for Aroclors 1242 and 1248 to less than 3,169 mg/kg for Aroclor 1221 (Fischbein, 1974, as cited in ATSDR 1987). Because only ranges of median lethal doses were reported, the lowest dose (1,269 mg/kg) is indicated on Figures 3.3 and 3.6 (ATSDR 1987).

Systemic/Target Organ Toxicity (Dermal) - The study of capacitor workers by Maroni et al. (1981a,b), as cited in ATSDR (1987), indicated that dermal exposure to PCBs at 2-28 $\mu g/cm^2$ of skin (on the hands) was not associated with clear evidence of liver disease, but may have been associated with liver enzyme induction in some of the workers. Assuming a total surface area for the hands of 910 sq. cm (Hawley 1985, as cited in ATSDR 1987) and body weight of 70 kg, the dermal exposure would have been 0.026-0.364 mg/kg/day. Because the workers were also exposed to PCBs by inhalation (48-275 $\mu g/m^3$), and because interpretation of the study is confounded by the lack of a control group, the dermal exposure range is not plotted on Figures 3.3 and 3.6.

Dermal application of Aroclor 1260 to rabbits on 5 day/wk at a dose of 118 mg/day for 38 days (27 total applications) produced degenerative lesions of the liver and kidneys, increased fecal porphyrin elimination, and hyperplasia and hyperkeratosis of the follicular and epidermal epithelium (Vos and Beems 1971, as cited in ATSDR 1987). As body weight appeared to be approximately 2.7 kg, the FEL of 118 mg/day is equal to a dose of 43.7 mg/kg/day (ATSDR 1987).

Developmental and Reproductive Toxicity (Dermal) - Pertinent data regarding developmental and reproductive effects of dermal exposure to PCBs were not located in the available literature (ATSDR 1987).

Genotoxicity (Dermal) - The PCBs have produced generally negative results in in vivo and in vitro genotoxicity tests (ATSDR 1987).

