Appendix J
Toxicity Profiles for COCs

Toxicity information available for the following compounds:

Volatile Organic Compounds (VOCs)*

Benzene
Tetrachloroethene
Trichloroethene
1,1-Dichloroethene
cis-1,2-Dichloroethene
Vinyl Chloride
1,1,1-Trichloroethane
1,1-Dichloroethane
Chlorobenzene

Semi-Volatile Organic Compounds (SVOCs)*

Acenaphthene
Fluoranthene
Naphthalene
Benzo(a)anthracene
Benzo(a)pyrene
Benzo(b)fluoranthene
Benzo(k)fluoranthene
Chrysene
Acenaphthylene
Anthracene
Benzo(g,h,i)perylene
Fluorene
Phenanthrene
Dibenzo(a,h)anthracene
Indeno(1,2,3-cd)pyrene
Pyrene
2-Methylnaphthalene

Polychlorinated Biphenyls (PCBs)

Metals*

Arsenic
Cadmium
Chromium
Copper
Iron
Lead
Mercury
Nickel
Selenium
Silver
Thallium
Tin
Zinc

Sources:

MA DEP, *Documentation for the Risk Assessment Shortform Residential Scenario*, Appendix B, WSC/ORS-142-92, October 1992.
ERM-Group, *Toxicity Profiles*, 1994.

*Insufficient toxicity information available for the following compounds:

Volatile Organic Compounds (VOCs)

Trichlorofluoromethane
1,2,3-Trichlorobenzene
1,2-Dichlorobenzene
1,3-Dichlorobenzene
1,4-Dichlorobenzene

Semi-Volatile Organic Compounds (SVOCs)

1-Methylnaphthalene
1-Methylphenanthrene
Perylene
Biphenyl
bis (2-ethylhexyl)phthalate

Extractable Petroleum Hydrocarbons (EPH)

C9-C18 Aliphatics
C19-C36 Aliphatics
C11-C22 Aromatics

Metals

Aluminum
Antimony
Barium
Beryllium
Cobalt
Manganese
Vanadium

Volatile Organic Compounds (VOCs)

BENZENE

GENERAL BACKGROUND INFORMATION

Benzene is a clear, volatile, highly flammable, aromatic hydrocarbon which exists naturally and is produced by volcanoes and forest fires. Benzene is also a very common industrial solvent, produced from petroleum. It is used as a solvent for fats, inks, paints, plastics, rubber, in the extraction of oils from seeds and nuts, in photogravure printing, as a chemical intermediate and in the manufacture of detergents, explosives, pharmaceuticals and dyestuffs. It is also a component of gasoline and other petroleum-based fuels. Exposure to benzene can occur via inhalation, ingestion, especially of contaminated drinking water, and dermal contact (as in contact with liquid benzene found in gasoline.) (Sittig, 1981; ATSDR, 1989)

PHARMACOKINETICS

Benzene is readily absorbed through ingestion, moderately absorbed through inhalation and poorly absorbed through intact skin (see section on Relative Absorption Factors). Once in the bloodstream, benzene is distributed throughout the body, with the concentration in any one compartment dependent on the degree of perfusion of tissues by blood. Since benzene is lipid-soluble, it accumulates in fat, but the rate of accumulation is slow since fat is poorly perfused. The metabolites of benzene are responsible for its toxic effects. These include phenol (which is either formed via an unstable benzene oxide precursor or directly from benzene), catechol, hydroquinone and conjugated phenolic compounds. The primary site of benzene metabolism is the liver via the cytochrome P450 mixed function oxidase system. Some benzene metabolism may also occurs in the bone marrow via the same enzyme system. Benzene is excreted either unchanged from the lungs or as metabolites in the urine (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

Benzene targets its effects on the hemopoietic, immune and nervous systems (ATSDR, 1989). Exposure to benzene has produced irritation of the skin, eyes and upper respiratory tract. Acute exposure has produced central nervous system depression, headache, dizziness, nausea, convulsions, coma and death at extremely high concentrations (Sittig, 1981). Health effects in humans have been reported starting as low as 50 ppm via inhalation. Twenty-five ppm for 6 hrs had no obvious effects though benzene was detected in blood (Sandmeyer, 1981). Early autopsy reports found benzene-induced hemorrhages of the brain, pericardium, urinary tract, mucous membranes and skin (Sittig, 1981). Chronic exposure to benzene produces blood changes involving an initial increase in levels of erythrocytes, leukocytes and

thrombocytes, followed by aplastic anemia indicated by anemia, leukopenia and thrombocytopenia (Sittig, 1981).

MAMMALIAN TOXICOLOGICAL PROFILE

The following effects have been produced experimentally in laboratory animals, following exposure to benzene: decreased leukocyte and/or erythrocyte counts, reduction in cellular immunity and bone marrow depression (reduced number of granulopoietic stem cells). Animal studies do not indicate that benzene is teratogenic, but the following fetotoxic effects have been found: reduced fetal weight, altered fetal hematopoiesis, fetal skeletal variations and increased resorptions in pregnant exposed animals. In addition, benzene has produced histopathological changes in ovaries and testes of test animals (ATSDR, 1989).

GENOTOXICITY

Benzene and its metabolites have been shown to be mutagenic in a number of in vitro and in vivo studies. Genotoxic effects produced experimentally include structural and numerical chromosome aberrations in humans, animals and cell cultures, and sister chromatid exchanges and micronuclei in in vivo animal studies. Benzene exposure has been found to produce an increase in the number of chromosome aberrations associated with myelotoxicity (Sittig, 1981). In addition, sperm head abnormalities, inhibition of DNA and RNA synthesis, DNA binding and interference with cell cycle progression have been shown in in vitro studies (ATSDR, 1989). The epidemiologic data indicate that benzene is leukemogenic. The evidence is most convincing for acute myelogenous and acute erythroleukemia, although a correlation has also been found with chronic leukemia. Benzene has been designated a group A human carcinogen (leukemogen) by inhalation. Although data are insufficient to validate the carcinogenicity of benzene via ingestion, it would not be unreasonable that benzene is carcinogenic via this route as well if present in sufficient quantities. The carcinogenicity of benzene via dermal exposure is considered to be lower since benzene is absorbed poorly through the skin (ATSDR, 1989).

