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Toxicological Profile for

TETRACHLOROETHYLENE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about tetrachlorocthylene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). Tetrachloroethylene has been found in at least 714 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for tetrachloroethylene. As EPA evaluates more sites, the number of sites at which tetrachloroethylene is found may change. This information is important for you to know because tetrachloroethylene may cause harmful health effects and because these sites are potential or actual sources of human exposure to tetrachloroethylene.

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

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

1.1 WHAT IS TETRACHLOROETHYLENE?

Tetrachloroethylene is a synthetic chemical that is widely used for dry cleaning fabrics and for metal-degreasing operations. It is also used as a starting material (building block) for making other chemicals and is used in some consumer products. Other names for tetrachloroethylene include perchloroethylene, PCE, perc, tetrachloroethene, perclene, and perchlor. It is a nonflammable liquid at room temperature. It evaporates easily into the air producing a sharp, sweet odor. Most people can smell tetrachloroethylene when it is present in the air at a level of 1 part in 1 million parts of air (ppm) or more. You can smell tetrachloroethylene in water if there is 0.3 ppm or more of it. For more information, see Chapters 3 and 4.

leaves your body in a few days. A small amount of the tetrachloroethylene that you take in stays in the tissues of your body. Part of the tetrachlorocthylene that is stored in fat may stay in your body for several days or weeks. For more information on how tetrachloroethylene enters and leaves your body, see Chapter 2.

1.5 HOW CAN TETRACHLOROETHYLENE AFFECT MY HEALTH?

Tetrachloroethylene has been used as a general anesthetic agent. Therefore, when concentrations in air are high--particularly in closed, poorly ventilated areas--single exposures to tetrachloroethylene can cause dizziness, headache, sleepiness, confusion, nausea, difficulty in speaking and walking, and possibly unconsciousness and death. Skin irritation may result from repeated or extended contact with the chemical. As you might expect, these symptoms occur almost entirely in work (or hobby) environments where individuals have been accidentally exposed to high concentrations. Some people may be exposed to levels lower than those causing dizziness, sleepiness, and other nervous system effects. The health effects of breathing in air or drinking water with low levels of tetrachloroethylene are not known. The effects of exposing babies to tetrachloroethylene through breast milk are unknown. Results from some studies suggest that women who work in dry cleaning industries may have more menstrual problems and spontaneous abortions than women who are not exposed to tetrachloroethylene. However, we do not know if tetrachloroethylene was responsible for these problems because other possible causes were not considered. The chemical does not seem to cause birth defects in children whose parents are exposed to it.

Animal studies, conducted with amounts much higher than those that most people are exposed to, show that tetrachloroethylene can cause liver and kidney damage and liver and kidney cancers. However, it has not been shown to cause cancer in people. The Department of Health and Human Services has determined that tetrachloroethylene may reasonably be anticipated to be a carcinogen. Tetrachloroethylene can be toxic to the fetuses of rats and mice. The only developmental effects seen in the offspring of rats that breathed very high levels of the chemical while they were pregnant were minor changes in the brain and behavior of the offspring. Since this was the only study showing developmental effects, we do not know how meaningful these results are.

For more information on the health effects of tetrachloroethylene, see Chapter 2.

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

One way of testing for tetrachloroethylene exposure is to measure the amount of the chemical in the breath, much the same way breath alcohol measurements are used to

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of tetrachloroethylene and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for tetrachloroethylene based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989b), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Human deaths caused by tetrachloroethylene inhalation have been reported. A 33-year-old man was found unconscious after performing work on a plugged line in a commercial dry cleaning establishment and died on the way to the hospital (Lukaszewski 1979). Exposure to tetrachloroethylene was presumably by inhalation since an autopsy revealed no tetrachloroethylene in the stomach content, but high levels of the compound in the blood and brain (4.4 mg/100 mL and 36 mg/100 g, respectively). In another report, a 53-year-old male dry cleaner died after being overcome by tetrachloroethylene fumes (Levine et al. 1981). In both of these reports, the level of tetrachloroethylene exposure was not reported. However, at high vapor concentrations tetrachloroethylene is both a potent anesthetic agent and a cardiac epinephrine sensitizer. Therefore, sudden death resulting from acute exposure to anesthetic vapor concentrations is presumed to be due either to excessive depression of the respiratory center or to the onset of a fatal cardiac arrhythmia induced by epinephrine sensitization.

There were no major differences between mice and rats in susceptibility to lethal effects of tetrachloroethylene following acute or intermediate exposure. In addition, no sex differences in response were detected. A 4-hour inhalation LC_{50} of 5,200 ppm for female albino mice has been established. Data used to derive the LC_{50} show that the highest concentration of tetrachloroethylene for a 4-hour exposure that was not lethal to mice was 2,450 ppm; the lowest concentration that caused death was 3,000 ppm (Friberg et al. 1953). In another study, the highest concentration for a 4-hour exposure that did not result in death in B6C3F_1 mice or Fischer-344 rats of both sexes was 2,445 ppm; the lowest concentrations causing death were 2,613 ppm in mice and 3,786 ppm in rats (NTP 1986). A single 10- or 14-hour exposure of rats to 2,000 ppm and a single 4-hour exposure to 3,000 ppm did not produce death, while death occurred with exposure to 3,000 ppm for 5 hours or longer (Rowe et al. 1952).

Rats and mice were exposed to tetrachloroethylene by inhalation for 14 days or 13 weeks (NTP 1986). In the 14-day study, mortality occurred in rats exposed to 1,750 ppm tetrachloroethylene but not in mice. Compound-related mortality did not occur in either species at exposure concentrations of 875 ppm or lower. In the 13-week inhalation study, mortality occurred in rats and mice exposed to 1,600 ppm tetrachloroethylene but not to concentrations of 800 ppm or lower.

Mortality in rats exposed to 200 or 400 ppm tetrachloroethylene and mice exposed to 100 or 200 ppm tetrachloroethylene by inhalation in a 103-week carcinogenesis bioassay was a result of compound-related lesions and neoplasms (NTP 1986). This study is discussed in Sections 2.2.1.2 and 2.2.1.8.

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

2.2.1.2 Systemic Effects

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

No studies were located regarding gastrointestinal or musculoskeletal effects in humans or animals after inhalation exposure to tetrachloroethylene.

Respiratory Effects. Intense irritation of the upper respiratory tract was reported in volunteers exposed to high concentrations (>1,000 ppm) of tetrachloroethylene (Carpenter 1937; Rowe et al. 1952). These older acute inhalation studies in humans were limited by a small number of experimental volunteer subjects, incomplete characterization of subjects, variable concentrations of tetrachloroethylene, and reliance on symptomatology, which are subjective data. Despite these limitations, some of the end points identified at high concentrations provide important toxicological data on tetrachloroethylene effects in humans. Respiratory irritation (irritation of the nasal passages) was reported in workers exposed to tetrachloroethylene vapors at levels of 232–385 ppm in a degreasing operation (Coler and Russmiller 1953) and in volunteers exposed to concentrations as low as 216 ppm for 45 minutes to 2 hours (Rowe et al. 1952). Volunteers exposed to concentrations as high as 1,060 ppm could tolerate no more than 1–2 minutes of exposure before leaving the chamber (Rowe et al. 1952). Pulmonary edema occurred in a case of accidental exposure although this lesion may have been a secondary finding (Patel et al. 1973).

Compound-related lung lesions have not been reported in animals exposed to tetrachloroethylene by inhalation. However, in a study in mice evaluating susceptibility to infection from inhaled Streptococcus zooepidemicus and pulmonary bacteriocidal activity to inhaled Klebsiella pneumoniae, exposure to 50 ppm tetrachloroethylene for 3 hours affected both parameters. The primary adverse effect of tetrachloroethylene was hypothesized to be on alveolar macrophage activity, although other pulmonary and extrapulmonary defense mechanisms may also have been involved (Aranyi et al. 1986). However, owing to variability in control group mortality and the lack of evaluation of specific immunological end points, the relevance of the findings is unclear.

Cardiovascular Effects. There was a case report of a 24-year-old man who experienced cardiac arrhythmia (frequent premature ventricular beats). The patient had been employed for 7 months in a dry cleaning facility where he treated clothes with tetrachloroethylene (Abedin et al. 1980). Plasma tetrachloroethylene was measured at 0.15 ppm on his 5th day of hospitalization. The patient was discharged the next day, but returned in 2 weeks for outpatient evaluation with a recurrence of skipping of heartbeats, headache, and dizziness. At that time, plasma tetrachloroethylene was measured at 3.8 ppm. The patient was reported to be asymptomatic 1 month after finding different employment.

Epinephrine-induced cardiac arrhythmia was not induced in beagle dogs exposed by face mask to 5,000 or 10,000 ppm tetrachloroethylene (Reinhardt et al. 1973). This study was complicated by the dogs' struggling, which could represent early anesthetic effects of tetrachloroethylene, as well as irritant effects of these high tetrachloroethylene concentrations on the upper respiratory tract.

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to tetrachloroethylene. There is one case report of polycythemia vera, a proliferative disorder of bone marrow pluripotent stem cells, in a father and son who were exposed to organic solvents including tetrachloroethylene. The son had 22 years of exposure history, including transient exposure above 300 ppm for 5 minutes out of any 3 hours (Ratnoff and Gress 1980). Because genetic and other environmental factors may predispose a person to development of polycythemia vera, this condition cannot be related to exposure to tetrachloroethylene specifically or solvents in general.

Rats exposed to 230 or 470 ppm tetrachloroethylene for up to 160 days had splenic congestion and increased hemosiderin deposits (Carpenter 1937). Study limitations include use of sick animals (parasites, pneumonia), nonstandard study protocols, rats of undefined strain, and inadequate controls.

Hepatic Effects. The liver is a target organ in humans, particularly in those accidentally exposed to high concentrations. Hepatocellular damage was documented by biopsy in a case study of a woman exposed occupationally to tetrachloroethylene fumes (Meckler and Phelps 1966). Liver damage also has been diagnosed by the presence of hepatomegaly, icterus, and elevations of serum biomarkers of liver dysfunction (Coler and Rossmiller 1953; Hake and Stewart 1977; Meckler and Phelps 1966; Saland 1967). There was one case report of diffuse fatty liver in a dry cleaner who died shortly after being exposed to tetrachloroethylene fumes (Levine et al. 1981). Because of the brief interval between exposure and death, this liver lesion may have been pre-existent.

Hepatic effects as measured by elevations in serum alanine aminotransferase (also known as serum glutamic pyruvic transaminase) were not detected in 22 dry cleaning workers in Belgium exposed to a time-weighted average (TWA) of 21 ppm tetrachloroethylene over an average of 6 years (Lauwerys et al. 1983).

Liver is also a target organ in animals, with hepatic lesions induced in experimental animals by inhalation exposure to tetrachloroethylene. Mice appear to be the most sensitive species to this effect. Hepatocellular vacuolization occurred after a single 4-hour exposure of mice to 200 ppm or greater concentrations of tetrachloroethylene (Kylin et al. 1963, 1965). This lesion was also reported in male B6C3F_1 mice exposed to 875 or 1,750 ppm tetrachloroethylene for 14 days and in females exposed to the highest dose. Vacuolization was not present at 425 ppm (NTP 1986). A number of lesions reported in rats after acute exposure to tetrachloroethylene were relatively nonspecific; no trend of damage to a specific organ could be identified (Carpenter 1937; NTP 1986; Rowe et al. 1952).

Liver lesions differed markedly between mice and rats after longer duration exposure. In a 13-week study, male mice exposed to 200 ppm and higher concentrations had mitotic alterations in the liver while both sexes had leukocytic infiltrations, centrilobular necrosis, and bile stasis at 400 ppm and higher concentrations (800, 1,600 ppm) of tetrachloroethylene. Rats, on the other hand had liver congestion at 200 ppm, but had no hepatocellular lesions at any exposure concentration (NTP 1986).