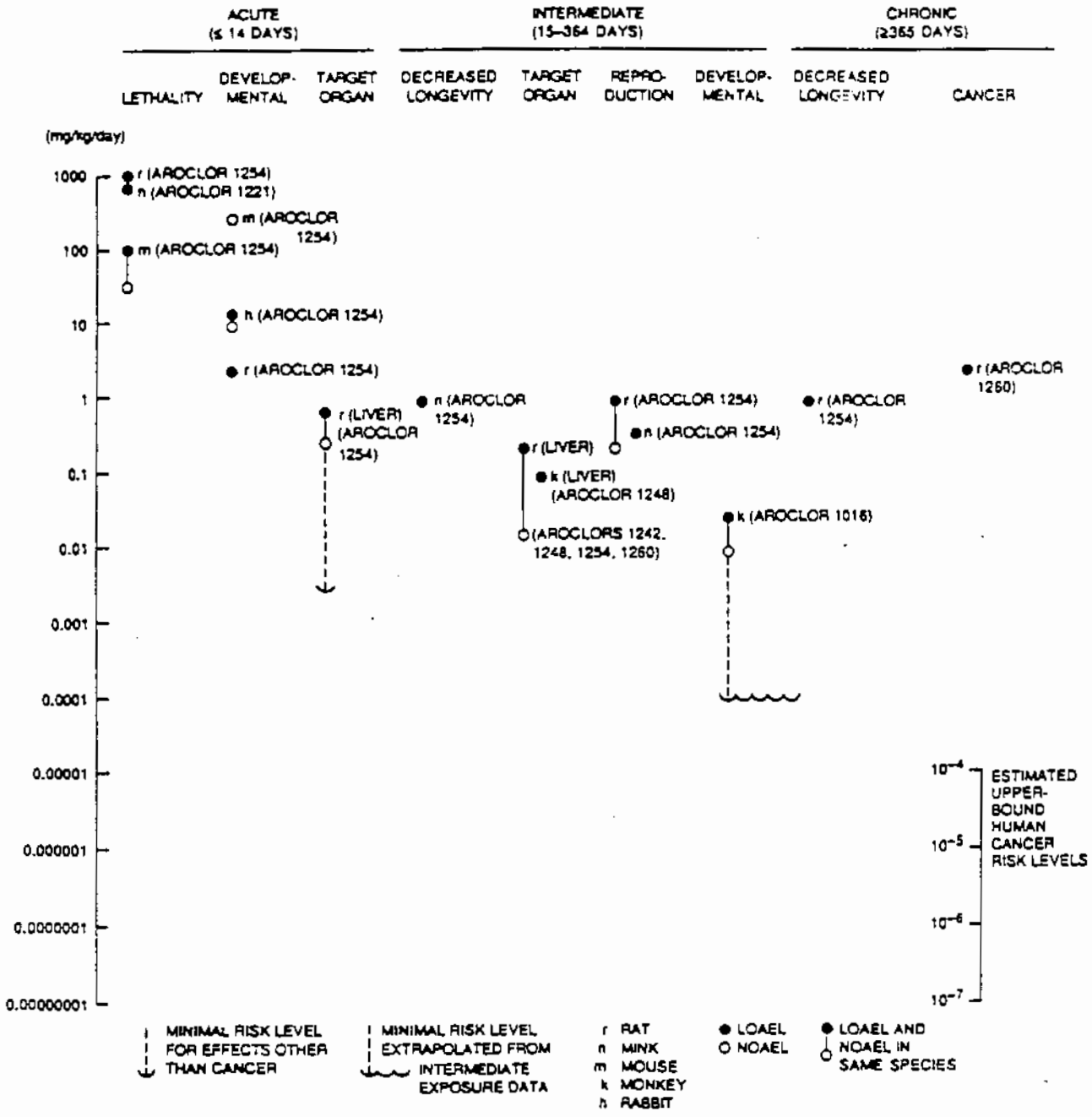

FIGURE 3.5. Levels of Significant Exposure for PCBs, Oral

Bertazzi et al. (1987), as cited in IRIS (1990), conducted a mortality study of 544 male and 1556 female employees of a capacitor-making facility in Northern Italy. Aroclor 1254 and pyralene 1476 were used in this plant until 1964. These were progressively replaced by Pyralene 3010 and 3011 until 1970, after which lower chlorinated Pyralenes were used exclusively. In 1980 the use of PCBs was abandoned. Some employees also used TCE but, according to the authors, were "presumed" to be protected by efficient ventilation. Air samples were collected and analyzed for PCBs in 1954 and 1977 because of reports of chloracne in workers. Quantities of PCBs on workers' hands and workplace surfaces also were measured in 1977. In 18 samples, levels ranged from 0.2-159.0 $\mu g/m^2$ on workplace surfaces and 0.3 to 9.2 $\mu g/m^2$ on worker hands (IRIS 1990).

The authors compared observed mortality with that expected between 1946 and 1982 based on national and local Italian mortality rates. With vital status ascertainment 99.5% complete, relatively few deaths were reported by 1982 [30 males (5.5%) and 34 females (2.2%)]. In cohort males, the number of deaths from malignant tumors was significantly higher than expected compared with local or national rates, as was the number of deaths from cancer of the GI tract (6 observed vs. 1.7 national expected and 2.2 local expected). Of the six GI cancer deaths, one was caused by liver cancer and one by biliary tract cancer.

Deaths from hematologic neoplasms in males were also higher than expected, but excess was not statistically significant. Total cancer deaths in females were significantly elevated in comparison to local rates (12 observed vs. 5.3 expected). None of these were liver or biliary cancers. The number of deaths from hematologic neoplasms in females was higher than expected when compared with local rates (4 observed vs. 1.1 expected).

This study is limited by several factors, particularly the small number of deaths that occurred by the cut-off period. The power of the study is insufficient to detect an elevated risk of site-specific cancer. In addition, the authors stated that after an examination of the individual cases, interpretation of the increase in GI tract cancer in males was limited. This is because it appeared likely that some of these individuals had only limited

PCB exposure. Confounding factors may have included possible contamination of the PCBs by dibenzofurans and exposure of some of the workers to TCE, alkylbenzene, and epoxy resins (IRIS 1990).

Two occurrences of ingestion of PCB-contaminated rice oil have been reported: the Yusho incident of 1968 in Japan and the Yu-Cheng incident of 1979 in Taiwan. Amano et al. (1984), as cited in IRIS (1990), completed a 16-year retrospective cohort mortality study of 581 male and 505 female victims of the Yusho incident. A consistently high risk of liver cancer in females over the entire 16 years was observed; liver cancer in males was also significantly increased.

Several serious limitations are evident in this study. There was a lack of information regarding job histories or the influence of alcoholism or smoking. The information concerning the diagnosis of liver cancer was obtained from the victims' families, and it is not clear whether this information was independently verified by health professionals. For some of the cancers described, the latency period is shorter than would be expected. Furthermore, the contaminated oils contained polychlorinated dibenzofurans and polychlorinated quinones as well as PCBs, and the study lacks data regarding exposure to the first two classes of compounds. There is strong evidence indicating that the health effects seen in Yusho victims were caused by ingestion of polychlorinated dibenzofurans, rather than to PCBs themselves (reviewed in EPA 1988, as cited in IRIS 1990). The results of the Amano et al. study can, therefore, be considered as no more than suggestive of carcinogenicity of PCBs (IRIS 1990).