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TETRACHLOROETHYLENE

GENERAL BACKGROUND INFORMATION

The major use for tetrachloroethylene (perchloroethylene, PCE) is in the dry-cleaning industry. Its popularity in this area is due to its nonflammability, ease of recovery for reuse and its compatibility with various fabrics. It is also used in cold cleaning and vapor degreasing of metals. Its remaining uses are as a chemical intermediate in the synthesis of fluorocarbons, various manufacturing and industrial processes as well as medicinal uses (IRP, 1985).

PHARMACOKINETICS

PCE is readily absorbed by humans through the lungs into the blood. Pulmonary uptake is proportional to ventilation rate, duration of exposure and (at lower concentrations of PCE) to the concentration of PCE in the inspired air (Hake and Stewart, 1977). PCE is also rapidly aborbed following oral administration, but is poorly absorbed following dermal exposure (see section on Relative Absorption Factors). Distribution occurs rapidly with the highest concentrations of PCE achieved in tissues of high fat content (ATSDR, 1990). Metabolism of PCE is believed to be mediated by the microsomal mixed function oxidase enzyme system involving the formation of an epoxide intermediate. Major metabolites of PCE are trichloroacetic acid and trichloroethanol. Unmetabolized PCE is excreted largely by exhalation with urinary excretion of metabolites representing a small percentage (ATSDR, 1990).

HUMAN TOXICOLOGICAL PROFILE

Stewart et al. (1977) found that exposure of 11 subjects to a mean PCE concentration of 101 ppm for 7 hours produced symptoms of headache, dizziness, difficulty in speaking, and sleepiness. Long-term exposed subjects are also reported to experience effects such as short-term memory defects, ataxia, irritability, disorientation, and sleep disturbances (USEPA, 1985). PCE causes hepatotoxicity in humans. A number of reports of liver damage after inhalation of PCE in acute or chronic exposure situations have been documented (Hake and Stewart, 1977). PCE ingestion in humans results in symptoms indicative of liver damage, including elevated SGOT and SGPT levels, hepatomegaly, and fatty degeneration of the liver cells (Koppel et al., 1985).

MAMMALIAN TOXICOLOGICAL PROFILE

Male and female rats treated via stomach tube showed symptoms of tremors, ataxia, CNS depression, and finally, death (Hayes et al., 1986). Moderate fatty degeneration of the liver was observed in mice 1 day after a single 4-hour exposure to 200 ppm PCE, but not 3 days after exposure (Kylin et al., 1963). Chronic exposure in animals has been found to damage the CNS, producing symptoms such as hypertrophy and proliferation of astroglial cells in the brain (Rosengren et al., 1986). In this study, there was a decreased DNA content observed in the brain of gerbils exposed continuously to PCE concentrations as low as 60 ppm. It was suggested that this may represent the development of brain atrophy. Rowe et al. (1952) exposed rats, rabbits, guinea pigs, and monkeys to PCE vapors at levels of 100 to 400 ppm, 7 hour/day, 5 days/week for 6 months. Only guinea pigs showed adverse effects due to exposure. These effects included increased liver weights with some fatty degeneration, a slight increase in hepatic lipid content, and the presence of several small hepatic fat vacuoles. PCE also causes renal effects in rodents. Groups of rats and mice of each sex were exposed to PCE in corn oil by gavage 5 days/week for 78 weeks (NCI, 1977). Toxic nephropathy occurred at all dose levels in both sexes of rats and mice. PCE has been found to be fetotoxic, but not teratogenic at concentrations that are also maternally toxic (Schwetz, 1975). Fetotoxicity was usually expressed by decreased fetal weight and delayed skeletal ossification. There is some evidence that PCE causes adverse effects on reproductive systems. The finding of abnormal sperm in mice exposed to 500 ppm PCE is an indication of chemical effects on the sperm. However, definitive evidence that PCE or its metabolites reached germinal tissue and damaged DNA is not provided (U.S. EPA, 1985).

GENOTOXICITY

In vitro studies of PCE genotoxicity have been perfórmed in prokaryotic, eukaryotic and mammalian cells. The results using prokaryotic systems were all negative, whereas in studies using yeast or mammalian cells, the results were mixed (Bronzetti et al., 1983; Price et al., 1978). NTP (1985) conducted inhalation carcinogenicity studies in F344/N rats and B6C3F1 mice of each sex for 6 hours/day, 5 days/week for 103 weeks. There were increases in mononuclear cell leukemia in rats and hepatocellular adenomas and carcinomas in mice. In chronic oral studies (NCI, 1977), PCE produced hepatocellular carcinomas in mice, but not in rats.

Epidemiological studies of dry-cleaning and laundry workers have determined significant excesses in mortality due to cancers of the lung, cervix, kidney, skin and colon (Blair et al., 1979; Kaplan, 1980). Although these studies suggest an association between chronic occupational exposure to PCE and increased cancer risk, the evidence is inconclusive, because workers were exposed to other solvents as well. Considering the inconclusive evidence for

carcinogenicity in humans, the U.S. EPA places PCE in Group B2, meaning that is considered a probable human carcinogen.

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TRICHLOROETHYLENE

GENERAL BACKGROUND INFORMATION

Trichloroethylene (TCE) is widely used as an industrial solvent, particularly in metal degreasing, which consumes about 90% of TCE produced annually in the U.S. TCE is also used for dry-cleaning, as a low-temperature heat exchange fluid, as a fumigant, as a diluent in paints and adhesives, in aerospace operations, and in textile processing. Previously, TCE was used as an extractant in food-processing. These uses were discontinued in 1975 due to evidence of possible carcinogenic activity. Its earlier use in anesthetics was also discontinued (IRP, 1985).

PHARMACOKINETICS

Absorption of TCE from the gastrointestinal and respiratory tracts is extensive. TCE is extensively metabolized in humans to trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid. Although the liver is the primary site of TCE metabolism, there is evidence for extrahepatic metabolism in the lungs and kidneys (ATSDR, 1988).