Another inhalation study in mice and rats correlated light microscopic and ultrastructural liver lesions with liver levels of cyanide-insensitive palmitoyl CoA oxidase, a marker for peroxisomal β-oxidation (Odum et al. 1988). Animals were exposed to 200 ppm of tetrachloroethylene for 28 days or 400 ppm for 14, 21, or 28 days. Centrilobular hepatocellular vacuolization was induced in mice by tetrachloroethylene exposure; this lesion corresponded to lipid accumulation ultrastructurally. Centrilobular hepatocytes with cytoplasmic eosinophilia on light microscopy had marked proliferation of cytoplasmic peroxisomes at the ultrastructural level, and there was a significant increase in the marker enzyme. These changes occurred in mice at both doses and all exposures and were most pronounced in male mice. Exposed male rats in both dose groups and female rats exposed to 400 ppm developed centrilobular hepatocellular hypertrophy, which ultrastructurally consisted of proliferation of smooth endoplasmic reticulum. There was no increase in peroxisomes (Odum et al. 1988).

NMRI mice were exposed to 0, 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days (Kjellstrand et al. 1984). Exposed mice developed hepatocellular vacuolization and enlargement. Lesions were observed at 37 ppm, and were noted to be most pronounced at exposures to 75 and 150 ppm tetrachloroethylene. It was not possible to determine if a dose-response relationship existed for this effect because the nature and extent of the lesions at each dose were not reported. Relative liver weights were not calculated; however, absolute liver weights were significantly elevated at exposure concentrations of 9 ppm and higher. Liver weights were still increased (10%) 120 days following 30 days of continuous exposure to 150 ppm. Plasma butyrylcholinesterase (BuChe) also was elevated in some exposed mice but

the significance of this increase is unclear for two reasons: there was wide variability in BuChe activity in the controls, and plasma BuChe can be modulated by nonhepatic factors (Kjellstrand et al. 1984). Based on the LOAEL of 9 ppm in this sensitive species, an intermediate inhalation MRL of 0.009 ppm was calculated as described in the footnote in Table 2-1.

The hepatic effects of tetrachloroethylene in guinea pigs were evaluated in an older subchronic inhalation study, but there have been no subsequent investigations in this species. Changes reported were increased liver weight (≥200 ppm) and cirrhosis (400 ppm) (Rowe et al. 1952). Major limitations on use of these data include use of rodents of undefined strain, lack of standardized protocols, small numbers of animals per exposure group, incomplete necropsy examination, inadequate controls, selective histopathological evaluation, and lack of quantitative supporting data.

Hepatocellular degeneration and necrosis occurred in male mice exposed to 100 and 200 ppm tetrachloroethylene for 103 weeks and in females exposed to 200 ppm. Liver lesions were not reported in rats exposed chronically to 200 or 400 ppm tetrachloroethylene, but the effects of mononuclear cell leukemia infiltrates may have obscured subtle compound-induced changes (NTP 1986). Both sexes of mice also had increased incidences of hepatocellular tumors at both exposure concentrations. This study is discussed further in Section 2.2.1.8.

Renal Effects. Symptoms of renal dysfunction, including proteinuria and hematuria have been associated with accidental exposure to anesthetic concentrations of tetrachloroethylene vapor (Hake and Stewart 1977). Weak or no renal effects, depending on the parameters evaluated, were reported in people with chronic occupational exposure. Workers in dry cleaning shops exposed for an average of 14 years to an estimated TWA of 10 ppm of tetrachloroethylene had increased urinary levels of lysozyme and β-glucuronidase suggestive of mild tubular damage (Franchini et al. 1983). In another report, serum creatinine and urinary albumin, β-μ-globulin and retinol-binding protein levels were normal in dry cleaning workers exposed to a TWA of 21 ppm of tetrachloroethylene for 6 years (Lauwerys et al. 1983).

In animal studies, lesions compatible with toxicity occurred in rodents exposed to tetrachloroethylene. Hyaline droplets in proximal tubules but no tubular damage or cell proliferation occurred in male rats exposed to 1,000 ppm by inhalation for 10 days (Green et al. 1990). Male rats exposed to 400 ppm tetrachloroethylene (the same concentration used in the NTP [1986] chronic study) for 28 days did not develop kidney lesions (Green et al. 1990). In other intermediate-duration studies, rats exposed to 470 ppm for 150 days or to 7,000 ppm for 40 or more exposures had intratubular casts and swelling and desquamation of tubular epithelium (Carpenter 1937). On the other hand, abnormal renal function or histopathological findings were not observed in rats or guinea pigs exposed to tetrachloroethylene vapor concentrations of 0, 100, 200, or 400 ppm for about 6 months (Rowe et al. 1952). Guinea pigs that received 18 exposures of 7 hours each to 2,500 ppm tetrachloroethylene over a period of 20 days had increased kidney weights, with slight-to-moderate cloudy swelling of tubular epithelium. The major limitations and data unreliability of Carpenter (1937) and Rowe et al. (1952) have been discussed under hematological effects and hepatic effects, respectively, in this section (Section 2.2.1.2).

Renal tubular karyomegaly (nuclear enlargement) occurred in both sexes of mice exposed to 200, 400, 800, and 1,600 ppm tetrachloroethylene for 13 weeks but did not occur in mice exposed to 100 ppm. Kidney lesions did not occur in rats exposed to 1,600 ppm; kidneys from lower-dose groups were not examined microscopically (NTP 1986).

Peroxisomal proliferation induced in hepatocytes by tetrachloroethylene exposure appeared to be correlated with hepatotoxicity and cell proliferation. However, peroxisomal proliferation in renal tubular epithelium of rats or mice was not induced by exposure to 200 or 400 ppm tetrachloroethylene for up to 28 days (Odum et al. 1988).

In the chronic inhalation toxicity/oncogenicity study of tetrachloroethylene, Fischer-344 rats of each sex were exposed to 0, 200, or 400 ppm tetrachloroethylene, and B6C3F$_1$ mice were exposed to 0, 100, or 200 ppm tetrachloroethylene for 103 weeks (NTP 1986). Dose-related renal tubular cell karyomegaly occurred in both species and sexes at all exposure concentrations. This alteration was accompanied by low incidences of renal tubular cell hyperplasia in male rats.

Dermal/Ocular Effects. Intense irritation of the eyes of humans was noted following acute exposure to high concentrations (>1,000 ppm) of tetrachloroethylene vapors (Carpenter 1937; Rowe et al. 1952). Burning or stinging sensations in the eyes occurred after exposure to 600 or 280 ppm: very mild irritation was reported by four subjects at exposure to 216 or 106 ppm (Rowe et al. 1952). The limitations of the Carpenter (1937) and Rowe et al. (1952) studies regarding human data have been discussed under respiratory effects in this section (Section 2.2.1.2).

No studies were located regarding dermal or ocular effects in animals after inhalation exposure to tetrachloroethylene.

2.2.1.3 Immunological Effects

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

There are also no reliable data to assess immunological effects in animals following inhalation exposure. However, in a mouse study (see the discussion on respiratory effects in Section 2.2.1.2), there was increased host susceptibility to pulmonary bacterial infection after a 3-hour inhalation exposure to 50 ppm tetrachloroethylene (Aranyi et al. 1986). The specific mechanism of the increased susceptibility is unknown. The significance of the study is unclear because of variability in control group mortality and lack of evaluation of specific immunological end points.

Rats exposed continuously to tetrachloroethylene vapors (4.2 or 19.3 ppm) for 94 days did not produce titers to tetrachloroethylene as measured by the passive hemagglutination reaction (Tsulaya et al. 1977). The significance of this negative result is unclear. Major study limitations include no mention of whether controls were chamber-housed, no details on animal husbandry in chambers, no indication of whether rats were free of intercurrent respiratory infections, incomplete documentation of technique, and a general paucity of quantitative data to support summary statements in the text.

2.2.1.4 Neurological Effects

The brain is a major target organ in humans exposed to tetrachloroethylene by inhalation. Acute exposure, depending on concentration, can result in reversible mood and behavioral changes, impairment of coordination, or anesthetic effects.

There have been several experimental studies of acute neurological effects in adult humans exposed to tetrachloroethylene. In one study, symptoms of neurological impairment were not reported after exposure

to 106 ppm for 1 hour (Rowe et al. 1952). Neurological symptoms of dizziness and drowsiness occurred at exposure to 216 ppm for 45 minutes to 2 hours; loss of motor coordination occurred at exposure to 280 ppm for 2 hours or 600 ppm for 10 minutes. Volunteers in this study were allowed to leave the exposure chamber when they experienced discomfort. Consequently, exposure times varied between subjects and exposure concentrations, and ranged from 3 minutes to 2 hours (Rowe et al. 1952). In another study, exposure to 100 ppm for 7 hours produced symptoms such as headache, dizziness, difficulty in speaking, and sleepiness (Stewart et al. 1970). Of five objective tests of central nervous system performance in humans exposed for 7 hours, none showed any abnormality except the Romberg test of balance, which was abnormal in three of the five subjects exposed for 7 hours a day for 5 consecutive days. Only one exposure level (100 ppm) was used in this study, and no control subjects were included (Stewart et al. 1970).

A comprehensive investigation was conducted with 19 volunteers (10 males and 9 females) exposed 5 days/week for 1 month to tetrachloroethylene vapor concentrations of 20, 100, or 1,500 ppm (Stewart et al. 1981). The findings of this study were initially reported in 1974 and subsequently published in 1981. Electroencephalogram (EEG) results indicated that major changes in the EEG of three of four male subjects and four of five female subjects occurred during exposure to 100 ppm. In the majority of subjects, the EEG changes were characterized by a reduction in overall wave amplitude and frequency, most strikingly evident in the occipital leads. The study authors stated that the altered EEG pattern was similar to that seen in healthy adults during drowsiness, light sleep, and the first stages of anesthesia.

In another study, four male volunteers were exposed to concentrations of 0, 20, 100, and 150 ppm tetrachloroethylene for 7.5 hours/day. Exposure at each concentration lasted for 5 days. Neurological effects were not identified by a battery of behavioral and neurological tests. However, electroencephalograph scores suggested cerebral cortical depression in subjects exposed to 100 ppm for 7.5 hours/day for 5 days. Coordination scores, as measured in males by the Flanagan coordination test, were significantly decreased at some time points during exposure to 100 or 150 ppm tetrachloroethylene (Hake and Stewart 1977). Based on a NOAEL of 20 ppm, an acute inhalation MRL of 0.6 ppm was calculated as described in the footnote in Table 2-1.

The anesthetic and preanesthetic central nervous system effects of tetrachloroethylene were documented in four volunteer subjects (one male, sex not specified for the other three) exposed acutely to concentrations ranging from 500 to 2,000 ppm. Mood changes, slight ataxia, faintness, and dizziness occurred with exposure to concentrations of 1,000–1,500 ppm for <2 hours. At exposure to 2,000 ppm for 5–7 minutes, subjects experienced a sensation of impending collapse (Carpenter 1937). Limitations of this study regarding the human experiments were discussed under respiratory effects in Section 2.2.1.2. Dizziness has been reported after brief accidental exposure to high concentrations of tetrachloroethylene fumes (Saland 1967) while longer exposures resulted in collapse, coma, and seizures (Hake and Stewart 1977; Morgan 1969).

The previously described experimental studies suggest that the threshold for neurological effects in humans resulting from acute-duration exposures is in the range of 100–200 ppm. A more precise determination of a threshold is not possible because of the small number of experimental subjects used, differences in exposure regimens, inconsistent results at the same exposure concentration, and the subjective and/or reversible nature of neurological effects evaluated.