Animal Carcinogenicity Data - The animal carcinogenicity data are considered sufficient. PCB mixtures assayed in the following studies were commercial preparations and may not be the same as mixtures of isomers found in the environment. Although animal feeding studies demonstrate the carcinogenicity of commercial PCB preparations, it is not know which of the PCB congeners in such preparations were responsible for these effects, or if decomposition products, contaminants or metabolites were involved in the toxic response. Early bioassays with rats (Kimura and Baba, 1973; Ito et al., 1974, as cited in IRIS 1990) were inadequate to assess carcinogenicity because of

the small number of animals and short duration of exposure to PCBs. A long-term bioassay of Aroclor 1260 reported by Kimbrough et al. (1975), as cited in IRIS (1990), produced hepatocellular carcinomas in female Sherman rats when 100 ppm was administered for 630 days to 200 animals. Hepatocellular carcinomas and neoplastic nodules were observed in 14 and 78%, respectively, of the dosed animals, compared with 0.58 and 0%, respectively, of the controls (IRIS 1990).

The National Cancer Institute (NCI) (1978), as cited in IRIS (1990), reported results for 24 male and 24 female Fischer 344 rats treated with Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Although carcinomas of the GI tract were observed among the treated animals only, the incidence was not statistically significantly elevated. An apparent dose-related incidence of hepatic nodular hyperplasia in both sexes as well as hepatocellular carcinomas among mid- to high-dose treated males was reported (4-12%, compared to 0% in controls).

Norback and Weltman (1985), as cited in IRIS (1990), fed 70 male and 70 female Sprague-Dawley rats a diet containing Aroclor 1260 in corn oil at 100 ppm for 16 months, followed by a 50-ppm diet for an additional 8 months, then a basal diet for 5 months. Control animals (63 rats/sex) received a diet containing corn oil for 18 months, then a basal diet alone for 5 months. Among animals that survived for at least 18 months, females exhibited a 91% incidence (43/47) of hepatocellular carcinoma. An additional 4% (2/47) had neoplastic nodules. In males corresponding incidences were 4% (2/46) for carcinoma and 11% (5/46) for neoplastic nodules. Concurrent liver morphology studies were carried out on tissue samples obtained by partial hepatectomies of three animals per group at eight time points. These studies showed the sequential progression of liver lesions to hepatocellular carcinomas (IRIS 1990).

Orally administered PCB resulted in increased incidences of hepatocellular carcinomas in two mouse strains. Ito et al (1973), as cited in IRIS (1990), treated male dd mice (12/group) with Kanechlors 500, 400 and 300 each at dietary levels of 100, 250, or 500 ppm for 32 weeks. The group fed 500 ppm of Kanechlor 500 had a 41.7% incidence of hepatocellular carcinomas and a

58.3% incidence of nodular hyperplasia. Hepatocellular carcinomas and nodular hyperplasia were not observed in mice fed 100 or 250 ppm of Kanechlor 500, nor among those fed Kanechlors 400 or 300 at any concentration (IRIS 1990).

Schaeffer et al. (1984), as cited in IRIS (1990), fed male Wistar rats diets containing 100 ppm of the PCB mixtures Clophen A 30 (30% chlorine by weight) or Clophen A 60 (60% chlorine by weight) for 800 days. The PCB mixtures were reported to be free of furans. Clphen A 30 was administered to 152 rats, Clophen A 60 to 141 rats, and 139 rats received a standard diet. Mortality and histologic lesions were reported for animals necropsied during each 100-day interval for all three groups.

Of the animals that survived the 800-day treatment period, 1/53 rats (2%) in the control group, 3/87 (3%) in the Clophen A 30 group and 52/85 (61%) in the Clophen A 60 group were significantly elevated in comparison to the control group. Neoplastic liver nodules were reported in 2/53 control, 35/87 Clophen A 30, and 34/85 Clophen A 60-treated animals. The incidence of nodules was significantly increased in both treatment groups in comparison to the control group. Neoplastic liver nodules and hepatocellular carcinomas appeared earlier and at higher incidence in the Clophen A 60 group relative to the Clphen A 30 group. The authors interpreted the results as indicative of a carcinogenic effect related to the degree of chlorination of the PCB mixture. The authors also suggested that these findings support those of others, including Ito et al. (1973) and Kimbrough et al. (1975), both as cited in IRIS (1990), in which hepatocellular carcinomas were produced by more highly chlorinated mixtures (IRIS 1990).