HUMAN TOXICOLOGICAL PROFILE

TCE is assumed to be responsible for the deaths of four men employed at degreasing operations using TCE as the solvent (Kleinfeld and Tabershaw, 1954). Toxicological analysis revealed TCE in varying concentrations in various tissues. Kleinfeld and Tabershaw (1954) reported that, despite treatment, a man died 11 days after he accidentally drank an unknown quantity of TCE. TCE has been shown to affect the central nervous system. Short-term exposure to high concentrations of TCE caused dizziness, headache, nausea, confusion, facial numbness, blurred vision, and, at very high levels, unconsciousness. Longer exposures cause ataxia, decreased appetite, sleep disturbances, and trigeminal neuropathy (U.S. EPA, 1985). Information regarding hepatotoxicity in humans is limited and derived from acute overexposures. U.S. EPA (1985) has concluded that it is unlikely that chronic exposure to trichloroethylene at concentrations found or expected in ambient air would result in liver damage.

MAMMALIAN TOXICOLOGICAL PROFILE

In laboratory animals, the acute toxicity of trichloroethylene is low. Oral LD_{50} values of 4920 mg/kg in the rat, 3200 mg/kg in the mouse and 2800 mg/kg in the dog have been reported. In a study by Baker (1958), several dogs died within 20 minutes of being exposed to TCE at 30,000 ppm. Rats exposed to 20,000 ppm for 5 hours died (Adams, 1951). A 2-year study

in rats conducted by the NTP (1986a) showed decreased survival due to TCE treatment. Deaths were attributed to toxic nephrosis. Behavioral changes were observed in rats at TCE vapor concentrations as low as 100 ppm (Silverman and Williams, 1975). Liver enlargement is the most commonly observed hepatic effect seen in TCE-exposed animals (Kjellstrand et al., 1983). Mice, especially males, appear to be particularly sensitive to the hepatotoxic effects of TCE. The only reproductive effects observed were reduced testis and epididymis weights in rats exposed to dietary TCE (NTP, 1986b). There were no effects of reproductive system histology, fertility, or other reproductive performance parameters in treated males or females in these studies.

GENOTOXICITY

Perocco and Prodi (1981) found positive results for unscheduled DNA synthesis both with and without metabolic activation in human lymphocytes in vivo. Another study reported a significant increase in sister chromatid exchange in six workers exposed to TCE (Gu et al., 1981). In vitro mutagenicity tests in bacteria, yeasts, and molds demonstrated weak positive responses. Most of these tests required metabolic activation of the compound (Crebelli et al., 1985). TCE has been shown to be carcinogenic in animals. Inhalation and oral exposure produced liver and lung tumors in mice and kidney adenocarcinomas, testicular Leydig cell tumors, and possibly leukemia in rats. These studies are deemed sufficient to place TCE in CAG classification B2, probable human carcinogen (U.S. EPA, 1987). Further support that TCE is a probable human carcinogen comes from studies that indicate that metabolism is qualitatively similar in humans and test animals (U.S. EPA, 1987). The available carcinogenicity studies indicate that mice are more susceptible to TCE carcinogenicity than the rat. Factors contributing to this difference may be an increased rate of metabolic conversion to trichloracetic acid in mice, and the more pronounced trichloroacetic acid-mediated peroxisomal proliferation and cell proliferation in mice (Elcombe et al., 1985). The peroxisomal proliferation may lead to an increase in the reactive oxygen species and DNA damage, which may lead to hepatocellular carcinoma.

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1,1-DICHLOROETHYLENE

GENERAL BACKGROUND INFORMATION

1,1-Dichloroethylene (1,1-DCE or vinylidene chloride) is a synthetic chemical used to make certain plastic products and flame retardant fabrics. It is released into the environment primarily as a result of air and water emissions coming from factories where 1,1-DCE is manufactured, hazardous waste sites where 1,1-DCE has been improperly disposed of, or as a result of accidental spills. 1,1-DCE is also found as a breakdown product of other chemicals present in the environment. Although high percentages of 1,1-DCE in soil and water quickly escape to the air, small concentrations remain and undergo biodegradation into other compounds. Once in the air, the compound rapidly decomposes through a variety of processes. It is estimated that 1,1-DCE released into the atmosphere persists for only about two days (ATSDR, 1988).

PHARMACOKINETICS

1,1-DCE is rapidly absorbed by the oral and inhalation routes. In animal studies, it was found to accumulate preferentially in the kidney, liver, and lung. 1,1-DCE undergoes complex biotransformation processes and numerous metabolites have been identified. The initial metabolic step is possibly the formation of an unstable reactive epoxide intermediate. Metabolites are ultimately conjugated with glutathione and excreted in urine (ATSDR, 1988).

HUMAN TOXICOLOGICAL PROFILE

Humans exposed to high concentrations of 1,1-DCE (approximately 4,000 ppm) show central nervous system depression which sometimes progresses to convulsions, spasm, and unconsciousness (Tierney et al., 1979). Repeated exposure to 1,1-DCE causes hepatotoxicity. Preliminary clinical findings on workers exposed to 1,1-DCE for up to 6 years in a polymerization plant in New Jersey revealed a high incidence of hepatotoxicity (U.S. EPA, 1985).

MAMMALIAN TOXICOLOGICAL PROFILE

Signs of central nervous system toxicity are the predominant effects observed in animals acutely exposed to high concentrations of 1,1-DCE via the inhalation route. The toxic signs consist primarily of central nervous system depression, lacrimation, dyspnea, tremor, convulsions, and narcosis, finally resulting in death (Klimisch and Freisberg, 1979a,b; Zeller et al., 1979). Rodents acutely exposed to high levels of 1,1-DCE (500 - 15,000 ppm) via inhalation show irritation of the mucous membranes and pulmonary edema, congestion and

hyperemia (Zeller et al., 1979). Acute inhalation exposure to 1,1-DCE produces cardiovascular effects, such as contraction of the main vessels, dilation of the right side, and hyperemia (Klimisch and Freisberg, 1979; Zeller et al., 1979). The liver is a major target organ for 1,1-DCE toxicity. Four-hour inhalation exposure to 200-250 ppm of 1,1-DCE resulted in increased liver weight, hepatic enzyme induction and massive histologic injury (Jackson and Conolly, 1985; Jaeger, 1977). Glutathione appears to play an important role in reducing the toxic effects of 1,1-DCE. For example, fasted rats which have depleted glutathione levels, display much greater 1,1-DCE induced toxicity (Reynolds et al., 1980). Acute exposure to 1,1-DCE also results in renal damage, with the severity of the kidney lesions increasing with increasing dose and duration of exposure (Reitz et al., 1980).