Long-term neurotoxic effects may be a sequel of organic solvent exposure. The population studied for these effects included dry cleaning workers exposed for one year or longer to tetrachloroethylene. While

acute work-related symptoms, such as headache, seemed to improve after cessation of exposure of workers to solvents, symptoms suggestive of chronic encephalopathy, particularly memory and concentration impairment, persisted. These latter symptoms remained unchanged even after workers had been free of organic solvent exposure for 6.6 years and continued in workers still being exposed (Gregersen 1988). Limitations of the study reporting this 10-year follow-up of solvent-exposed workers are: the combining of workers exposed to organic solvents other than tetrachloroethylene (white spirit, toluene, and styrene) with dry cleaners for purposes of analysis; unknown exposure amounts and durations; possible skewed recruitment of the study population when the study was started in 1975; different methods employed in the two follow-up studies; and failure to confirm symptoms of chronic encephalopathy by a neuropsychological investigation.

In a study of dry cleaning workers (primarily women) in Belgium exposed to a TWA of 21 ppm tetrachloroethylene over an average of 6 years, no significant alterations were detected in neurological symptoms or psychomotor performances (Lauwerys et al. 1983). However, 17 of 22 subjective neurologic symptoms were more prevalent in the exposed group, particularly memory loss and difficulty in falling asleep. The major limitation of this study was the small size of control and exposed groups.

Dry cleaning workers exposed to a TWA of 12 or 54 ppm tetrachloroethylene had significantly impaired perceptual function, attention, and intellectual function compared to a control population when evaluated by a battery of psychological tests and questionnaires (Seeber 1989). Duration of exposure averaged 141 days for the low-exposure group and 127 days for the high-exposure group. Study showed no dose-response (no significant differences between high- and low-exposure groups), no correlation between test results and individual exposure levels as measured by blood tetrachloroethylene and urinary trichloroacetic acid (TCA) levels, and variable deviations between exposed and control populations.

Neurological effects and biochemical changes have been reported in animals. Many experimental studies did not correlate biochemical with behavioral effects or either parameter with morphologic changes in the brain. The significance of many of these studies regarding neurotoxicity is therefore unclear.

Neurological signs typical of an anesthetic effect of inhaled tetrachloroethylene have been reported in numerous animal studies (Table 2-1). These clinical signs consist of hyperactivity (excitability), ataxia, hypoactivity, and finally, loss of consciousness (Friberg et al 1953; NTP 1986; Rowe et al. 1952). In one study, mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at concentrations of 2,328 ppm (NTP 1986). Mice exposed to concentrations of 0, 100, 200, 425, 875, and 1,750 ppm for 6 hours per day, 5 days per week for 2 weeks experienced dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia at the highest concentration (NTP 1986). In another study, anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloroethylene (Friberg et al. 1953). Rats exposed to 0, 100, 200, 425, 875, and 1,750 ppm tetrachloroethylene for 6 hours per day, 5 days per week, for 2 weeks were observed to have dyspnea, hypoactivity, and ataxia at the highest dose (NTP 1986). In additional studies, rats exposed to 3,000 ppm tetrachloroethylene became anesthetized in several hours, while those exposed to 6,000 ppm were anesthetized in minutes (Rowe et al. 1952). Rats in a pole-climbing experiment became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dogs given 5,000 ppm tetrachloroethylene by face mask for less than 10 minutes became excited and struggled (Reinhardt et al. 1973). This response may have represented the early stages of anesthesia combined with irritant respiratory effects of tetrachloroethylene.

Behavioral alteration has been observed in rodents after inhalation exposure to tetrachloroethylene. Open-field behavior (ambulation) was elevated in groups of 10 male rats exposed to 200 ppm

tetrachloroethylene of unspecified purity for 6 hours a day for 4 days (Savolainen et al. 1977). Ambulation was significantly increased 1 hour, but not 17 hours, after the last exposure. Biochemical changes in the brains following several additional exposures were reduced ribonucleic acid (RNA) content and increased nonspecific cholinesterase content. There was no histologic examination of brain tissue so these findings could not be correlated with brain structural damage.

Behavioral and biochemical brain changes in rats were reported after prenatal exposure to tetrachloroethylene inhaled by their dams (Nelson et al. 1980). This study is discussed in Section 2.2.1.5.

Biochemical changes were reported in brains of rats and Mongolian gerbils exposed by inhalation to tetrachloroethylene. Gerbils exposed to 320 ppm continuously for 3 months followed by a 4-month exposure-free period had changes in levels of S-100 protein, a marker for astrocytes as well as other cells in the peripheral nervous system and skin (Rosengren et al. 1986). Rats exposed to 320 ppm continuously for 30 days had changes in brain cholesterol, lipids, and polyunsaturated fatty acids (Kyrklund et al. 1988). Gerbils exposed to 60 or 320 ppm had decreased deoxyribonucleic acid (DNA) content in portions of the cerebrum (Karlsson et al. 1987; Rosengren et al. 1986). Gerbils exposed to 120 ppm continuously for 12 months had altered phospholipid content (phosphatidylethanolamine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984). In another study, gerbils with a similar exposure regimen had decreased taurine content and increased glutamine content in areas of subcortical brain tissue (Briving et al. 1986). These studies are limited by failure to examine nervous tissue histologically in order to correlate biochemical changes with behavioral alterations or with morphologic evidence of brain damage. In addition, all but the Rosengren et al. (1986) study involved exposure to only one concentration of tetrachloroethylene.

Histologic lesions in the central nervous system have not been observed in chronic inhalation studies in rats and mice (NTP 1986).

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

2.2.1.5 Developmental Effects

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

Tetrachloroethylene has not been shown to be teratogenic in experimental animals. A slight but significant increase in maternal and fetal toxicity occurred in Sprague-Dawley rats and Swiss Webster mice exposed to 300 ppm tetrachloroethylene by inhalation on days 6–15 of gestation (Schwetz et al. 1975). Maternal or fetal toxicity or teratogenicity was not, however, reported for rats exposed on days 1–19 and rabbits on days 1–24 of gestation by inhalation to 500 ppm tetrachloroethylene (Hardin et al. 1981). Limitations of this study include use of only one dose level, the use of summary and nonquantitative data, and conduct of portions of the study at two separate laboratory facilities. Tetrachloroethylene was not teratogenic in rats or rabbits exposed to 0, 100, or 500 ppm before and during gestation (NIOSH 1980).

In a behavioral teratology study, pregnant Sprague-Dawley rats were exposed to 0, 100, or 900 ppm tetrachloroethylene on days 14–20 of gestation, and to 0 or 900 ppm tetrachloroethylene on days 7–13 (Nelson et al. 1980). Effects occurred after exposure to 900 ppm for both durations, but not after exposure to 100 ppm. Dams had reduced feed consumption and weight gain, without liver or kidney

histological alterations. Pups of dams exposed to 900 ppm on gestation days 7–13 had decreased performance during tests of neuromuscular ability (ascent on a wire mesh screen and rotorod balancing) on certain days. Offspring (before weaning) from dams exposed to 900 ppm on days 14–20 performed poorly on the ascent test on test day 14 only, but later in development, their performance in the rotorod balancing test was superior to controls, and they were more active in an open-field test. Brains of 21-day-old offspring exposed to 900 ppm prenatally had significant decreases in neurotransmitters (dopamine in those exposed on gestation days 14–20 and acetylcholine in those exposed on days 7–13 or 14–20). The lower concentration (100 ppm) produced no significant differences from controls. There were no microscopic brain lesions.

The highest NOAEL values and all reliable LOAEL values for developmental effects in rats and mice following acute exposure to tetrachloroethylene are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

Some adverse reproductive effects in women have been reported to be associated with occupational exposure to tetrachloroethylene in dry cleaning operations. These effects include menstrual disorders and spontaneous abortion. However, no definitive conclusions can be made because of the limitations associated with these studies.

A small scale exploratory study described menstrual disorders in dry cleaning workers (Zielhuis et al. 1989). Limitations of the study are lack of exposure measurement data, methodologic problems (self-administered questionnaire with no follow-up and failure to account for various confounding factors such as smoking, alcohol consumption, and medicinal drugs), and a relatively small study population.

Several recent case-control studies of women workers in Nordic countries exposed to tetrachloroethylene in dry cleaning operations suggested that exposed women had increased risk of spontaneous abortion (Ahlborg 1990; Kyyrönen et al. 1989). Limiting factors include a low number of pregnancies among exposed women (Ahlborg 1990) as well as a small group of exposed affected workers and biological monitoring not concurrent with the first trimester of pregnancy (Kyyrönen et al. 1989). In another small study, spontaneous abortions and birth defects occurred at a higher incidence in Italian dry cleaning workers than in housewives, but this difference was not statistically significant (Bosco et al. 1987). No increase in spontaneous abortion rates for laundry and dry cleaning workers in Canada was detected in a cross-sectional study (McDonald et al. 1986).

No studies were located that evaluated reproductive performance in occupationally exposed men.

Adverse effects on reproductive performance were not detected in rats exposed by inhalation to 70, 230, or 470 ppm tetrachloroethylene for 28 weeks, as judged by the number of pregnancies, number of litters conceived, and number of offspring per litter (Carpenter 1937). This older study has numerous limitations that have been discussed under hematological effects in Section 2.2.1.2. No studies were located that evaluated reproductive parameters in male animals.

2.2.1.7 Genotoxic Effects

Assays of clastogenic effects in humans following occupational exposure to tetrachloroethylene show inconsistent results. Increases in chromosome aberrations and sister chromatid exchanges were not detected in lymphocytes from 10 workers who were occupationally exposed to tetrachloroethylene (Ikeda et al. 1980).

The exposure concentrations for these workers were estimated to be between 10 and 220 ppm for 3 months to 18 years. The small number of workers and the wide range of exposure concentrations and durations limit the generalizations that can be made from this study. Twenty-seven workers exposed to an 8-hour TWA of 10 ppm tetrachloroethylene were compared to unexposed occupational controls with respect to incidence of sister chromatid exchanges (Seiji et al. 1990). The difference in sister chromatid exchange frequency between the exposed workers who smoked and the nonsmoking controls was statistically significant, although the authors had found no significant effect of cigarette smoking alone in either the exposed workers or the controls. The authors proposed a synergistic effect of chemical exposure and cigarette smoking. The number of workers examined was small (12 smokers and 2 nonsmokers among the exposed men; 9 smokers and 3 nonsmokers among the controls). The lack of any effect of cigarette smoking alone on the frequency of sister chromatid exchange is somewhat surprising, as this is a recognized effect that is well documented in the literature (Hook 1982).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

There have been a number of epidemiology studies of dry cleaning and laundry workers. Many of these studies are complicated by potential exposure to other petroleum solvents.

The only investigation of dry cleaning workers with no known exposure to petroleum solvents was a retrospective mortality study of a subcohort of 615 workers employed only in shops where tetrachloroethylene was the prime solvent (Brown and Kaplan 1987). Excess risk for cancer at any site was not identified in this subcohort. In the entire cohort, which was composed of 1,690 workers (including workers who had potential occupational exposure to petroleum solvents), there were significant excesses of mortality from kidney, bladder, and cervical cancer. The authors state that the increased incidence of cervical cancer may reflect the lower socioeconomic status of the cohort, as other studies have reported a correlation between lower socioeconomic status and increased risk of cervical cancer (Brown and Kaplan 1987; Hoover et al. 1975). A limitation of this study was lack of evaluation of smoking habits of the study cohort, since cigarette smoking has been associated with an increased risk of bladder cancer (Matanoski and Elliott 1981).