Kimbrough and Linder (1974), as cited in IRIS (1990), dosed groups of 50 male BALB/cJ mice (a strain with a low spontaneous incidence of hepatoma) with Aroclor 1254 at 300 ppm in the diet for 11 months or 6 months, followed by a 5-month recovery period. Two groups of 50 mice were fed a control diet for 11 months. The incidence of hepatomas in survivors fed Aroclor 1254 for 11 months was 10/22. One hepatoma was observed in the 24 survivors fed Aroclor 1254 for 6 months (IRIS 1990).

Supporting Data for Carcinogenicity - Most genotoxicity assays of PCBs have been negative. The majority of microbial assays of PCB mixtures and

various congeners showed no evidence of mutagenic effects (Schoeny et al., 1979; Schoeny, 1982; Wyndham et al., 1976, all as cited in IRIS 1990). Of various tests on the clastogenic effect of PCBs (Heddle and Bruce, 1977; Green et al., 1975, as cited in IRIS 1990), only Peakall et al. (1972), as cited in IRIS (1990), reported results indicative of a possible clastogenic action by PCBs in dove embryos (IRIS 1990).

Chlorinated dibenzofurans (CDFs), known contaminants of PCBs, and chlorinated dibenzodioxins (CDDs) are structurally related to, and produce certain biologic effects similar to, those of PCB congeners. While CDDs are known to be carcinogenic, the carcinogenicity of CDFs is still under evaluation (IRIS 1990).

Quantitative Estimate of Carcinogenic Risk - The Oral Slope Factor for PCBs is 7.7/mg/kg/day. The Drinking Water Unit Risk is 2.2E-4/μg/L. The extrapolation method used was the linear multistage procedure with extra risk. Drinking water concentrations at specified risk levels is as follows:

Risk Level	Concentration
E-4 (1 in 10,000)	5E-1 μg/L
E-5 (1 in 100,000)	5E-2 μg/L
E-6 (1 in 1,000,000)	5E-3 μg/L

Dose-Response Data (Carcinogenicity, Oral Exposure) - The tumor type developed was trabecular carcinoma/adenocarcinoma, neoplastic nodule. The test animals were female Sprague-Dawley rats. The route of exposure was an oral diet. The dose-response data are provided in Table 3.1 (Norback and Weltman, 1985, as cited in IRIS 1990).

Human equivalent dosage assumes a TWA daily dose of 3.45 mg/kg/day. This reflects the dosing schedule of 5 mg/kg/day (assuming the rat consumes an amount equal to 5% of its body weight per day) for the first 16 months, 2.5 mg.kg/day for the next 8 months, and no dose for the last 5 months (IRIS 1990).

TABLE 3.1. PCB Oral Exposure Carcinogenicity Dose-Response Data

Dose		
Administered (mg/kg/day) (TWA)	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	1/49
3.45	0.59	45/47

A slope factor of 3.9/mg/kg/day was based on data from a study by Kimbrough et al. (1975), as cited in IRIS (1990), of female Sherman rats fed Aroclor 1260. The estimate based on the data of Norback and Weltman (1985), as cited in IRIS (1990), is preferred because Sprague-Dawley rats are known to have low incidence of spontaneous hepatocellular neoplasms. Moveover, the latter study spanned the natural life of the animal, and concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas (IRIS 1990).

Though it is known that PCB congeners vary greatly as to their potency in producing biological effects, for purposes of this carcinogenicity assessment, Aroclor 1260 is intended to be representative of all PCB mixtures. There is some evidence that mixtures containing more highly chlorinated biphenyls are more potent inducers of hepatocellular carcinoma in rats than mixtures containing less chlorine by weight (reviewed in Kimbrough 1987 and Schaefer et al. 1984, as cited in IRIS 1990).

The unit risk should not be used if the water concentration exceeds 50 μg/L, because above this concentration, the slope factor may differ from that stated (IRIS 1990).

No quantitative estimate of carcinogenic risk from inhalation exposure of PCBs is available at this time.

4.0 CHLOROFLUOROCARBONS

Chlorofluorocarbons (CFCs) are in common use in public buildings as propellents and refrigerants. These CFCs have the potential to impact human health in two ways: 1) the toxicological effects of the contaminants themselves, and 2) the health impact associated with their role in reducing the stratospheric ozone layer. Considerable research and controversy are occurring on the reduction of the stratospheric ozone layer. In this report, three CFCs were selected to examine direct health effects: 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113), trichlorofluoromethane, and dichlorodifluoromethane. Because the human health impact of the reduction of the stratospheric ozone layer is part of a very involved and ongoing investigative process, only a very general discussion of the potential health effects from the reduction of the stratospheric ozone layer will be provided.