Long-term inhalation exposure to 1,1-DCE is associated with adverse respiratory effects as evidenced by irritation of the upper respiratory tract. Nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage, 1970). Other pulmonary effects seen in rats, guinea pigs, and dogs exposed to similar concentrations of 1,1-DCE for 90 days include discoloration and morphologic changes in the lungs (Prendergast et al., 1967). Quast et al. (1986) reported hepatotoxic effects in rats exposed to 21 ppm 1,1-DCE 6 hours/day, 5 days/week for six months. Studies by Short et al. (1977) demonstrated that inhalation exposure of pregnant rats to 1,1-DCE produced a statistically significant increase in early embryo resorptions in rats at 57 and 449 ppm, and in mice exposed at 57 ppm. Maternal lethality was also increased. 1,1-DCE induced weak teratogenic effects in laboratory animals. Prenatal exposure caused tissue anomalies in rats and skeletal defects in rats, mice and rabbits.

GENOTOXICITY

1,1-DCE is mutagenic in a number of test systems. In in vitro test systems, 1,1-DCE required metabolic activation before demonstrating mutagenicity. 1,1-DCE was mutagenic in Salmonella after metabolic activation with an exogenous activation system derived from human liver samples (Jones and Hathway, 1978), showing that human liver is capable of activating 1,1-DCE into mutagenic metabolites. In in vivo mutagenicity studies, 1,1-DCE did not produce mutations (Anderson et al., 1977). Inhalation of 1,1-DCE was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats (Reitz et al., 1980). Out of several carcinogenicity studies conducted with 1,1-DCE, only one inhalation study provides evidence of a positive carcinogenic effect (Maltoni et al., 1985). In this study, increases in renal adenocarcinomas were noted in male Swiss mice exposed by inhalation to 25 ppm 1,1-DCE.

Van Duuren et al., (1979) evaluated the carcinogenicity of 1,1-DCE in mice treated by dermal application amd by subcutaneous injection. 1,1-DCE was inactive as a complete carcinogen when applied repeatedly for a lifetime to mouse skin, and did not induce sarcomas after subcutaneous injection. However, a dermal initiation-promotion study indicated 1,1-DCE was

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active as a tumor-initiating agent (Van Duuren et al., 1979). U.S. EPA has classified 1,1-DCE as a Group C agent (possible human carcinogen) for which there is limited evidence of carcinogenicity in animals.

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1,2-DICHLOROETHYLENE

GENERAL BACKGROUND INFORMATION

There are two isomers of 1,2-dichloroethene (1,2-DCE), cis and trans. Neither of these isomers has developed wide industrial usage in the United States partly due to their flammability. The trans isomer is more widely used in industry than either the cis isomer or the 60:40 cis/trans mixture. It is used as either a low-temperature extraction solvent or as a direct solvent in materials such as dyes, perfume oils, waxes, resins and thermoplastics. It is also used as a chemical intermediate in the synthesis of polymers. 1,2-DCE is highly volatile, weakly adsorbed by soil and has no significant potential for bioaccumulation. It may volatilize from soil surfaces, but that portion not subject to volatilization is likely to be mobile in groundwater (IRP, 1985).

PHARMACOKINETICS

1,2-DCE is absorbed by all routes of exposure (see section on Relative Absorption Factors) (ATSDR, 1989). Distribution is expected to be rapid. Due to the lipophilic nature of 1,2-DCE, tissues of high lipid content would be expected to attain the highest levels. 1,2-DCE is metabolised via the mixed function oxidase enzyme system to chloroethylene epoxides which undergo rearrangement to dichloroacetaldehyde or chloroacetic acids (Henschler, 1977; Liebman and Ortiz, 1977). Excretion of 1,2-DCE and its metabolites has been largely uncharacterized (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

1,2-DCE was once used as a general inhalation anesthetic in humans (Proctor and Hughes, 1978). Exposure to the trans isomer at a level of 2000 ppm causes burning of the eyes, vertigo and nausea (Proctor and Hughes, 1978). Within the limited industrial usage, only one toxic effect in humans was reported - a fatality due to very high vapor inhalation in a small enclosure (Rosenthal-Deussen, 1931). 1,2-DCE causes eye and skin irritation upon contact (Grant, 1974). There are no reports of long-term human exposure to 1,2-DCE isomers.

MAMMALIAN TOXICOLOGICAL PROFILE

Toxicological data for 1,2-DCE are limited, since it is not widely used. The only available data are old, and the purity of the samples could not be verified. According to Smyth (1956), the cis isomer did not kill or anesthetize rats in 4 hours at 8000 ppm. At 16,000 ppm, rats became anesthetized in 8 minutes and died in 4 hours. Smyth also stated that he found the trans isomer to be twice as toxic as the cis isomer. A 6-hour LC_{50} value of 22,000 ppm was reported for mice exposed to the trans isomer (Mathies, 1970). Adverse lung effects were reported in rats receiving a single 8-hour exposure to 200 ppm of the trans isomer (Freundt, 1977). Dogs repeatedly exposed to dichloroethylene vapor developed superficial corneal clouding which was reversible within 24 to 48 hours (Grant, 1974). There are conflicting data about the chronic toxicity of 1,2-DCE. Torkelson reported no adverse effects in rats, rabbits, guinea pigs and dogs exposed to either 500 or 1000 ppm of 1,2-DCE 7 hours daily, 5 days per week for 6 months. The sample consisted of 60% cis- and 40% trans-1,2-DCE (ACGIH, 1980). Similarly, no effects were seen in rats dosed subcutaneously, percutaneously or by ingestion (ACGIH, 1980). In contrast, Freundt et al. (1977) reported marked effects in rats exposed 8 hours daily, 5 days per week for 16 weeks to vapor levels of 200 ppm of the trans isomer. Liver and lungs were affected and leukocyte counts were decreased. No data on reproductive toxicity are available on the 1,2-DCE isomers (IRP, 1985).

GENOTOXICITY

Both isomers of 1,2-DCE were tested in Salmonella with and without activation in vitro and in vivo host-mediated assays. Both isomers were toxic but did not induce any genetic effects (Bronzetti et al., 1982). No carcinogenicity data are available for either the cis- or trans-isomers of 1,2-DCE. Neither IARC nor the NTP have evaluated 1,2-DCE (IRP, 1985).