Additional epidemiological studies of dry cleaning and laundry workers have shown significant excesses in mortality due to cancers of the lung, cervix, esophagus, kidney, skin, lymphatic/hematopoietic system, and/or colon (Blair et al. 1979, 1990; Duh and Asal 1984; Katz and Jowett 1981). Although these studies suggest a possible association between chronic occupational exposure to tetrachloroethylene and increased cancer risk, the evidence must be regarded as inconclusive, for the following reasons. Workers were exposed to petroleum solvents and other dry cleaning agents as well as tetrachloroethylene. Other confounding factors such as smoking, alcohol consumption, and low socioeconomic status were not considered in the analyses. The numbers of deaths from cancer of specific organs or involving the hematopoietic system were low. Also, in several of these studies, attempts were not made to distinguish between laundry and dry cleaning workers.

Two other epidemiological studies of laundry and dry cleaning workers did not identify an occupational risk of bladder cancer compared to control subjects (Chapman et al. 1981; Smith et al. 1985). It must be mentioned that in the epidemiological study conducted by Smith et al. (1985), smoking status was examined to evaluate confounding or interactive effects and smoking was found to be associated with an increased risk of bladder cancer. While an increased risk of bladder cancer specifically in laundry or dry cleaning

workers of both sexes was not detected by Chapman et al. (1981), the authors found that women exposed to solvents as a group were in the high-risk category.

A cohort of white male chemical workers in Louisiana exposed to a variety of chemicals including tetrachloroethylene did not have an increased risk for total mortality or cancer (Olsen et al. 1989). This non-positive study was confounded by the healthy worker effect, defined as the observation that employed persons have lower mortality rates than the general population. Blacks and women were not analyzed in this study because of the small numbers of representatives from these groups.

A single case-control study in New Jersey of cases of primary liver cancer identified an increased risk of primary liver cancer in male workers categorized as craftsman or operators in laundry or dry cleaning operations (Stemhagen et al. 1983). The specific solvents to which the workers were exposed and exposure levels were not identified. The study controlled for alcohol consumption and smoking.

A retrospective cohort study of 14,457 aircraft maintenance workers at Hill Air Force Base, Utah, was undertaken by Spirtas et al. (1991) to determine if occupational exposure to over 20 solvents, including trichloroethylene and tetrachloroethylene, posed an increased risk of mortality. Deaths due to multiple myeloma or non-Hodgkin's lymphoma were elevated in female workers exposed to tetrachloroethylene for at least 1 year. However, confidence in these data is low primarily because multiple and overlapping exposure to more than one chemical was considerable. Additionally, the levels of tetrachloroethylene to which the workers were exposed were not provided, and lifestyle factors such as smoking and alcohol consumption were not assessed.

An association between exposure to tetrachloroethylene and increased risk of developing cancer has been suggested in results from animal experiments. A 103-week inhalation toxicity/oncogenicity study of tetrachloroethylene was conducted using male and female Fischer-344 rats and B6C3F$_1$ mice. Exposure levels were 0, 200, or 400 ppm tetrachloroethylene for rats and 0, 100, or 200 ppm tetrachloroethylene for mice (NTP 1986). In rats, there were significant and dose-related increases in the incidences of mononuclear cell leukemia in exposed male and female rats (males: 28/50--control, 37/50--low dose, 37/50--high dose; females: 18/50--control, 30/50--low dose, 29/50--high dose). It should be noted that this neoplasm occurs spontaneously in Fischer-344 rats and that incidences of mononuclear cell leukemia in control groups (54% for males, 36% for females) for this study were higher than for historical chamber controls for the laboratory or for untreated controls from the NTP database. However, NTP's Board of Scientific Counselors considered the incidence of rat leukemias to be a valid finding despite high background frequencies because there was a decreased time to onset of the disease and the disease was more severe in treated animals than in control animals.

Low incidences of renal tubular cell adenomas or adenocarcinomas (1/49, 3/49, 4/50) occurred in male rats; however, these tumors are considered uncommon in untreated male rats. Although the incidence of these tumors was not statistically significant, there was a significant trend. In exposed mice of both sexes, there were significantly increased incidences of hepatocellular neoplasms (Table 2-2). Study limitations include numerous instances of rats and mice loose from their cages within the exposure chambers, with the potential for aberrations in exposure and animal identification.

In summary, a number of epidemiology studies of men and women exposed occupationally by inhalation to tetrachloroethylene have not identified an increased risk of cancer. Individuals chronically exposed to a variety of solvents in addition to tetrachloroethylene appear to have increased risk of cancer in a number of organ systems, although some of these risks may also be related to personal habits and socioeconomic

status. In experimental animals exposed by inhalation, the most definitive cancer end point is liver tumors in male and female mice; however, increases in renal tumors in male rats and mononuclear cell leukemia in rats of both sexes also were associated with exposure. The cancer effect levels (CELs) for rats and mice are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2 Oral Exposure

2.2.2.1 Death

One human death following oral treatment with 3 mL of tetrachloroethylene for hookworm infestation has been reported (Chaudhuri and Mukerji 1947). This individual was a severely emaciated "street beggar" with preexistent chronic malnutrition and septic cholecystitis; thus, it is difficult to determine the specific cause of his death.

Mortality was produced in rats and mice by gavage exposure to tetrachloroethylene. Single-dose LD_{50} values of 3,835 and 3,005 mg/kg were determined for male and female rats given tetrachloroethylene by gavage. Death occurred within 24 hours after dosing and was preceded by tremors, ataxia, and central nervous system depression (Hayes et al. 1986). An oral LD_{50} of 5,000 mg/kg was reported for mice (Wenzel and Gibson 1951).

Osborne-Mendel rats of each sex received tetrachloroethylene in corn oil by gavage at doses of 316, 562, 1,000, 1,780, or 3,160 mg/kg for 6 weeks. Deaths (number unspecified) occurred in both males and females at the two highest doses but not at 1,000 mg/kg or lower (NCI 1977).

In a bioassay of tetrachloroethylene administered by gavage to rats and mice, compound-related mortality occurred due to toxic nephropathy in both species and hepatocellular tumors in mice (NCI 1977). Increased deaths occurred in groups of male and female rats exposed to 471 and 474 mg/kg/day tetrachloroethylene, respectively, 5 days per week for 78 weeks. Similarly exposed mice had increased numbers of deaths at concentrations of 536 and 386 mg/kg/day for males and females, respectively. This study is discussed in Sections 2.2.2.2 and 2.2.2.8.

All reliable LOAEL and LD_{50} values for death in each species are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-2. No studies were located regarding respiratory, gastrointestinal, or musculoskeletal effects in humans or animals after oral exposure to tetrachloroethylene.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans or animals after oral exposure to tetrachloroethylene. However, cardiovascular effects of chronic ingestion of solvent-contaminated (including tetrachloroethylene) drinking water were investigated in family members of leukemia cases in Woburn, Massachusetts (Byers et al. 1988). Fourteen adults in a group of 25 complained of cardiac symptoms of tachycardia at rest, palpitations, or near syncope. Eleven of these were selected for detailed testing that included resting and exercise tolerance electrocardiograms, Holter monitoring, echocardiograms, and serum lipid levels. Of these 11, 8 had serious ventricular dysfunctions, 7 had

multifocal premature ventricular beats, and 6 required cardiac medication. None of the subjects had clinically significant coronary artery disease. No rationale was given as to the factors that were involved in the selection of the 11 given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was given on any of the 25 family members. Other limitations of this study, including undefined contaminants, are described in Section 2.2.2.8.

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

Hematologic effects have been reported in mice exposed to tetrachloroethylene, alone or in mixture with other contaminants, in drinking water as discussed below. These effects have not been reported in studies where tetrachloroethylene was administered in corn oil by gavage.

Mice exposed to 0.1 mg/kg/day tetrachloroethylene in water for 7 weeks had high relative concentrations of tetrachloroethylene in the spleen, increased spleen weight, increased hemosiderin deposits and congestion of red pulp, increased serum lactic dehydrogenase (LDH) isozyme I, which was interpreted as being indicative of erythrocyte hemolysis, and a relative decrease in bone marrow erythropoiesis (Marth 1987). Milder or no hematological effects, depending on the parameters evaluated, occurred at exposures to 0.05 mg/kg/day. All hematological effects were reversible within an 8-week recovery period. There are several limitations of this study. First, only one sex of mouse was evaluated. Second, splenic hemosiderosis, one of the parameters evaluated, is present in normal mouse spleens; therefore, the presence of this pigment in the spleen is not necessarily an indicator of hemolysis unless it is more widespread and severe compared to control spleens. Third, grading of lesions by distribution and severity for either spleen or bone marrow was not documented in the paper. Fourth, the author did not provide documentation that LDH isozyme I is the isozyme found in mouse erythrocytes.

Mild microcytic anemia and bone marrow and immune function changes occurred in $B6C3F_1$ mice exposed via drinking water to tetrachloroethylene plus 24 other groundwater contaminants (Germolec et al. 1989). The observed changes in bone marrow function consisted of suppression of granulocyte-macrophage progenitor cells accompanied by a decrease in bone marrow cellularity. A dose-related suppression of antigen-induced antibody forming cells was also observed. This study is discussed in more detail in Section 2.2.2.3.

Hepatic Effects. The liver has not been shown to be a target organ in humans exposed by the oral route to tetrachloroethylene except for the following case report. Obstructive jaundice and hepatomegaly was reported in an infant exposed to tetrachloroethylene via breast milk (Bagnell and Ellenberger 1977).

The liver is a principal target organ in rodents exposed orally to tetrachloroethylene. Hepatic effects in rodents from oral exposure to tetrachloroethylene are similar to those produced by inhalation exposure. Mice are more sensitive than rats to tetrachloroethylene-induced toxicity; these effects are related to tetrachloroethylene metabolism--particularly the formation of TCA--as discussed in Section 2.3.

Tetrachloroethylene administered by gavage at the dose of 1,000 mg/kg/day for 10 days to male $B6C3F_1$ mice increased relative liver weights and elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisomal proliferation (Goldsworthy and Popp 1987). The same dose administered to Fischer-344 rats did not elevate cyanide-insensitive palmitoyl CoA oxidase levels significantly above controls, although relative liver weights were increased.

Toxic effects induced in male Swiss Cox mice given tetrachloroethylene by gavage at doses of 0, 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg/day for 6 weeks were increased relative liver weight and triglycerides beginning at 100 mg/kg/day, decreased glucose-6-phosphate and increased alanine aminotransferase (also known as serum glutamic pyruvic transaminase) at 500 mg/kg, and hepatocellular lesions. Lesions consisted of centrilobular hepatocellular hypertrophy, karyorrhexis, centrilobular necrosis, polyploidy, and hepatocellular vacuolization. They were present in the two dose groups examined histologically (200 and 1,000 mg/kg/day) (Buben and O'Flaherty 1985). Using a NOAEL of 20 mg/kg/day based on liver changes, an intermediate oral MRL of 0.1 mg/kg/day was calculated as described in the footnote in Table 2-3.

Elevated liver weights, relative to body weight but not brain weight, occurred in both sexes of Sprague-Dawley rats given 1,400 mg/kg/day tetrachloroethylene in drinking water for 13 weeks. While the serum enzyme, 5'-nucleotidase, was increased in females given 1,400 mg/kg/day and in males given 400 or 1,400 mg/kg/day, results for other biochemical parameters did not suggest a hepatoxic effect. Additionally, gross necropsy examination did not reveal any abnormalities in selected organs including the liver (Hayes et al. 1986). The major limitation of this study was lack of microscopic examination of livers.

Tetrachloroethylene has been tested for initiating or promoting activity in a rat liver foci assay (Story et al. 1986). Mean liver weights and/or liver-to-body weight ratios were significantly increased relative to the controls in partially hepatectomized adult male Osborne-Mendel rats (10/group) administered tetrachloroethylene by gavage in corn oil at 995 mg/kg/day. In both the presence and absence of an initiator (30 mg/kg diethylnitrosamine) tetrachloroethylene (995 mg/kg/day) induced an increase in enzyme-altered foci (foci with increased γ-glutamyltranspeptidase activity).