4.1 DIRECT HEALTH EFFECTS OF CFCs

The EPA-maintained IRIS system addresses three CFCs of concern: 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113 or FREON 113), trichlorofluoromethane (Freon 11), and dichlorodifluoromethane (FREON 12).

4.1.1 1,1,2-Trichloro-1,2,2-Trifluoroethane (CFC-113 or FREON 113)

Freon 113 has a Hazard Rating of 1 (Sax and Lewis 1989).

Noncarcinogenic Effects - The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfDo for trichlorotrifluoroethane is 3E+1 mg/kg/day, with the critical effect being psychomotor impairment. The NOAEL is 5358 mg/m^3 (can be converted to 273 mg/kg/day) (IRIS 1990). IRIS noted that the RfDo for trichlorotrifluoroethane may change in the near future, pending the outcome of a further review being conducted by the Oral RfD Work Group.

Several animal inhalation studies reported negative results in dogs, rabbits, and rats chronically exposed to very high concentrations of trichlorotrifluoroethane (EPA 1983, as cited in IRIS 1990). No apparent adverse effects have been reported in humans occupationally exposed to trichlorotrifluoroethane at either 500 mg/m^3 levels for 11 years of 5358 mg/m^3 for 2.77 years (Imbus and Adkins, 1972, as cited in IRIS 1990).

Slight impairment of psychomotor performance was reported in male volunteers exposed to trichlorotrifluoroethane concentrations of 19,161 mg/m^3 for 2.75 hours (Stopps and McLaughlin 1967, as cited in IRIS 1990). This exposure period was too brief to consider a NOAEL for chronic exposure. Therefore, the RfD of 30 mg/kg/day is considered protective (IRIS 1990).

There is no RfDi for trichlorotrifluoroethane at this time.

The confidence in the RfDo is low. Confidence in the chosen study, database, and RfDo are all considered low. Despite the fact that the chosen study describes human data and the fact that several chronic studies in animals are supportive, uncertainties in both the exposure levels and route extrapolation preclude higher confidence ratings (IRIS 1990).

Human Carcinogenicity - Trichlorotrifluoroethane has not been evaluated by the EPA for evidence of human carcinogenic potential (IRIS 1990).

4.1.2 Trichlorofluoromethane (FREON 11)

FREON 11 has a Hazard Rating of 3 (Sax and Lewis 1989).

Noncarcinogenic Effects - The RfDo for trichlorofluoromethane is 3E-1 mg/kg/day, with survival and histopathology as the critical effects. No NOAEL was established. The LDAEL is 488 mg/kg/day (can be converted to 349 mg/kg/day) (IRIS 1990).

The NCI bioassay (NCI 1978, as cited in IRIS 1990) was performed on rats and mice exposed to various doses of trichloromonofluoromethane by gavage over a period of 78 weeks (50 animals/species/sex/dose for each of two doses with 20 animals/species/sex for each of two control groups). A statistically significant positive association between increased dosage and accelerated mortality by the Tarone test in male and female rats and female mice was observed. In treated rats of both sexes, there were also elevated incidences

of pleuritis and pericarditis not seen in controls. Inhalation studies that employed multispecies exposures to higher levels of the compound than used by the NCI (Leuschner et al. 1983, Colman et al. 1981, Hansen et al. 1984, all as cited in IRIS 1990) reported no adverse clinical/pathologic signs of toxicity from subchronic or short-term exposures (IRIS 1990).

The LOAEL of 488 mg/kg/day (mortality in rats) was converted to 349 mg/kg/day on a 7-day exposure basis (IRIS 1990).

The RfDo has been given a confidence level of medium. The chosen study is given a medium confidence rating because large numbers of animals per sex were tested in two doses for chronic exposures, but the study did not establish a NOAEL. The database is given a medium confidence rating because of the support of chronic data but lack of reproductive data. A medium confidence in the RfDo follows (IRIS 1990).

No RfDi is available at this time.

Human Carcinogenicity - Trichlorofluoromethane has not been evaluated by the EPA for evidence of human carcinogenic potential (IRIS 1990).

4.1.3 Dichlorodifluoromethane (FREON F-12)

FREON F-12 has a Hazard Rating of 1 (Sax and Lewis 1989).