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VINYL CHLORIDE

GENERAL BACKGROUND INFORMATION

About 90% of the vinyl chloride produced in the U.S. is used to manufacture polyvinyl chloride (PVC) and other vinyl polymers. The remainder is used to synthesize 1,1,1-trichloroethane. The major uses of PVC are in the building and construction industries, in consumer goods, packaging and electrical wire insulation. PVC is also used in packaging, such as plasticized film, bottles and bottle-cap liners and gaskets (IRP, 1985).

PHARMACOKINETICS

Respiratory and gastrointestinal absorption of vinyl chloride is rapid and nearly complete. Distribution may be widespread with the highest concentration of the parent compound located in the fat. Metabolism and excretion occur rapidly. The highest levels of excretory products are located in the liver and kidney (ATSDR, 1989).

HUMAN TOXICOLOGICAL PROFILE

Several epidemiologic studies have associated occupational exposure with impaired liver function and biochemical or histological evidence of liver damage (U.S. EPA, 1985a,b). Symptoms and signs of liver disease associated with occupational exposure to vinyl chloride include pain or discomfort, hepatomegaly, portal hypertension, thrombocytopenia, esophageal varices (Lee et al., 1977). Acute toxicity at high levels has resulted in lethality among occupationally exposed workers. Death appeared to be due to narcosis (U.S. EPA, 1985a). Acute inhalation exposure to high levels of vinyl chloride leads to CNS effects. Exposures to 8,000 to 20,000 ppm have been associated with dizziness, giddiness, euphoria, ataxia, headache, and narcosis (Nicholson et al., 1975; Lester et al., 1963). Dinceva et al. (1985) reported electroencephalogram changes that they thought were indicative of early evidence of neurotoxicity in workers exposed to vinyl chloride along with other organic solvents. Vinyl chloride disease is the name given to the total clinical syndrome associated with occupational exposure. It includes a syndrome known as acroosteolysis or dissolution of the ends of the distal phalanges of the hands, circulatory disturbance in the extremities, Raynaud syndrome, scleroderma, hematologic effects, and lung and liver effects (ATSDR, 1989).

MAMMALIAN TOXICOLOGICAL PROFILE

Patty et al. (1930) reported that narcosis and death occurred within 30 to 60 min in guinea pigs exposed to 10% vinyl chloride. U.S. EPA (1985a) reviewed a number of acute studies in animals and reported 2 hour LC_{50} values ranging from 117 to 500 ppm for mice to 230 to 800 ppm for rabbits. Liver injury is observed in chronically-exposed animals. A study by the Dow Chemical Company (1984) in rats chronically-exposed to vinyl chloride through inhalation established 0.13 mg/kg/day as NOAEL, and 1.3 mg/kg/day as a LOAEL for hepatotoxicity. Animals exposed orally or by inhalation manifest noncancerous liver effects similar to those seen in humans; but other effects seen in humans, such as acroosteolysis, Raynaud syndrome, and scleroderma, have not been reproduced in animals (ATSDR, 1989).

GENOTOXICITY

Vinyl chloride is mutagenic in S. typhimurium in numerous studies (ATSDR, 1989). Vinyl chloride was positive for recessive lethal effects but negative for dominant lethal effects, chromosomal translocation, and sex chromosome loss in D. melanogaster (Verburgt and Vogel, 1977). Positive results were obtained in mutation and cell transformation tests and in chromosomal aberration tests in vivo and in vitro mammalian systems (Styles, 1977; Laib et al., 1985; Anderson and Richardson, 1981). Genotoxicity studies of vinyl chloride in humans include a large number of chromosomal aberration tests in the peripheral lymphocytes of occupationally exposed workers. These tests have all been positive (ATSDR, 1989). Anderson et al. (1980) observed an increase in lymphocytes with chromosomal aberrations at exposure levels estimated at 50 ppm.

Maltoni and associates (1981) conducted vinyl chloride carcinogenicity studies in animals. They exposed rats, mice and hamsters for 4 hours/day, 5 days/week for one year to vapor concentrations of 1 ppm to 30,000 ppm or to 0.03 to 50 mg\kg bw vinyl chloride in olive oil by ingestion, 5 days/week for one year. Liver angiosarcomas were observed in all the animals tested. Bi et al. (1985) exposed adult male Wistar rats to 0, 10, 100, or 3000 ppm, 6 hours/day, 6 days/week for up to 12 months to evaluate effects on the testes. Relative testicular weight was significantly reduced at 100 or 3000 ppm. Vinyl chloride workers are at increased risk for developing cancer. Liver angiosarcomas, brain, skin and lung tumors, and tumors of the lymphatic and blood-forming systems are some of the cancers seen in exposed workers (Tamburro, 1984). Individuals residing near PVC processing plants may also be at risk. Five cases of angiosarcoma of the liver were diagnosed in persons living in the vicinity of vinyl chloride fabrication and polymerization plants for 8 to 62 years prior to the diagnosis of the disease (U.S. EPA, 1980).

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1,1,1-TRICHLOROETHANE

GENERAL BACKGROUND INFORMATION

1,1,1-Trichloroethane (also known as 1,1,1-TCA) is a colorless man-made chemical. It can be found in a liquid state, vapor, or dissolved in water or other chemicals. When found as a liquid, it evaporates rapidly and becomes a vapor in the air. 1,1,1-TCA has a sweet, sharp odor (ATSDR, 1990). 1,1,1-Trichloroethane is often used as a solvent to dissolve other substances such as glue or paint. Industrially, it is used to remove oil or grease from manufactured metal parts. Residentially, it is used for spot removal cleaners, aerosol sprays and glues. 1,1,1-Trichloroethane can be found in hazardous waste sites in the soil, water and in the air (ATSDR, 1990). It can be found in rivers, lakes, soil, drinking water, and drinking water from underground wells.

PHARMACOKINETICS

1,1,1-Trichloroethane is rapidly and completely absorbed by ingestion and inhalation (U.S. EPA, 1984). It distributes throughout the body and crosses the blood-brain barrier (U.S. EPA, 1984). If spilled topically, absorption via the skin would occur in small amounts because of quick evaporation into the air (U.S. EPA, 1984; ATSDR, 1990). Regardless of how 1,1,1-trichloroethane enters the body, most will quickly leave as exhalation occurs (ATSDR, 1990). What does not exit from expiration (metabolites) will be excreted through the urine and breath in a few days.