Chemically related nonneoplastic liver lesions were not reported for Osborne-Mendel rats or $B6C3F_1$ mice given tetrachloroethylene by gavage in a chronic bioassay (NCI 1977). This study, including its limitations, is discussed in Section 2.2.2.8.

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

Compound-induced kidney damage has been reported in animals after oral exposure to tetrachloroethylene. Daily administration of 1,000 mg/kg tetrachloroethylene by gavage to male Fischer-344 rats for 10 days produced an increase in protein droplet accumulation and cell proliferation in the P2 segment of the kidney. This effect, not seen in female rats, was correlated with an increased presence of α-2μ-globulin, a male-rat specific protein, in the proximal convoluted epithelial cells (Goldsworthy et al. 1988). Results from an earlier study by the same investigator indicated peroxisomal proliferation in the rat kidney was not associated with administration of 1,000 mg/kg/day tetrachloroethylene (Goldsworthy and Popp 1987). This was the only endpoint investigated in this experiment. Male rats exposed to 1,500 mg/kg tetrachloroethylene by gavage for 42 days developed typical α-2μ-globulin nephropathy (Green et al. 1990). Male $B6C3F_1$ mice exposed to 1,000 mg/kg per day by gavage for 10 days had peroxisomal proliferation as evidenced by elevated cyanide-insensitive palmitoyl CoA oxidase levels (Goldsworthy and Popp 1987).

Osborne-Mendel rats and $B6C3F_1$ mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in a carcinogenicity bioassay (NCI 1977). TWA doses for the study were 536 and 1,072 mg/kg/day for male mice, 386 and 772 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats; untreated and vehicle control groups were included. Study limitations are discussed in Section 2.2.2.8. Toxic nephropathy occurred at all dose levels in both sexes of rats and mice,

as did increased mortality. The nephropathy in both species was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium and hyalin intraluminal casts. Rat kidneys also had occasional basophilic tubular cytomegaly, chronic inflammation, and mineralization.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans or animals after oral exposure to tetrachloroethylene.

In family members of leukemia cases from the Woburn study, 13 of 25 adults who had been chronically exposed to solvent-contaminated drinking water (including tetrachloroethylene) developed skin lesions. These were maculopapular rashes that occurred approximately twice yearly and lasted 2–4 weeks. These skin conditions generally ceased within 1–2 years after cessation of exposure to contaminated water (Byers et al. 1988). There is no evidence that skin lesions were related to solvent exposure in general or to tetrachloroethylene specifically.

2.2.2.3 Immunological Effects

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

There was, however, a study suggesting immunological effects in humans with chronic exposure to a solvent-contaminated domestic water supply. Several wells in Woburn, Massachusetts, were contaminated by a variety of solvents. The two main volatile hydrocarbons measured before well closure were trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) (Byers et al. 1988). A potential association between water contamination in Woburn and cases of childhood leukemia is discussed in Section 2.2.2.8.

Immunological abnormalities were found in 23 adults in Woburn who were exposed to contaminated water and who were family members of children with leukemia. These immunological abnormalities, tested for 5 years after well closure, were persistent lymphocytosis, increased numbers of T lymphocytes, and depressed helper:suppressor T cell ratio. A follow-up test 18 months later revealed reductions in lymphocyte counts, decreased numbers of suppressor T cells, and increased helper:suppressor ratio. Auto-antibodies, particularly anti-nuclear antibodies, were detected in 48% (11/23) of the adults tested.

In the Woburn population, there was also a suggestion of an association between cumulative exposure to contaminated wells and increased urinary tract infections and respiratory disorders (asthma, bronchitis, pneumonia) in children (Lagakos et al. 1986).

Interpretation of the results reported by Byers et al. (1988) and Lagakos et al. (1986) is limited because of the possible bias in identifying risk factors for immunological abnormalities in a small, nonpopulation-based group identified through probands with leukemia. There is evidence that some genetic factor or factors may predispose to both altered immunologic parameters as well as an increased risk of developing leukemia. Other limitations of this study are described in Section 2.2.2.8.

Immunological effects were detected in a study exposing female B6C3F_1 mice to a chemical mixture of 25 groundwater contaminants including tetrachloroethylene (maximum concentration of 6.8 ppm) for 14 or 90 days. Mice exposed to the highest concentration of this contaminant stock solution had a dose-related suppression in antibody plaque-forming units to sheep red blood cells and increased host susceptibility to infection by the protozoan, Plasmodium yoelii. There were no changes in lymphocyte

number or T cell subpopulations, no alterations of T cell, NK cell or macrophage activities, and no effect on host susceptibility to challenge with intravenous Listeria monocytogenes (bacteria) or PYB6 tumor cells. These findings indicate an immunotoxic effect on B cells/humoral immunity (Germolec et al. 1989). These effects cannot be attributed to tetrachloroethylene alone.

No studies were located regarding immunological effects in animals after oral exposure to tetrachloroethylene.

2.2.2.4 Neurological Effects

Acute neurological effects in humans after ingesting tetrachloroethylene appear to parallel those seen after inhalation.

A 6-year-old child who ingested 12–16 g of tetrachloroethylene was conscious upon admission to a hospital 1 hour after ingestion, but his level of consciousness deteriorated to somnolence and subsequently coma (Koppel et al. 1985). Other symptoms included drowsiness, vertigo, agitation, and hallucinations.

The oral administration of tetrachloroethylene as an anthelminthic in humans was common at one time; however, newer therapeutic agents have since replaced tetrachloroethylene for this use. Narcotic effects, inebriation, perceptual distortion, and exhilaration, but not death, were observed in patients receiving doses ranging from 2.8 to 4 mL (about 4.2–6 g) of tetrachloroethylene orally as an anthelminthic (Haerer and Udelman 1964; Kendrick 1929; Sandground 1941; Wright et al. 1937).

No studies were located regarding neurological effects in animals after oral exposure to tetrachloroethylene.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to tetrachloroethylene.

In the Woburn, Massachusetts study of residents exposed to drinking water contaminated with solvents, including 21 ppb tetrachloroethylene, there was a suggestion that eye/ear anomalies and central nervous system/chromosomal/oral cleft anomalies were associated with exposure (Lagakos et al. 1986). However, several scientists have questioned the biological relevance of grouping these anomalies for purposes of statistical analysis (Lagakos et al. 1986).

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to tetrachloroethylene.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in either animals or humans after oral exposure to tetrachloroethylene.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to tetrachloroethylene. However, controversial study of a population in Woburn, Massachusetts, found a potential association between ingestion of drinking water contaminated with solvents and increased risk of childhood leukemia, particularly acute lymphocytic leukemia (Lagakos et al. 1986). Numerous investigators (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whittemore 1986) have evaluated the data and have identified a number of shortcomings in the study. The two wells in question began pumping in 1964–1967. Measurements of well contaminants before their closure in 1979 revealed numerous volatile organic compounds in the drinking water with highest concentrations being trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) (Byers et al. 1988).

There are several major drawbacks to the studies performed at the Woburn site. Of particular importance is the fact that no more than 6 of the 20 cases of leukemia could be linked to drinking water from the contaminated wells; several cases occurred in children with no access to these wells. The extent and duration of the contamination in the wells of concern are also not known. Geophysical modeling has suggested that the contamination had probably been present before the measurements of the contaminants were taken. Therefore, it is not possible to determine when exposure to the chemicals first occurred or whether the level of exposure varied over time. Two approaches were used in classifying exposures in the study by Lagakos et al. (1986). The use of continuous measurement based on estimates of the use and distribution of water from the contaminated wells actually showed less significance than the cruder measurement which accounted for water consumed from other sources, such as schools or workplaces. This toxicological profile attempts, where possible, to identify exposures to the specific chemical under discussion. The contamination of the two wells at Woburn involved more than one measurable contaminant.

The study by Lagakos et al. (1986) used family members of children affected with leukemia and other community members as interviewers, introducing possible interviewer bias. In addition, the study was performed following considerable publicity about the well contamination and the possible health effects that could follow these exposures, thus contributing to recall bias of the participants.

Cancer has been reported in experimental animals after oral exposure to tetrachloroethylene. Osborne-Mendel rats and B6C3F$_1$ mice of each sex were exposed to tetrachloroethylene in corn oil by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in an NCI (1977) carcinogenicity bioassay. Because of numerous dose-adjustments during the study, doses had to be represented as TWAs. TWA doses were 471 and 941 mg/kg/day for male rats, 474 and 949 mg/kg/day for female rats, 536 and 1,072 mg/kg/day for male mice, and 386 and 772 mg/kg/day for female mice. The high early mortality, which occurred in both sexes of rats and mice, was related to compound-induced toxic nephropathy (see Section 2.2.2.2). No increases in tumor incidences were observed for the treated rats. Statistically significant increases in hepatocellular carcinomas occurred in the treated mice of both sexes. Incidences in the untreated control, vehicle control, low-dose, and high-dose groups were 2/17, 2/20, 32/49, and 27/48 in male mice, and 2/20, 0/20, 19/48, and 19/48 in female mice.

Study limitations included control groups smaller than treated groups (20 versus 50), numerous dose adjustments during the study, early mortality related to compound-induced toxic nephropathy, suggesting that a maximum tolerated dose was exceeded, and pneumonia due to intercurrent infectious disease (murine respiratory mycoplasmosis) in both rats and mice.

Because of its carcinogenic activity in mouse liver, tetrachloroethylene has been tested for initiating or promoting activity in a rat liver foci assay. Tetrachloroethylene administered by gavage in corn oil at 995 mg/kg/day did not exhibit initiating activity as indicated by an increase in γ-glutamyltranspeptidase-positive type I altered foci. Tetrachloroethylene did promote the appearance of type II altered foci, in the presence or absence of an initiator (in this case, diethylnitrosamine) (Story et al. 1986).

All reliable CELs are recorded in Table 2-3 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to tetrachloroethylene.

2.2.3.2 Systemic Effects

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

Dermal/Ocular Effects. Chemical burns characterized by severe cutaneous erythema, blistering, and sloughing have resulted from prolonged (more than 5 hours) accidental contact exposure to tetrachloroethylene used in dry cleaning operations (Hake and Stewart 1977; Ling and Lindsay 1971; Morgan 1969).

Intense ocular irritation has been reported in humans after acute exposure to tetrachloroethylene vapor at concentrations greater than 1,000 ppm (Carpenter 1937; Rowe et al. 1952). Vapors of tetrachloroethylene at 5 or 20 ppm were irradiated along with nitrogen dioxide in an environmental chamber in order to simulate the atmospheric conditions of Los Angeles County. These conditions did not produce appreciable eye irritation in volunteers exposed to the simulated atmosphere (Wayne and Orcutt 1960).

Rabbits were exposed dermally to 2 mL/kg body weight pure tetrachloroethylene which was covered by an occlusive dressing for 24 hours to prevent evaporation of the chemical. The animals did not develop toxic signs, and skin lesions were not reported (Kinkead and Leahy 1987).

No studies were located regarding ocular effects in animals after ocular exposure to tetrachloroethylene.

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

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to tetrachloroethylene.

In a mouse skin initiation-promotion assay, tetrachloroethylene applied at amounts of 18 or 54 mg did not produce skin tumors over a 440–594-day study duration when applied either as an initiator or a promoter (Van Duuren et al. 1979).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The primary route of exposure to tetrachloroethylene is inhalation. Tetrachloroethylene is readily absorbed by humans through the lungs into the blood. Pulmonary uptake of tetrachloroethylene is proportional to ventilation rate, duration of exposure, and, at lower atmospheric concentrations of tetrachloroethylene, to the concentration of tetrachloroethylene in the inspired air (Hake and Stewart 1977). Absorption was measured in male volunteers exposed to concentrations between 72 and 144 ppm for 4 hours (Monster et al. 1979). The data indicated that increased uptake was influenced more by lean body mass than by ventilation rate or the amount of adipose tissue. In addition, uptake decreased as a function of exposure time, so that after 4 hours it was 75% of its initial value. This latter finding may be attributable to a large percentage uptake of tetrachloroethylene during the first few minutes of exposure, or the decreased uptake may be due to a decrease in retention of tetrachloroethylene with exposure time.