Noncarcinogenic Effects - The RfDo for dichlorodifluoromethane is 2E-1 mg/kg/day, with reduced body weight the critical effect. The NOEL is 300 ppm (can be converted to 15 mg/kg/day). The LOAEL is 3000 ppm (can be converted to 150 mg/kg/day) (IRIS 1990).

The study reported by the Haskell Laboratory (Sherman 1974, as cited in IRIS 1990) involved 2-year feeding studies in which dogs and rats received 300 ppm or 3000 ppm of dichlorodifluoromethane. This report contained data on clinical biochemical, urine analytical, hematological or histopathological evaluations. Additionally, carcinogenic and three-generation reproductive studies were conducted in rats. Except for decreased weight gain in rats (about 20% in females) that received 3000 ppm dichlorodifluoromethane in the diet, no other adverse effects were attributable to this compound in either rats or dogs (IRIS 1990).

The Haskell Laboratory study is sufficiently complete to derive an RfD for adequate protection against adverse human health effects. The high dose (3000 ppm) caused decreased body weights in rats and is therefore considered a LOAEL, whereas the low dose (300 ppm) in rats produced no adverse effects attributable to the oral administration of dichlorodifluoromethane (IRIS 1990).

The confidence in the RfDo is medium. The Haskell Laboratory study is a chronic oral study in two species that incorporated extensive clinical and toxicologic parameters. Therefore, a high level of confidence in the study is appropriate. Confidence in the database is medium because of the lack of teratology and reproductive data. Medium confidence in the RfDo follows (IRIS 1990).

There is no RfDi available at this time.

4.2 HEALTH EFFECTS OF STRATOSPHERIC OZONE LAYER REDUCTION

The stratospheric ozone layer has several interesting effects. Because of the absorption characteristics of ozone, it filters ultraviolet radiation on its way to the earth's surface. Thus, it reduces the amount of photochemical activitity to which humans are exposed. This reduction is essential because humans can not survive exposure to the ultraviolet radiation from the sun without some attenuation by the ozone layer. Consequently, any significant reduction of this ozone layer could directly affect human health.

Nevertheless, humans need some ultraviolet radiation. The amount of sunlight humans are exposed to directly affects the amount of vitamin D produced in the skin. A substantial reduction in ultraviolet radiation would lead to vitamin D deficiencies in humans. On the other hand, if the ultraviolet radiation increased considerably, severe skin problems would result. The vast problem of global warming and all of its impacts on humans are also part of the concern over the depletion of the ozone layer.

The CFCs considered are only one of several contributors to the problem of the stratospheric ozone layer depletion. For example, proposed supersonic

jet flights in the upper atmosphere have been a major concern. Nitric oxides released from these planes react with ozone to reduce the average ozone concentration at those altitudes.

5.0 IMPLICATIONS OF RISK ASSESSMENT IN INDOOR AIR

The number of hazardous chemical contaminants potentially present in the indoor air of public buildings is overwhelming. However, the overall health impact is probably not as great as would be expected because of the normally low concentrations of these chemicals in the indoor air. The information needed to adequately assess the magnitude of the health impact of each of these chemicals is quite limited. In addition, these chemicals exist in the indoor air environment in the form of complex mixtures, which in many cases causes the chemicals to behave differently (in terms of effect on human health) than they do when considered separately.

The health effects information presented in this document reflects current research and conclusions, but several limitations exist. First, health effect data was normally determined by exposing animals to fairly high doses of chemicals. This approach requires that the data be extrapolated back down to the normally low doses of the chemical that a person is exposed to in public buildings. This extrapolation process is complicated by the assumptions that must be made; for example, whether there is a threshold effect for the chemical and whether the data is linear at low doses or how it should be extrapolated for these low doses.

This data interpretation process is further complicated by the fact that the data must be translated from the effects on animals to the effects on humans. In addition, as mentioned, chemicals exist in the indoor air environment in the form of complex mixtures. Considerably more research needs to be conducted to draw definitive conclusions as to the full impact on human health by the host of potential hazardous chemicals that may be found in the indoor environment of public buildings.

Normally, the assumptions made regarding the development of the health effect parameters and factors presented in this document are conservative (i.e., they err on the side of overpredicting adverse effects). Thus, while research continues on health effects of the host of chemicals and complex chemical mixtures that could exist in public buildings, these parameters and factors (which should be updated regularly as research progresses) should be

used to provide estimates of the health impact and risk for particular building situations. In making building-specific health or risk assessments, specific building conditions should be determined as accurately as possible to consider the most realistic set of chemicals, mixture combinations, concentrations of chemicals, and physical conditions.