HUMAN TOXICOLOGICAL PROFILE

The toxic effects of 1,1,1-TCA are generally seen at concentrations well above those likely in an ambient environment. The most notable toxic effects of 1,1,1-TCA in humans are central nervous system depression, including anesthesia at very high concentrations, and impairment of coordination, equilibrium, and judgement at lower concentrations. Exposure to high concentrations may also result in cardiovascular effects, including premature ventricular contractions, decreased blood pressure and sensitization of the heart to epinephrine-induced arrhythmias, leading possibly to cardiac arrest (U.S. EPA, 1985; ATSDR, 1990). Acute exposure to minimal concentrations of 1,1,1-trichloroethane did not produce respiratory or lung volume effects (Dornette, 1960; Torkelson et al., 1958).

MAMMALIAN TOXICOLOGICAL PROFILE

Similar effects as noted above are observed in animals exposed to 1,1,1-TCA. In addition, animal experiments investigating the influence of 1,1,1-TCA on liver and kidney function yield conflicting results highly dependent on species, doses, and treatment schedules. Fatty changes in rodent livers following exposure by inhalation have been reported (U.S. EPA, 1985).

GENOTOXICITY

No studies were located regarding genotoxic effects in humans or animals following exposure to 1,1,1-trichloroethane (ATSDR, 1990). Evidence for or against an association between exposure to 1,1,1-TCA and cancer in humans has not been reported. Animal studies fail to provide any definitive link between exposure and carcinogenicity (ATSDR, 1990).

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1,1-DICHLOROETHANE

GENERAL BACKGROUND INFORMATION

1,1-Dichloroethane (1,1-DCA) is a colorless, oily, lipophilic liquid which evaporates quickly at room temperature and has an ether-like odor. Its liquid and vapor forms ignite easily and may pose a fire hazard when handled improperly. It does not dissolve easily in water. 1,1-DCA is used primarily as an industrial solvent and as a dissolving agent for paint, varnish, finish removers and grease (ATSDR, 1990).

PHARMACOKINETICS

Little information exists quantitating the absorption of 1,1-DCA. However, based on its chemical and physical properties, it would be predicted to be readily absorbed via any route of exposure (ATSDR, 1990). Once absorbed, it should be readily distributed to bodily tissues, with highest concentrations achieved in tissues of greatest lipid content (Sato and Nakajima, 1987). A large percentage of an administered dose is exhaled unchanged (Mitoma et al., 1985). The remainded undergoes biotranformation mediated by the microsomal mixed function oxidase enzyme system to yield reactive acylchloride metabolite(s) which covalently bind to cellular macromolecules (Colacci et al., 1985). An alternative MFO-mediated pathway yields 2,2-dichloroethanol which undergoes subsequent oxidation to dichloroacetaldehyde and dichloroacetic acid (McCall et al., 1983). These metabolites are excreted through urine or further metabolized to CO_2 (Sato and Nakajima, 1987).

HUMAN TOXICOLOGICAL PROFILE

Relatively little information is available on the health effects of 1,1-dichloroethane in humans. It induces central nervous system depression and anesthesia upon inhalation. In fact, it was used as an inhalation anesthetic in the past. The use of 1,1-DCA as an inhalation anesthetic was discontinued when it was discovered that this compound induced cardiac arrhythmias in humans at anesthetic doses ((Reinhardt et al., 1971). No studies were located concerning threshold effects of exposure on any other organ system.

MAMMALIAN TOXICOLOGICAL PROFILE

Limited data indicate that 1,1-dichloroethane is less toxic than its isomer, 1,2-dichloroethane and most other chlorinated aliphatic solvents (Parker et al., 1979). Exposure of animals to 1,1-DCA results in central nervous system depression which may be fatal if exposure levels are high (Plaa and Larson, 1965). Nephrotoxicity has been observed in cats and mice

following subchronic exposure. One study (Schwetz et al., 1974) suggests that exposure in utero results in retarded fetal development.

GENOTOXICITY

Results from in vitro genotoxicity test are conflicting. 1,1-DCA tested negative in the Ames assay (Nohmi et al., 1985) and in yeast cells (Bronzetti et al., 1987). However, it did increase the transformation frequency in hamster embryo cells (Hatch et al., 1983). In vivo studies suggest that 1,1-DCA may be genotoxic since it was found to covalently bind to DNA (Colacci et al., 1985). This chemical has been classified as a possible human (C) carcinogen by EPA. This classification is based on conflicting chronic bioassay results in mice (NCI, 1977; Klaunig et al., 1986).

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CHLOROBENZENE

GENERAL BACKGROUND INFORMATION

Chlorobenzene is a clear liquid with an almond-like odor. Although chlorobenzene does not occur naturally in the environment, it is used in industry as a solvent, in the manufacture of aniline, phenol and chloronitrobenzene, and as an intermediate in the manufacture of dyestuffs and pesticides (ATSDR, 1990; Sittig, 1981).

PHARMACOKINETICS

Chlorobenzene is assumed to be readily absorbed via ingestion, moderately absorbed through inhalation and poorly absorbed through the skin, based on its structural similarity to benzene (see section on Relative Absorption Factors). The major metabolites of chlorobenzene are p-chlorophenylmercapturic acid and 4-chlorocatechol. Excretion of chlorobenzene occurs via urine in the form of its two metabolites, with the excretion of p-chlorophenylmercapturic acid reported to be much lower than of 4-chlorocatechol. A portion of an absorbed dose is excreted as unchanged chlorobenzene through the lungs (ATSDR, 1990).

HUMAN TOXICOLOGICAL PROFILE

Acute exposure to chlorobenzene has produced the following health effects in workers exposed to high levels: irritation of the eyes and nose, skin irritation, central nervous system depression with symptoms such as drowsiness, incoherence, numbness, nausea and vomiting. However, these workers were simultaneously exposed to other solvents so it is not clear whether chlorobenzene is responsible for these effects (ATSDR, 1990; Sittig, 1989).