Six volunteers were exposed by inhalation to 0.02–0.4 mmol/m^3 (0.5–9.8 ppm) tetrachloroethylene for durations of 1–60 minutes (Opdam and Smolders 1986). The concentration of tetrachloroethylene in alveolar air was determined for residence times (i.e., the time interval between the beginning of inhalation and the end of the next exhalation) in the lung ranging from 1 to 50 seconds. Measurements were made both during and after exposure periods. During exposures, the concentrations of tetrachloroethylene in alveolar air decreased as a function of the residence time. The concentration seemed to stabilize at residence times of 10–12 seconds, but decreased even more rapidly at residence times longer than 12 seconds. In the post-exposure period, the alveolar concentration of tetrachloroethylene increased for residence times of 5–10 seconds. The decreasing concentration of tetrachloroethylene in alveolar air for times less than 10 seconds could be explained by absorption by mixed venous blood. Furthermore, the alveolar air concentration of tetrachloroethylene measured during exposures for residence times of 10–12 seconds provided a valid estimate of the concentration of the chemical in mixed venous blood in the pulmonary artery. This study is discussed further in Section 2.3.4.1.

In another study (Pezzagno et al. 1988), 15 volunteers were exposed to tetrachloroethylene during periods of rest and during periods of rest alternated with periods of exercise. The experiments were designed to assess the relationship between pulmonary uptake and urinary concentration of tetrachloroethylene, and between pulmonary uptake and ventilation and/or retention of the chemical. Urinary concentration of tetrachloroethylene was found to be positively correlated with uptake of the chemical. The retention index decreased with increasing ventilation at rest and during exercise. The urinary concentration of tetrachloroethylene was ventilation and retention index-dependent, increasing when either of these two parameters increased. A group of workers occupationally exposed to tetrachloroethylene (occupation not specified) were also monitored to determine if urinary concentration of tetrachloroethylene correlated with

tetrachloroethylene dose in mice (Schumann et al. 1980). Mice given a single oral dose of tetrachloroethylene (500 mg/kg) excreted 83% of the absorbed dose as the unmetabolized compound in the expired air; 10% appeared as metabolites in the urine. Exposure at the high dose (500 mg/kg) resulted in saturation of oxidative metabolism in the mouse. There was a shift in the route of elimination from metabolism and urinary excretion to excretion in expired air.

2.3.4.3 Dermal Exposure

Volunteers who immersed their thumbs for 30 minutes in liquid tetrachloroethylene exhaled the compound unchanged for time periods exceeding 5 hours (Stewart and Dodd 1964). The maximum mean alveolar air concentration of tetrachloroethylene in these subjects was 0.3 ppm, and the authors were able to construct concentration-time curves for the mean alveolar tetrachloroethylene concentrations.

Pertinent data regarding the excretion of tetrachloroethylene and metabolites following dermal exposure in animals were not found in the available literature.

2.4 RELEVANCE TO PUBLIC HEALTH

An acute-duration inhalation MRL of 0.6 ppm was derived for tetrachloroethylene based on the results of the study of Hake and Stewart (1977) in which human male volunteers were exposed to 0, 20, 100, or 150 ppm tetrachloroethylene for 7.5 hours/day for 5 days. Findings from electroencephalographs suggested cerebral cortical depression in subjects exposed to 100 ppm tetrachloroethylene; the NOAEL and LOAEL for human central nervous system effects were, therefore, set at 20 and 100 ppm, respectively. An intermediate-duration MRL has also been derived for tetrachloroethylene. The findings of a study conducted in NMRI mice exposed to 0, 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days indicated that hepatotoxicity was observed in all treatment groups (Kjellstrand et al. 1984). Therefore, using 9 ppm as the LOAEL, the intermediate-duration inhalation MRL was calculated to be 0.009 ppm. Because of technical problems (i.e., early deaths) the results from the available chronic-duration inhalation studies were not considered adequate for derivation of a chronic inhalation MRL.

The available acute oral studies performed with tetrachloroethylene were not suitable for deriving an MRL. The studies were performed with single doses, and in general the doses selected for investigation were high (i.e., ≥995 mg/kg). An immediate-duration oral MRL has, however, been determined from the results of a 6-week study in which mice received oral gavage administration of 0, 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg/day tetrachloroethylene (Buben and O'Flaherty 1985). Using a NOAEL of 20 mg/kg/day (based on increased liver weight) an intermediate oral MRL of 0.1 mg/kg/day was determined. Technical problems (i.e., high rate of early deaths, no threshold established, and respiratory infections) in the available long-term studies precluded the calculation of a chronic oral MRL.

Dermal MRLs were not derived because of the lack of appropriate methodology.

The major routes of exposure of humans to tetrachloroethylene are the inhalation and oral routes. Inhalation exposure may occur near hazardous waste sites as well as in urban and industrial areas. Oral exposure is primarily through drinking contaminated groundwater. Some large aquifers have been found to be contaminated with a number of solvents, including tetrachloroethylene. Occupational exposure to tetrachloroethylene (dry cleaners, chemical workers) is generally by inhalation.

The brain, liver, and kidney have been identified as target organs in humans for adverse effects of tetrachloroethylene exposure. In addition, there is a suggestion that reproductive effects may be induced in women. Carcinogenic effects have not been documented in exposed workers; however, cancer has been induced in experimental animals exposed by inhalation and oral routes.

Death. At high concentrations (>1,000 ppm), tetrachloroethylene vapor acts as an anesthetic agent, producing collapse, loss of consciousness, and death in humans. Death may be related to depression of respiratory centers of the central nervous system or cardiac arrhythmia and heart block. Death following acute inhalation of concentrations that produce unconsciousness has been confirmed by animal studies. Oral exposure of a child to high concentrations of tetrachloroethylene resulted in coma, which was reversible with therapy. Animal studies of oral exposure suggest that anesthesia and death would be likely occurrences in humans if high concentrations were swallowed. There are no reports of fatalities in humans or animals exposed solely by the dermal route.

It appears unlikely that death would occur in humans exposed to levels of tetrachloroethylene that occur in the environment or in the vicinity of hazardous waste sites.

Systemic Effects

Respiratory Effects. Upper respiratory tract irritation occurred in humans exposed acutely by inhalation to high concentrations of tetrachloroethylene. Respiratory irritation was not reported in people with chronic occupational exposure by inhalation. Respiratory effects were not reported in humans or animals after oral exposure. Environmental exposure to tetrachloroethylene in air or water is unlikely to pose a risk to the respiratory system.

Cardiovascular Effects. Despite the relatively large number of people occupationally exposed to tetrachloroethylene, there are few reported cases of tetrachloroethylene-associated cardiotoxicity. Cardiac arrhythmias in a small number of Woburn residents cannot be directly related to chronic tetrachloroethylene exposure. The case report of Abedin et al. (1980) suggests an association of inhaled tetrachloroethylene with effects on the heart, but the patient described may have been an unusually sensitive individual. These investigators hypothesized that exposure to tetrachloroethylene may sensitize the myocardium to endogenous epinephrine. In an experiment in dogs, however, inhalation exposure to high levels of tetrachloroethylene failed to sensitize the heart to epinephrine (Reinhardt et al. 1973). In contrast, intravenous administration of tetrachloroethylene to rabbits and dogs enhanced myocardial sensitivity to an exogenous epinephrine challenge (Kobayashi et al. 1982). Taken together, the available studies provide no strong evidence that people exposed to environmental levels of tetrachloroethylene or levels at hazardous waste sites would develop cardiovascular effects.

Hematological Effects. There are no studies that support hematological effects in humans after acute or chronic exposure to tetrachloroethylene by any route.

Several animal studies indicate that tetrachloroethylene exposure in drinking water can affect the hematopoietic system, particularly the erythron. Tetrachloroethylene in the blood may enter the polar phospholipid layer of the rodent erythrocyte membrane and alter the structure, thus resulting in mechanical fragility and hemolysis (Marth 1987). Hematopoietic effects could theoretically be exacerbated by ingestion of combinations of similar solvents (Germolec et al. 1989). Thus, there is a potential, though unsubstantiated, risk of subclinical hematological effects resulting from exposure to tetrachloroethylene in drinking water

Hepatic Effects. Tetrachloroethylene has been shown to cause hepatoxic effects in humans and animals by the inhalation and oral routes of exposure. The types of tetrachloroethylene-induced hepatic effects in humans are not well documented, and the exposures or doses producing these effects are not adequately characterized. For humans, reports of hepatotoxicity consist entirely of case studies of accidental exposures in which reliable quantitative exposure information was not available. In most cases, hepatic effects in humans have been reported as transient in nature. In animals, interpretation of hepatotoxicity is complicated by differences in exposure schedule, sensitivity of end points, and sensitivity of species. The animal data indicate that the mouse is a particularly sensitive species by virtue of its higher rate of oxidative metabolism of tetrachloroethylene (particularly to TCA) as compared to rats. This conclusion is supported by data indicating that short-term inhalation exposure to tetrachloroethylene caused a marked increase in TCA blood levels in mice that was approximately 7–13 times the peak blood levels seen in rats (Odum et al. 1988). Since TCA is a known hepatic peroxisome proliferation inducer, it was not unexpected that significant peroxisome proliferation was detected by Odum et al. (1988) in mouse liver but not in rat liver or in the kidneys of either species. Similar results after gavage treatment of rats and mice with tetrachloroethylene have been reported by Goldsworthy and Popp (1987). The in vitro study results of Elcombe (1985) further suggest that greater stimulation of hepatic peroxisome proliferation occurs at a higher rate in freshly isolated mouse hepatocytes than in rat hepatocytes and that rat hepatocytes are more active than human hepatocytes. The data also suggest that similar hepatic effects may be produced by intermittent and continuous exposures when the TWA dose is the same, and that tetrachloroethylene-induced hepatic effects of intermediate-duration exposures are not totally reversible. Intermediate-duration inhalation and oral MRLs were derived from hepatic effects in mice.

Renal Effects. Reversible kidney damage has been reported in humans accidentally exposed to acutely toxic amounts of tetrachloroethylene vapors (Hake and Stewart 1977). There are also data that suggest that occupational exposure to hydrocarbon solvents as a class may contribute to chronic renal disease (Kluwe et al. 1984). Subtle renal perturbations have been detected in at least one study of chronically exposed workers in dry cleaning workshops (Franchini et al. 1983).

Studies of tetrachloroethylene in animals support the fact that renal effects are produced. One acute study of tetrachloroethylene administered intraperitoneally to dogs resulted in alteration of phenolsulfonphthalein excretion indicative of tubular dysfunction, in the absence of microscopic lesions (Klaassen and Plaa 1967). Inhalation or oral exposure of rodents to tetrachloroethylene induces renal effects. However, the data showing an increased incidence of protein droplet nephropathy in male rats have questionable relevance to human health as discussed below.

Chemically induced protein droplet nephropathy in sexually mature male rats is characterized by accumulation of α-2μ-globulin in lysosomes, degeneration and necrosis of tubular cells, formation of granular casts, and regeneration of the tubular epithelium (Swenberg et al. 1989). Chemicals that are known to induce protein droplet nephropathy bind to α-2μ-globulin, yielding a complex that is more resistant to proteolytic enzymes in the lysosomes, leading to the accumulation of the complex in the tubule cells. α-2μ-Globulin has not been found in immature male rats, female rats, or humans (Alden 1986). Humans synthesize and excrete trace amounts of proteins similar to α-2μ-globulin. However, human male urine has a very low protein content compared to male rat urine (1% of male rat urine). In addition, human urinary proteins are primarily high molecular weight compared to rats, and human urinary protein has a relatively small proportion of cationic to total proteins. These findings suggest that humans are not necessarily at risk for tetrachloroethylene-induced renal damage analogous to the type found in male rats (Olson et al. 1990). Nevertheless, because of tubular effects detected in workers and in animal species

other than rats, risks of subclinical renal changes to humans exposed to environmental levels of tetrachloroethylene or levels near hazardous waste sites cannot be discounted.