6.0 REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR). 1987. *Toxicological Profile for Selected PCBs*. U.S. Public Health Service, Centers for Disease Control, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia.

American Conference of Governmental Industrial Hygienists (ACGIH). 1988. *Threshold Limit Values and Biological Exposure Indices for 1988-1989*. ISBN: 0-936712-78-3. Cincinnati, Ohio.

Baechler, M. C., H. Ozkaynak, J. D. Spengler, L. A. Wallace, and W. C. Nelson. 1989. "Assessing Indoor Exposure to Volatile Organic Compounds Released From Paint Using the NASA Data Base." In *Proceedings of 82nd Annual Meeting and Exhibition, Air and Waste Management Association*, Anaheim, California.

Girman, J. R., and A. T. Hodgson. 1986. "Source Characterization and Personal Exposure to Methylene Chloride from Consumer Products." In *Proceedings of the 79th Annual Meeting of Air Pollution Control Association (APCA)*, Minneapolis, Minnesota.

Girman, J. R., A. T. Hodgson, A. S. Newton, and A. W. Winkes. 1987. "Volatile Organic Emissions from Adhesives with Indoor Applications." In *Proceedings of the International Conference on Indoor Air Quality and Climate, Institute for Water, Soil and Air Hygiene*, Berlin.

Hazardous Substances Data Bank (HSDB). 1990. *On Line (An Active On-Line Data Base Available on the MEDLARS System)*. Maintained by National Library of Medicine). National Library of Medicine, MEDLARS Management Section, Rockville, Maryland.

Integrated Risk Information System (IRIS). 1990. *On Line (An Active On-Line Data Base Available on the TOXNET System)*. Maintained by EPA. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

Jungers, R. H., and L. S. Sheldon. 1987. "Characterization of Volatile Organic Chemicals in Public Access Buildings." In *Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Institute for Water, Soil and Air Hygiene*, Berlin.

Kalf, G. F., G. B. Post, and R. Snyder. 1987. "Solvent Toxicology: Recent Advances in the Toxicology of Benzene, The Glycol Ethers, and Carbon Tetrachloride." *Ann. Rev. Pharmacol. Toxicol.* pp. 399-427, Annual Review Incorporated.

Krause, C., W. Mailahn, R. Nagel, C. Schulz, B. Seifert, and D. Ullrreh. 1987. "Occurrence of Volatile Organic Compounds in the Air of 500 Homes in the Federal Republic of Germany." In *Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Institute for Water, Soil and Air Hygiene*, Berlin.

Krzyzanowski, M., J. J. Quackenboss and M. D. Lebowitz. 1989. *Chronic Respiratory Effects of Indoor Formaldehyde Exposure*. University of Arizona Health Sciences Center, Tucson, Arizona.

Molhave, L. 1982. "Indoor Air Pollution Due to Organic Gases and Vapours of Solvents in Building Materials." *Environment International*, 8:117-127.

National Institutes of Health (NIH). 1989. *National Library of Medicine: MEDLARS The World of Medicine At Your Fingertips*. NIH Publication No. 89-1286, U.S. Department of Health and Human Services, Bethesda, Maryland.

Nied, G. J., and P. K. TerKonda. 1983. *Health Effects from Formaldehyde Emissions*. Department of Health, Division of Air Pollution Control, Cleveland, Ohio and University of Missouri-Rolla, Rolla, Missouri.

Registry of Toxic Effects of Chemical Substances (RTECS). 1987. *Hard-Copy (An Active Online Data Base Available through National Institute of Occupational Safety and Health [NIOSH])*, Cincinnati, Ohio.

Rinsky, R. A., R. J. Young, and A. B. Smith. 1981. "Leukemia in Benzene Workers." *Am. J. Ind. Med.* 2:217-245.

Rinsky, R. A., A. B. Smith, R. Hornung, T. G. Filloon, R. J. Young, A. H. Okun, and P. J. Landrigan. 1987. "Benzene and Leukemia: An Epidemiologic Risk Assessment." *N. Engl. J. Med.* 316(17):1044-1050.

Sax, N. I. and R. J. Lewis, Sr. 1989. *Dangerous Properties of Industrial Materials*, Volumes I, II, and III. Van Nostrand Reinhold, New York, New York.

Tichenor, B. A., and M. A. Mason. 1986. "Characterization of Organic Emissions from Selected Materials in Indoor Use." In *Proceedings of the Air Pollution Control Association (APCA), 79th Annual Meeting*, Minneapolis, Minnesota.