MAMMALIAN TOXICOLOGICAL PROFILE

Acute lethality via both inhalation and ingestion is relatively low in animals. One study produced 100% mortality in mice after 2 hrs of exposure to 4,300 ppm. In rats exposed to a single dose of 4000 mg/kg and mice exposed to a single dose of 1000 mg/kg via corn oil by gavage, death occurred in 2-3 days (ATSDR, 1990). Animal studies indicate that exposure to chlorobenzene via either inhalation or ingestion can produce severe kidney and liver damage. Typical signs of liver damage reported include increased serum enzymes, changes in liver weights, degeneration, necrosis and interference with porphyrin metabolism. Signs of kidney damage include degeneration or focal necrosis of proximal tubules and increased kidney weights. Animal evidence also exists that chlorobenzene is immunotoxic via ingestion with the potential of producing thymic necrosis and lymphoid or myeloid depletion of bone marrow, spleen or thymus. Neurological effects, manifested by miscellaneous spasms and

narcosis, have been shown in animals acutely exposed via inhalation to chlorobenzene. There are very few animal data on the developmental and reproductive effects of chlorobenzene. The available data do not indicate that chlorobenzene produces developmental or reproductive effects via either inhalation or ingestion.

GENOTOXICITY

There were no data located regarding the mutagenicity of chlorobenzene in either animals or humans following oral exposure. Limited in vitro mutagenicity testing in bacterial and mammalian test systems suggest that chlorobenzene may not be genotoxic in humans (ATSDR, 1990). In a National Toxicology Program (NTP) chronic, oral carcinogenic bioassay conducted in both sexes of mice and rats, the only significant finding was an increase in the incidence of neoplastic nodules of the liver of male rats in the higher dose group but not at the lower dose. On the basis of these data, EPA has classified chlorobenzene as a Class D carcinogen (inadequate evidence of carcinogenicity in both humans and animals) (ATSDR, 1990; NTP, 1985).

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Semi-Volatile Organic Compounds (SVOCs)

ACENAPHTHENE

GENERAL BACKGROUND INFORMATION

Acenaphthene is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The database for acenaphthene is very limited.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of acenaphthene.

HUMAN TOXICOLOGICAL PROFILE

No data were found regarding the human toxicology of acenaphthene.

MAMMALIAN TOXICOLOGICAL PROFILE

Adverse effects on the lungs, glands, and blood were observed in rats following aerosol administration of 12 mg/m^3 acenaphthene for 5 months (U.S. EPA, 1981).

GENOTOXICITY

Mutagenicity tests for acenaphthene were negative (U.S. EPA, 1981). Carcinogenicity tests were negative (IARC, 1983).

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FLUORANTHENE

GENERAL BACKGROUND INFORMATION

Fluoranthene is a member of the polyaromatic hydrocarbons (PAH). PAHs constitute a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. Fluoranthene has been detected in food, cigarette smoke, and smoke from industrial and natural burning.

PHARMACOKINETICS

No data were found regarding the pharmacokinetics of fluoranthene.

HUMAN TOXICOLOGICAL PROFILE

The database for the toxicological effects of fluoranthene on humans, separate from other PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

MAMMALIAN TOXICOLOGICAL PROFILE

The database on the toxicity of fluoranthene is limited. A 13 week subchronic study where CD-1 mice were gavaged with up to 500 mg/kg-day of fluoranthene indicated nephropathy, increased liver weights, hematological alterations and clinical effects (EPA, 1988). A developmental study in which fluoranthene was administered once via intraperitoneal injection to pregnant mice reported only an increased rate of embryo resorption (Irvin and Martin, 1987).

Chronic dermal application of up to 1 percent fluoranthene to the backs of mice did not induce skin tumors following lifetime application (Hoffman et al, 1972; Horton and Christian, 1974; and Wydner and Hoffman, 1959a). Fluoranthene is not a complete carcinogen (ATSDR, 1990) and does not exhibit iniation activity (Hoffman et al, 1972).

GENOTOXICITY

There is some evidence that fluoranthene is genotoxic (ATSDR, 1990). Genotoxic effects have been reported in human cells with exogenous metabolic activation, but negative results were recorded without metabolic activation.

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NAPHTHALENE

GENERAL BACKGROUND INFORMATION

Naphthalene is a white solid substance at room temperature. It has a distinct odor of mothballs or tar. Humidity and sunshine cause evaporation into the air within a few hours. When placed in water or soil, bacteria will destroy naphthalene, or will render it airborne within a few hours (ATSDR, 1990). Tobacco smoke is known to release 3 ug of naphthalene per cigarette (U.S. EPA, 1982). The compound is used in the production of dyes, solvents, lubricants, motor fuels (U.S. EPA, 1980) and is a major component of many moth ball preparations.

PHARMACOKINETICS

Humans can absorb naphthalene by dermal, inhalation and oral routes (see section on Relative Absorption Factors). Metabolism occurs via the P450 mixed function oxidase enzyme system to yield multiple intermediates which are then conjugated. Key metabolites are responsible for each toxicity endpoint following intraperitoneal administration: 2-naphthoquinones --> hemolysis; 1,2-naphthoquinones --> cataracts; 3-GSH adducts --> pulmonary toxicity (Buckpitt et al., 1984). Excretion of metabolites occurs via urine and feces (ATSDR, 1990).

HUMAN TOXICOLOGICAL PROFILE

Adults and children exposed to airborne naphthalene experience vomiting, abdominal pain and anemia (ATSDR, 1990). Most of the data is for inhalation of naphthalene from mothballs. The primary site of toxicity is the erythrocyte resulting in hemolytic crisis (hemolytic anemia). Jaundice is seen upon dermal, inhalation, and oral exposures, as are kidney effects (ATSDR, 1990). Near-blindness resulted in male and female subjects with 5 gram ingestion (ATSDR, 1990).

MAMMALIAN TOXICOLOGY PROFILE

Oral doses in rats have hepatic effects. Dogs (1800 mg/kg) for 5 days of exposure showed signs of lethargy and ataxia, and decreased hemoglobin levels (ATSDR, 1990)

GENOTOXICITY

No studies of genotoxic effects in humans or laboratory animals were located. No human epidemiological evidence for cancer.

Inconclusive evidence for cancer in rats and mice were found (ATSDR, 1990).

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BENZO[a]ANTHRACENE

GENERAL BACKGROUND INFORMATION

Benzo[a]anthracene (BaA) is a member of the polycyclic aromatic hydrocarbons (PAH). PAHs are a class of non-polar compounds that contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. The overall database for benzo[a]anthracene is limited. Human exposures to BaA can come from the oral, inhalation or dermal routes. BaA is produced when gasoline or other organic material is burned. It is also found in cigarette smoke and cooked food. People most at risk from exposure to BaA are those in the coal tar and asphalt production industries, cooking plants, coal gasification plants, smoke houses and industrial plants that burn wood, trash, coal or oil.