Dermal/Ocular Effects. Skin damage (burns) and intense ocular irritation have been reported in humans exposed to concentration of tetrachloroethylene liquid or vapors high enough to cause anesthetic effects (Morgan 1969). No damage to skin has been reported in animals exposed chronically (Van Duuren et al. 1979). Dermal/ocular effects are unlikely in environmentally exposed humans.

Immunological Effects. Immunological effects in humans related specifically to tetrachloroethylene exposure have not been reported, nor are there reliable data in animals. The relevance to public health is, therefore, unclear.

Neurological Effects. The symptomatology of acute inhalation exposure to high levels of tetrachloroethylene is well documented in humans and includes headache, dizziness, and drowsiness. EEG studies done on male and female volunteers resulted in major changes in the EEG of three of four male subjects and four of five female subjects during exposure to 100 ppm (Stewart et al. 1981). In the majority of subjects, the EEG changes were characterized by a reduction in overall wave amplitude and frequency, most strikingly evident in the occipital leads. This altered pattern is similar to that seen in a healthy adult during drowsiness, light sleep, and the first stages of anesthesia. It is important to note that human and animal data are consistent in indicating a threshold region for central nervous system effects. Human data (Hake and Stewart 1977; Rowe et al. 1952; Stewart et al. 1981) suggest that the threshold for acute effects may be in the concentration range of 100–200 ppm with preanesthetic/anesthetic effects occurring at a threshold of 1,000 ppm (Carpenter 1937). These values are supported by animal studies. An acute inhalation MRL was established based on depression of the central nervous system in humans.

Although it has been suggested that long-term exposure of workers to organic solvents, including tetrachloroethylene may cause irreversible neurological impairment (Gregerson 1988), the numerous study limitations preclude implicating tetrachloroethylene as a distinct causative agent. Additionally, tetrachloroethylene exposure has not been associated with structural brain damage in humans, and subchronic and chronic inhalation exposure in rats and mice (NTP 1986) did not result in brain lesions. Experimental studies in rodents have shown, however, that tetrachloroethylene alters the fatty acid pattern of brain phospholipids and amino acids (Briving et al. 1986; Kyrklund et al. 1984). Taurine is known to be a nonspecific membrane stabilizer; therefore, a reduction in the content of this amino acid may lead to alterations in nerve impulse transmission and could be partially responsible for tetrachloroethylene-induced neurotoxic effects. Alternatively, the effects of tetrachloroethylene on the central nervous system that were observed may have resulted from the incorporation of this lipophilic compound into brain membranes and the resultant alteration of parameters such as neural conduction velocity. Decreased DNA content concomitant with a decrease in astroglial protein was found in the brain of gerbils exposed continuously to tetrachloroethylene concentrations as low as 60 ppm (Rosengren et al. 1986). It was unclear, however, whether the astroglial response represents a direct effect of tetrachloroethylene toxicity or an indirect reaction in response to neuronal cell damage. It should be emphasized that the mechanisms behind the neurotoxicity of tetrachloroethylene have not been elucidated.

The relevance of neurotoxicity from occupational exposure by inhalation to individuals exposed to lower concentrations of tetrachloroethylene, most likely by the oral route through contaminated water, is unclear.

Developmental Effects. Except for indirect and somewhat controversial results from the Woburn study (Lagakos et al. 1986), there is no evidence that tetrachloroethylene is a human teratogen. Evidence of a toxic effect on the conceptus in humans is discussed under reproductive effects.

Results from inhalation studies in animals also suggest that tetrachloroethylene is fetotoxic but not teratogenic at concentrations that are also maternally toxic. Fetotoxicity in rodents is usually expressed by decreased fetal weight and delayed skeletal ossification. These effects have been associated with exposure to 300 ppm, and NOAELs have not been reported. Gestational exposure to higher concentrations of tetrachloroethylene (900 ppm) was associated with minor behavioral and neurochemical alterations in some rat offspring (Nelson et al. 1980). The relevance of these alterations to human health is obscure. In addition, the effects may actually reflect maternal nutritional deprivation rather than a direct effect of tetrachloroethylene.

A high concentration of the tetrachloroethylene metabolite TCA has been detected in the amniotic fluid of mice following maternal inhalation exposure to tetrachloroethylene (Ghantous et al. 1986). This finding suggests that TCA may be transported to the fetus via the transplacental route through the fetal membranes and amniotic fluid. Such a pathway indicates that the fetus may be exposed to a large extent by swallowing the amniotic TCA or absorbing it through the skin. Because TCA also appeared in the fetal urinary bladder, TCA may recirculate several times before leaving the fetoplacental compartment. This process may contribute to long-term retention in the murine fetus.

The mechanism by which tetrachloroethylene produces embryotoxicity in rodents is not known, however, in view of the high concentration of TCA found in the fetal tissues (Ghantous et al. 1986), it seems likely that the observed fetotoxicity might be due as much to metabolites as to the unmetabolized tetrachloroethylene. This assumption is strengthened by the fact that a low concentration of radioactivity from administered radiolabeled tetrachloroethylene was found in the fetal brain, and high activity appeared in other organs. These findings should be extrapolated to humans with caution because of major differences between mice and humans in metabolism and kinetics of tetrachloroethylene.

Reproductive Effects. Epidemiological studies of women occupationally exposed to tetrachloroethylene in the dry cleaning industry suggest that they may have an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions (Ahlborg 1990; Bosco et al. 1987; Kyyronen et al. 1989; McDonald et al. 1986; Zielhuis et al. 1989). Interpretation of these studies is complicated by limiting factors, such as small sample populations, failure to account for possible confounding factors, lack of exposure data, and inadequate data collection methods. The mechanisms for these adverse effects have not been elucidated. Therefore, it is difficult to speculate on whether adverse reproductive effects could occur in environmentally exposed people, particularly by the oral route of exposure, for example, from contaminated aquifers. There is only one reproductive study in animals, which had serious limitations in design and conduct (Carpenter 1937). Therefore, it provides no conclusive evidence for reproductive effects.

Genotoxic Effects. The lack of strong genotoxic effects seen in assays of human lymphocytes following occupational exposure to tetrachloroethylene is consistent with data on the metabolism of this compound. The metabolism of tetrachloroethylene by the hepatic cytochrome P-450 enzymes does not result in the formation of compounds that are mutagenic or that otherwise interfere with the integrity of the DNA. However, the metabolites that are formed are oxiranes and acyl chlorides; these are highly cytotoxic, which may contribute to the weak hepatocarcinogenic effect of tetrachloroethylene. The second pathway of biotransformation of this compound is glutathione conjugation. This process results in the formation of

strong mutagens, e.g., S-(1,2,2-trichlorovinyl)glutathione, in the kidney and could explain the carcinogenic effects seen in this organ in rats (Dekant 1986). See Section 2.3 for more information on the metabolism of tetrachloroethylene.

A large number of studies of *in vitro* genotoxicity of tetrachloroethylene have been performed using prokaryotic, eukaryotic, and mammalian cells. The results of *in vitro* and *in vivo* studies are summarized in Tables 2-4 and 2-5. Most of the studies using the Ames test with *Salmonella typhimurium* have indicated that tetrachloroethylene itself is not a mutagen (Bartsch et al. 1979; Haworth et al. 1983; NTP 1986; Williams and Shimada 1983). The mutagenic properties of several chlorinated aliphatic compounds were identified in the spent liquor from the softwood kraft pulping process (Kringstad et al. 1981). Tetrachloroethylene was one of several compounds isolated that was shown to be mutagenic for *S. typhimurium* TA 1535, without the addition of liver microsomes for metabolic activation. In contrast, purified tetrachloroethylene was not mutagenic under conditions favoring oxidative metabolism or if no exogenous metabolic activation was used. However, preincubation of tetrachloroethylene with purified rat liver glutathione (GSH) S-transferases in the presence of GSH and rat kidney fraction resulted in the formation of the S conjugate, S-(1,2,2-trichlorovinyl)glutathione, which was unequivocally mutagenic in the Ames test (Vamvakas et al. 1989). Tetrachloroethylene oxide, an epoxide intermediate of tetrachloroethylene, was found to be mutagenic in bacterial studies (Kline et al. 1982).

Studies of mutagenicity on *Escherichia coli* have been negative (Greim et al 1975; Henschler 1977), as well as tests for mitotic recombination in yeast (Callen et al 1980; Koch et al. 1988). Mixed results were obtained in yeast when no metabolic activation was used in the experiments by Bronzetti et al. (1983). Koch et al. (1988) postulated that their inability to accumulate data on the mutagenicity of tetrachloroethylene was because of its highly toxic effects on cells, and that lower doses would be required to demonstrate unequivocally the presence or absence of mutagenic effects.

Direct effects on the DNA by tetrachloroethylene have been investigated in several cell systems. Human fibroblasts were assayed for unscheduled DNA synthesis following exposure to tetrachloroethylene, but the results were equivocal (NIOSH 1980). This study is difficult to interpret because negative results were obtained using the higher concentrations, whereas the lower dose produced a weak positive response. In addition, the positive control chemicals produced only weak positive responses. Induction of single-strand breaks in mouse liver and kidney DNA, but not in lung DNA, following intraperitoneal injection of 4–8 mmol tetrachloroethylene/kg body weight was reported (Walles 1986). Most of the data do not support a directly mutagenic effect of tetrachloroethylene itself (Costa and Ivanetich 1980). The inconsistent results could be due to differences between tested species in metabolism or activation, protocol differences, or purity of the compound tested. Other investigators found no effects on the DNA of rat and mouse hepatocytes (Costa and Ivanetich 1980; Williams 1983; Williams and Shimada 1983). However, evidence of DNA binding of tetrachloroethylene in mouse liver and rat kidney was seen in experiments that utilized liver microsomes and the addition of glutathione transferases (Mazzullo et al. 1987), further substantiating the evidence that the glutathione metabolites may be responsible for the mutagenic and carcinogenic properties of tetrachloroethylene.

There are few data on clastogenic effects of tetrachloroethylene following *in vitro* exposure. When Chinese hamster ovary cells were assayed for sister chromatid exchanges, no increase in frequency was found (NTP 1986).

Two assays of cell transformation in mouse cells treated with tetrachloroethylene were negative (NTP 1986; Tu et al. 1985). However, Fisher rat embryo cells were transformed in the absence of metabolic activation.

Most of the studies on tetrachloroethylene have been done using commercial or technical grade chemical, which means that contaminants may be involved when effects are seen. Stabilizers are added to tetrachloroethylene to prevent decomposition. Stabilizers are amines or mixtures of epoxides and esters. Epoxides are themselves highly reactive due to the unstable three-member ring structure. They easily generate hydroxide radicals, which can have deleterious cellular effects. Problems with unusual dose-response curves, cytotoxic doses of chemical, and small sample sizes are examples of factors that limit the interpretation of these studies. There is growing evidence that the mutagenic properties of tetrachloroethylene depend on the metabolic pathway that involves glutathione conjugation. The metabolites formed via this pathway have been shown to be mutagenic. This characteristic, along with the cytotoxicity of tetrachloroethylene, may provide a mechanism for the carcinogenic effects seen with tetrachloroethylene. It is not clear that low levels found at most hazardous waste sites would be effective in causing observable genotoxic effects in humans.