Tichenor, B. A., and M. A. Mason. 1988. "Organic Emissions from Consumer Products and Building Materials to the Indoor Environment." *Journal of the Air Pollution Control Association (APCA)*, 38: 264-268.

Tichenor, B. A. 1989. *Indoor Air Sources: Using Environmental Test Chambers to Characterize Organic Emissions from Indoor Materials and Products*. EPA-600/8-89-074, U.S. Environmental Protection Agency, Air and Energy Engineering Research Laboratory, Research Triangle Park, North Carolina.

U.S. Department of Energy (DOE). 1984. *The Expanded Residential Weatherization Program - Final Environmental Impact Statement.* DOE/EIS-0095F, Bonneville Power Administration, Portland, Oregon.

U.S. Department of Energy (DOE). 1987. *Draft Environmental Impact Statement on New Energy-Efficient Homes Programs, Volume II.* DOE/EIS-0127, Bonneville Power Administration, Portland, Oregon.

U.S. Environmental Protection Agency (EPA). 1984a. *Health Effects Assessment for Benzene.* EPA/540/1-86/037, U.S. EPA, Office of Research and Development, Cincinnati, Ohio, and Office of Emergency and Remedial Response, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1984b. *Health Effects Assessment for Carbon Tetrachloride.* EPA/540/1-86/039, U.S. EPA, Office of Research and Development, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1984c. *Health Effects Assessment for Chloroform.* EPA/540/1-86/010, U.S. EPA, Office of Research and Development, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1985. *Health Assessment Document for Tetrachloroethylene (Perchloroethylene)* - Final Report. EPA/600/s-82/005F, U.S. EPA, Office of Research and Development, Research Triangle Park, North Carolina.

U.S. Environmental Protection Agency (EPA). 1987. *Health Effects Assessment for Trimethylbenzenes.* EPA/600/8-88/060, U.S. EPA, Office of Research and Development, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1988. *Indoor Air Facts - Sick Buildings.* U.S. EPA, Office of Research and Development and Office of Air and Radiation, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1988. Appendix to EPA 1985.

U.S. Environmental Protection Agency (EPA). 1988b. *Indoor Air Quality in Public Buildings: Volume I.* EPA/600/S6-88/009, U.S. EPA, Office of Acid Deposition, Environmental Monitoring and Quality Assurance, Washington, D.C.

U.S. Nuclear Regulatory Commission (NRC). 1986. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.* National Research Council, National Academy Press, Washington, D.C.

Wallace, L. A., E. D. Pellizzari, and S. M. Gordon. 1984. "Organic Chemicals in Indoor Air: A Review of Human Exposure Studies and Indoor Air Quality Studies" in *Indoor Air and Human Health. Seventh Life Sciences Symposium.* Oak Ridge National Laboratory, Lewis Publishers, Inc., Chelsea, Michigan.

Wallace, L. A. 1986. "Estimating Risk from Measured Exposures to Six Suspected Carcinogens in Personal Air and Drinking Water in 600 U.S. Residents." In *Proceedings of Air Pollution Control Association (APCA), 79th Annual Meeting*, Minneapolis, Minnesota.

Wallace, L. A. 1987. *The Total Exposure Assessment Methodology (TEAM) Study Summary and Analysis: Volume 1.* EPA/600/6-87/002, U.S. EPA, Office of Research and Development, Washington, D.C.

Wallace, L. A., R. Jungers, L. Sheldon, and E. Pellizzari. 1987a. "Volatile Organic Chemicals in 10 Public-Access Buildings." In *Indoor Air '87: Proceedings of the 4th International Conference on Indoor Air Quality and Climate.* Institute for Water, Soil and Air Hygiene, Berlin.

Wallace, L. A., E. Pellizzari, B. Leaderer, H. Zelon, and L. Sheldon. 1987b. "Emissions of Volatile Organic Compounds from Building Materials and Consumer Products." *Atmospheric Environment 21:385-393, Pergamon Journals Ltd.*

Walsh, P. J., C. S. Dudney, and E. D. Copenhaver. 1984. *Indoor Air Quality.* CRC Press, Inc., Boca Raton, Florida.

DISTRIBUTION

No. of Copies

OFFSITE

2 DOE/Office of Scientific and Technical Information

25 G. C. Insley
Bonneville Power Administration
P.O. Box 3621
Portland, Oregon 97208-3621

ONSITE

DOE Richland Operations Office

R. B. Goranson

No. of Copies

15 Pacific Northwest Laboratory

M. C. Baechler (5)
M. R. Brambley
D. L. Hadley
L. D. Kannberg
T. J. Marseille
Publishing Coordination
Technical Report Files (5)