PHARMACOKINETICS

BaA is absorbed by the dermal and oral routes. There is no information on absorption by inhalation. Biotransformation to reactive intermediates is necessary for toxicity (ATSDR, 1990). BaA accumulates in adipose tissue. The metabolism of BaA is similar to the metabolism of benzo[a]pyrene (Cooper et al., 1983). In brief, the aromatic ring is oxidized by arene oxides to form reactive intermediates. The reactive intermediates are subsequently hydrolyzed to diols (Sims and Grover, 1974). The diols are conjugated with glutathione and excreted.

HUMAN TOXICOLOGICAL PROFILE

There are no reports directly correlating human exposure to BaA with the development of excess tumors.

MAMMALIAN TOXICOLOGICAL PROFILE

The only toxicity endpoint that has been adequately studied for BaA is dermal carcinogenicity. There is some evidence that benz[a]anthracene is carcinogenic in laboratory animals by the oral route (Klein, 1963; Bock and King, 1959) and also by subcutaneous injection (IARC, 1973). BaA has been shown to cause skin tumors after dermal application (Bingham and Falk, 1969). Tumorigenicity of the diol epoxide metabolite has been shown (Levin et al., 1978) as well as the mutagenicity of the diol epoxide (Wood et al., 1977).

GENOTOXICITY

The metabolism of BaA is an essential event in producing genotoxic effects in both *in vitro* and *in vivo* biological test systems (ATSDR, 1990). The intermediates formed by BaA metabolism are reactive electrophiles which are capable of interacting with DNA.

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BENZO[a]PYRENE

GENERAL BACKGROUND INFORMATION

Benzo[a]pyrene (BaP) is a member of the class of compounds generally referred to as polyaromatic hydrocarbons (PAH).
PAHs contain two or more aromatic rings. They are ubiquitous in nature and are both naturally occurring and man-made. BaP is a component of fossil fuels and is produced from the incomplete combustion of organic compounds. BaP and other PAHs are found in coal tar, creosote oils and pitches formed from the distillation of coal tars (ATSDR, 1990).

PHARMACOKINETICS

BaP is readily absorbed by dermal, inhalation and oral routes (see section on Relative Absorption Factors). Distribution of BaP is rapid among several tissues. Following inhalation exposure to ^{3}H labeled BaP, maximum levels of radioactivity were found in the liver, esophagus, small intestine and blood after 30 minutes. After 12 hours, maximum levels were found in the cecum, stomach and large intestine (Sun et al., 1982). This and other studies provide evidence for the enterohepatic circulation of BaP metabolites.

Mammalian metabolism of BaP follows the mechanism established for smaller aromatic compounds (Williams, 1959). There is an initial oxidation of a double bond on one of the rings to an arene oxide. The oxide is then hydrolyzed to the diol. Oxidations may occur at multiple sites on the BaP molecule. Phase II metabolism is considered the detoxication pathway and involves the conjugation of the activated Phase I metabolites with easily eliminated substrates such as glutathione, glucuronide or sulfate (Cooper et al., 1983). In addition to being conjugated, the diol intermediate can undergo (1) further oxidation to several uncharacterized metabolites via the P-450 monooxygenase system, (2) spontaneous rearrangement to the phenol or (3) hydration to the trans-diols through a reaction catalyzed by epoxide hydrolase (Cooper et al., 1983). BaP 7,8-diol-9,10-epoxide has been established as an ultimate carcinogen (ATSDR, 1990). The primary route of excretion of BaP is through the feces. BaP undergoes first-pass metabolism and is reabsorbed via enterohepatic circulation (Chipman et al., 1982). Rats exposed by gavage to ^{14}C labeled BaP in peanut oil excreted up to 85% in the feces. Excretion in the urine was 1 to 3% of the administered dose (Hecht et al., 1979).

HUMAN TOXICOLOGICAL PROFILE

The database for the toxicological effects of BaP on humans, separate from PAHs, is limited. Toxic effects attributable to mixtures of PAHs include a variety of skin lesions and non-cancer lung diseases such as bronchitis (IARC, 1973).

MAMMALIAN TOXICOLOGICAL PROFILE

BaP is a moderately potent experimental carcinogen in numerous species by many routes of exposure (IARC, 1983). Mice exposed to doses of BaP ranging from 1.5 to 400 mg/kg/d developed benign and malignant tumors of the forestomach (Hartwell, 1951; Thompson, 1971). Acute intragastric doses of 50 to 67 mg/kg of BaP have been shown to elicit pulmonary adenomas and forestomach papillomas in mice (Sparnins et al., 1986; Wattenberg and Beuding, 1986). Intermittent gavage exposure of mice to 50 to 67 mg/kg BaP resulted in 100% forestomach and pulmonary tumor incidences at 30 weeks of age (Sparnins et al., 1986; Wattenberg and Leong, 1970). Mice fed BaP at concentrations equivalent to 33.3 mg/kg/d exhibited gastric neoplasms following two or more days of consumption. However, lower concentrations of BaP (equivalent to 13.3 mg/kg/d) administered for up to 7 days did not produce any forestomach tumors (Neal and Rigdon, 1967). Hamsters have developed papillomas and carcinomas of the alimentary tract following gavage or dietary exposure to BaP (Chu and Malmgrem, 1965). A single oral dose of 100 mg BaP (200mg/kg) produced mammary tumors in 88% of female Sprague-Dawley rats (Huggins and Yang, 1962). A 77% mammary tumor incidence was observed 90 weeks after a single oral dose of BaP of 50 mg (100mg/kg) was administered to rats (McCormick, 1981).

GENOTOXICITY

There are no studies relating exposure to BaP in humans to genotoxicity. In short-term *in vitro* and *in vivo* genetic toxicology tests, BaP has been shown to be a potent genotoxic agent when metabolically activated. In mice, oral exposure to 10 mg/kg BaP produced gene mutations in the mouse coat color spot test (Davidson and Dawson, 1976,1977). BaP shows positive mutagenic activity, in vitro, in several strains of *Salmonella typhimurium* in the presence of either rodent microsomes or hepatocytes for exogenous metabolic activation (ATSDR, 1990). Epidemiological studies have shown increased incidences of lung cancer in humans exposed via inhalation to mixtures of PAHs which include BaP (ATSDR, 1990).

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