Cancer. Some epidemiological studies of dry cleaning workers suggest a possible association between chronic tetrachloroethylene exposure and increased cancer risk (Blair et al. 1970; Chapman et al. 1981; Duh and Asal 1984; Katz and Jowett 1981). However, the results of these studies are inconclusive because of the likelihood of concomitant exposure to petroleum solvents, the effects of other confounding factors, such as smoking and other life-style variables, and methodological limitations in choosing control populations and maintaining complete follow-up. The Woburn study (Lagakos et al. 1986), which attempted to correlate an increased risk of childhood leukemia with exposure to solvent-contaminated water, has been refuted by many scientists.

Occupational exposure to tetrachloroethylene and other solvents did not generally result in increased risk of hematopoietic neoplasms. Although there was one report of familial chronic lymphocytic leukemia in 5 of 7 members of a family who had worked for years in the dry cleaning industry (Blattner et al. 1976), it appears that an inherited defect was the cause of this family's susceptibility to leukemia. In addition, there was a study on occupational exposure of parents whose children had acute nonlymphocytic leukemia. Paternal (but not maternal) exposure to agents categorized as "solvents" was reported to pose a significant risk for development of childhood leukemia (Buckley et al. 1989). However, the risk became nonsignificant when controlled for household exposure (including marijuana use) and paternal exposure to petroleum products.

The carcinogenicity of tetrachloroethylene has been documented in animals exposed by inhalation or oral (gavage) routes (NCI 1977; NTP 1986). By either route of exposure, mice but not rats developed compound-related hepatocellular neoplasms. One mechanism for tetrachloroethylene-induced hepatocellular tumors in mice has been hypothesized to be formation of a genotoxic epoxide intermediate during metabolism of tetrachloroethylene by mixed function oxidases (Buben and O'Flaherty 1985). However, there are data from numerous studies that indicate that chlorinated hydrocarbon-induced hepatocellular tumor development in rodents is related, by some as yet undefined mechanism, to peroxisomal proliferation. Tetrachloroethylene induces hepatocellular peroxisomal proliferation in mice but not in rats (Goldsworthy and Popp 1987). This species difference appears to be due to differences in metabolic rates between rats and mice, with mice forming higher blood levels of TCA, a major tetrachloroethylene metabolite (Odum et al. 1988). TCA itself induces peroxisomal proliferation in mouse liver (Goldsworthy and Popp 1987); both TCA and dichloroacetic acid, a minor metabolite of tetrachloroethylene, can induce hepatocellular tumors in mice (Herren-Freund et al. 1987). Humans are exposed to a number of disparate chemicals, including therapeutic hypolipidemic agents, that cause peroxisomal proliferation and liver cancer in rodents. There are, however, no definitive data indicating that TCA induces peroxisomal proliferation in humans.

Nevertheless, the mechanism of carcinogenicity of peroxisomal proliferators is not understood, and a cause and effect relationship has not been established. Since humans metabolize tetrachloroethylene poorly and TCA production is limited by saturation of the metabolic pathways at levels well below the concentrations causing significant peroxisomal proliferation in mice, the relevance of this end point to human risk remains unclear (Cohen and Grasso 1981; de la Iglesia and Farber 1982; Elcombe 1985).

Other cancer end points in the inhalation study of tetrachloroethylene in rats, but not in mice, were significantly increased incidences of mononuclear cell leukemia in both sexes and a low incidence of renal cancer in males.

Male rats exposed to a diverse group of hydrocarbon chemicals develop a unique form of kidney damage characterized by crystalloid phagolysosomal inclusions in the cytoplasm of renal proximal tubular epithelium (P2 segment) (Alden 1986). Biochemically, these inclusions are composed of the low-molecular-weight protein, α-2μ-globulin, complexed with a hydrocarbon chemical or its metabolite (Swenberg et al. 1989). This type of nephropathy, with concomitant increases in cell replication in the damaged segment of kidney, has been induced experimentally in male rats--but not in female rats--by treatment with more than 1,000 mg/kg/day tetrachloroethylene by gavage (Goldsworthy et al. 1988; Green et al. 1990). However, α-2μ-globulin accumulation was not seen in rats after inhalation exposure to tetrachloroethylene levels (400 ppm) that produced nephrotoxicity in both sexes and renal tumors in males (NTP 1986). This finding tends to argue against a major role for the α-2μ-globulin mechanism in tetrachloroethylene-induced renal carcinogenesis in male rats. The complete pattern of nephropathy attributed to α-2μ-accumulators has not been fully characterized for tetrachloroethylene. The available data do suggest, however, that since α-2μ-globulin accumulation was seen only after exposure to doses that were higher than those inducing nephrotoxicity in the cancer bioassay (NTP 1986), a threshold level for the α-2μ-globulin nephrotoxicity of tetrachloroethylene (above the doses known to cause tumors in male rats) may exist.

In addition, there is evidence that tetrachloroethylene can be metabolized by glutathione conjugation in the liver (DeKant et al. 1986, 1987; Green et al. 1990). The conjugate is further metabolized by the mercapturic acid pathway and excreted in urine as the N-acetyl cysteine derivative. The precursor of this metabolite, S-(1,2,2-trichlorovinyl)glutathione, is a substrate for the renal enzyme, cysteine conjugate β-lyase. The data presented by Green et al. (1990), which shows that the urinary level of the N-acetylated metabolite only begins to increase after saturation of the cytochrome P-450 pathway, has been used to support the speculation that hepatic glutathione conjugation of tetrachloroethylene is a "high-dose phenomenon" in rats. However, the saturation of the β-lyase pathway in the kidney would seem to be a more plausible explanation; at high doses, more of the cysteine conjugate would be converted and excreted because the competing β-lyase pathway approaches saturation. Additionally, S-(1,2,2-trichlorovinyl)-glutathione induces a powerful mutagenic response in the Ames bacterial mutation assay when activated by rat kidney fractions (DeKant et al. 1986; Vamvakas et al. 1989). The mutagenic response demonstrated for the cysteine conjugate of tetrachloroethylene suggests a possible genotoxic component in nephrocarcinogenicity of tetrachloroethylene in male rats.

Human metabolism of tetrachloroethylene can be saturated by exposure to more than 100 ppm for 8 hours/day (Ohtsuki et al. 1983). Although glutathione conjugation was not detected in in vitro studies of human liver tissues (Green et al. 1990), the results are inconclusive. The small number of human liver samples that were assayed, in conjunction with the relatively weak response reported for rat livers, does not resolve the issue of whether humans are at risk from renal damage caused by the electrophilic intermediate resulting from glutathione conjugation. Of the various mechanisms hypothesized to be involved in tetrachloroethylene-induced renal tumorigenesis in male rats (i.e., protein droplet nephropathy,

chronic nephrotoxicity, hepatic glutathione-S-transferase-conjugation resulting in the formation of a mutagenic cysteine conjugate), the formation of mutagenic metabolites in the kidney appears to be the likely mode of action.

Despite some indication of human risk of leukemia from solvent exposure, the relevance to human health of elevated incidences of mononuclear cell leukemia related to tetrachloroethylene exposure in Fischer-344 rats is unclear. This is a spontaneous and very prevalent hematopoietic neoplasm that is fairly specific for Fischer-344 rats, and the control incidences for this study were higher than historical values. However, NTP's Board of Scientific Counselors considered the incidence of rat leukemias to be a true finding because there was a decreased time to onset of the disease and the disease was more severe in treated as compared to control animals.

The weight-of-evidence carcinogenicity classification for tetrachloroethylene represents a departure from the strict categorization scheme outlined in EPA's Cancer Risk Assessment Guidelines. Since EPA's carcinogenicity classification of tetrachloroethylene has major ramifications and can influence the public's perceptions of risk, some historical perspective is provided on the major issues arising from the assessment. In 1986, EPA recommended a Group B2 (probable human carcinogen) weight-of-evidence classification for tetrachloroethylene based on sufficient evidence from animal studies and inadequate human evidence (EPA 1991a). Using information available through 1987, IARC assigned tetrachloroethylene a 2B classification, i.e., possibly carcinogenic to humans (IARC 1987); according to the NTP Annual Report on Carcinogens, tetrachloroethylene was classified as a substance "that may reasonably be anticipated to be a carcinogen" (NTP 1984). EPA's Science Advisory Board (SAB) reviewed tetrachloroethylene-related issues in late 1987; the summarized findings, presented in a letter to the EPA Administrator (March 9, 1988) were that the overall weight-of-evidence positions tetrachloroethylene "on a continuum between categories B2 and C" (possible human carcinogen). On February 22, 1991, EPA's Office of Health and Environmental Assessment (OHEA) requested that the SAB reevaluate the animal cancer data and related new ancillary information on mutagenicity and metabolism and determine the relationship of this information to a hazard classification of tetrachloroethylene (EPA 1991b). The SAB Executive Committee made the following statement:

> It is the Committee's view that the major issues arising from the assessment of tetrachloroethylene have not changed over the past four years, and that SAB's previous response remains appropriate. The available scientific evidence confirms that tetrachloroethylene should be considered as an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats. Complications within each study and in their biological interpretations have made it difficult to categorize this compound. We do not consider the evidence strong enough to classify this compound as a probable human carcinogen (i.e., B2); on the other hand, the evidence for carcinogenicity is stronger than for most other compounds classified as possible human carcinogens (i.e., C). Therefore, in the spirit of the flexibility encouraged by the Guidelines, our best judgement places this compound on a continuum between these two categories (EPA 1991b).

Tetrachloroethylene remains on a continuum between B2 and C; as of 1992, this decision is still under review by EPA.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

Patients who had detectable blood levels of volatile organic chemicals (often more than one chemical) and who had a variety of systemic symptoms were classified as "chemically sensitive" by Rea et al. (1987). Tetrachloroethylene was the most common chemical detected in the blood of the "chemically sensitive" individuals who were studied (found in 72 of 134 patients). Some adults also appear to have increased sensitivity to certain systemic effects of tetrachloroethylene, e.g., cardiac sensitization (Abedin et al. 1980).

Children or fetuses may be particularly susceptible to the toxic effects of tetrachloroethylene. Studies in mice suggest that tetrachloroethylene metabolites can cross the placental barrier and concentrate in the fetus (Ghantous et al. 1986). Unmetabolized tetrachloroethylene has been excreted in breast milk and was detected in an exposed infant with liver damage (Bagnell and Ellenberger 1977). In addition, possible chemical effects were detected in children in Woburn, Massachusetts. These children may have been exposed to solvent-contaminated drinking water as infants or in utero, and they had elevated incidences of acute lymphocytic leukemia or impaired immunity (Byers et al. 1988; Lagakos et al. 1986).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to tetrachloroethylene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tetrachloroethylene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Human exposure to tetrachloroethylene can occur by inhalation, oral, or dermal contact. The dermal route, however, is not likely to be the most relevant for the systemic toxic effects induced in humans exposed to tetrachloroethylene because of the limited dermal absorption. General recommendations for reducing absorption of tetrachloroethylene following acute inhalation exposure have included moving the patient to fresh air and administration of 100% humidified supplemental oxygen with assisted ventilation (HSDB 1992). General recommendations for reducing absorption following acute oral exposure have included the administration of water or milk, including emesis with ipecac syrup (unless the patient is or could rapidly become obtunded, comatose, or convulsive), gastric lavage, and/or administration of a charcoal slurry with or without a cathartic (HSDB 1992; Stutz and Janusz 1988). In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended (Bronstein and Currance 1988; Haddad and Winchester 1990; HSDB 1992; Stutz and Janusz 1988). For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with soap and water have been recommended (HSDB 1992; Stutz and Janusz 1988).

2.8.2 Reducing Body Burden

The body does not retain significant amounts of tetrachloroethylene; most of an absorbed dose is excreted within several days of either inhalation or oral exposure (see Section 2.3.4). However, methods aimed at