APPENDIX C
HEALTH HAZARD SUMMARIES

This appendix reviews the available human health hazard data for each chemical/process associated with commercial clothes cleaning. "Hazard" data include information from animal and/or human studies on the inherent toxicity of a chemical/process. The data are presented under one of two general categories: drycleaning (non-aqueous based) and wetcleaning (aqueous-based).

C.1 DRYCLEANING

Hazard data are presented on perchloroethylene and hydrocarbon solvents (data are presented for Stoddard solvent, which is assumed to be a representative hydrocarbon used in drycleaning).

C.1.1 Perchloroethylene

Summary

Inhalation of perchloroethylene (PCE) has caused neurotoxic effects; may cause cancer in liver, kidney, and other organs; and may have developmental and reproductive effects. This section details these hazards in the following subsections: absorption/metabolism; acute toxicity; irritation/sensitization; subchronic/chronic toxicity; neurotoxicity; developmental/reproductive toxicity; mutagenicity; and carcinogenicity. Appendix D contains the dose-response assessment for PCE, for both non-carcinogenic and carcinogenic effects.

PCE does not have marked acute toxicity by inhalation. Lethal concentrations for laboratory animals are in the range of several thousand parts per million (ppm). Deaths have been reported in humans following unmeasured, but likely high, levels of exposure.

Neurotoxic effects are well established in both humans and animals following inhalation of air containing PCE at a few hundred ppm for several hours. Humans exposed to short-term, non-lethal inhalation exposures of PCE have exhibited neurotoxic effects (dizziness, drowsiness, and other signs of central nervous system depression). Developmental effects have been seen in laboratory animals exposed to several hundred ppm PCE by inhalation for 7 hours/day during the critical period of gestation and suggest a potential for developmental effects in the fetuses of exposed pregnant women. But human data regarding the potential of PCE to cause developmental and reproductive effects are inconclusive.

Chronic (long-term) exposure to PCE adds concern for carcinogenicity and kidney and liver effects to those already mentioned. Kidney and liver effects have been seen in rats and mice exposed to PCE at concentrations ranging from 10 to 20 ppm and above. Increased incidences of tumors have been found in laboratory rats and mice following inhalation or ingestion exposure to PCE; however, controversy surrounds each of the tumor end points concerning their relevance to humans. Existing epidemiologic studies suggest there is "limited evidence" (IARC, 1995) for establishing a causal relationship between PCE exposure and cancer in humans.

Available animal data indicate that PCE itself is not mutagenic, but the following PCE metabolites have been shown to be mutagenic: perchloroethylene epoxide, trichloroacetaldehyde,

dichloroacetaldehyde, monochloroacetaldehyde, trichloroacetic acid, and S-(1,2,2-trichlorovinyl) glutathione. Some of the metabolic pathways that generate mutagenic metabolites of PCE in animals may not be operative in humans. The relevance of the mutagenic metabolites, therefore, to PCE's potential as a human carcinogen is not firmly established. Recently, the the International Agency for Research on Cancer (IARC) has classified PCE as a Group 2A carcinogen (probably carcinogenic to humans). Overall, USEPA has judged the existing evidence as sufficient for classifying PCE as a probable human carcinogen (group B2). USEPA's Science Advisory Board (the preface in USEPA, 1991) stated that the evidence of PCE's toxicity places PCE on the continuum from group C (possible human carcinogen) to group B2 (probable human carcinogen). Their view was framed to encompass a concern for high PCE exposures, which is consistent with the uncertainties regarding the modes of action associated with the several tumor types.

Absorption/Metabolism

Absorption

Human data indicate that PCE is absorbed well following inhalation exposure (ATSDR, 1993) although good, measured data on absorbed dose are not readily available. Dermal absorption, relative to inhalation, can be approximately equal to the amount absorbed via inhalation at low exposure levels (e.g., 60 ppm) or can be as low as 1% of the amount absorbed via inhalation at higher doses (e.g., 600 ppm) (Riihimaki and Pfaffli, 1978; McDougal et al., 1990). While inhalation is expected to be the principal route by which PCE enters the body, and is expected to be the principal route of exposure in the drycleaning industry, dermal absorption cannot be ruled out as a potentially important route of entry of PCE into the body.

Data from studies in rats and mice indicate that PCE is also absorbed well by the oral route (USEPA, 1985).

Metabolism—General Considerations

Once PCE is absorbed into the body, its metabolism is important, as much of the toxicity of PCE is generally considered to result from its reactive metabolites. For example, studies show that several parameters of liver toxicity (liver weight increase, liver triglyceride accumulation, serum SGPT activity) vary linearly with the amount of PCE metabolized.

There are major differences among mice, rats, and humans in their ability to metabolize PCE. Humans appear to metabolize PCE to a lesser degree than rats, and rats metabolize PCE to a lesser degree than mice. One study shows that the amount of PCE undergoing metabolism is five to 10 times greater in the mouse than in the rat (Schumann et al., 1980).

Human data indicate that the metabolism of PCE overall is relatively limited, as evidenced by the fact that a high percentage of the chemical is excreted unchanged in the breath. In one study, volunteers exposed to 72 or 144 ppm of PCE for 4 hours excreted 80-100% of the total uptake of PCE unchanged (ATSDR, 1993).

The metabolism of PCE appears to be saturable in both humans and rodents. In humans and in rats, saturation begins to occur at levels greater than or equal to 100 ppm (ACGIH, 1986). In mice, saturation occurs at much higher levels, but the inhalation exposure level at which this process begins could not be found. In one study (Odum et al., 1988, as reported in ECETOC, 1990), saturation had not occurred in mice exposed to 400 ppm PCE for six hours.

Metabolism—Pathways (from USEPA, 1991, unless noted otherwise)

PCE is metabolized through at least two distinct pathways. Oxidative metabolism via the cytochrome P-450 system, which probably occurs mainly in the liver, is believed to be the primary pathway. This pathway is operative in both humans and rodents. The major metabolite of this pathway is trichloroacetic acid, which is excreted in the urine. Trichloroacetic acid and other metabolites that have been demonstrated or postulated to occur by this pathway—dichloroacetic acid (DCA), PCE epoxide, and mono-, di-, and trichloroacetaldehyde (or, chloral hydrate)—are cytotoxic/genotoxic or carcinogenic (trichloracetic acid, DCA, and chloral hydrate produce liver tumors in mice).

A secondary but potentially important pathway of PCE metabolism is glutathione conjugation, by which the liver conjugates PCE with glutathione to form 1,2,2-trichlorovinylglutathione (TCVG). This metabolite, in turn, is transformed in the kidney to 1,2,2-trichlorovinylcysteine (TCVC). TCVC is further metabolized in the kidney by β-lyase to yield an unstable thiol that may give rise to cytotoxic and mutagenic intermediates.

In vitro studies (Green et al., 1990) on human liver samples failed to detect glutathione conjugation with PCE, although glutathione conjugation has been demonstrated in rats and mice (*in vivo* and *in vitro*). Because of the very low levels of enzyme activity being measured and the limited number of human liver samples tested, however, it is premature to conclude that humans are unlikely to carry out this metabolic step. In a more recent study, TCVC has been identified in the urine of workers exposed to PCE, indicating that glutathione-dependent bioactivation of PCE is operative in humans (Birner et al., 1996).

The β-lyase pathway has also been demonstrated to exist in human kidney (proximal tubule) cells in two *in vitro* studies. In one of these studies, the rate of metabolism of chemically synthesized TCVC by β-lyase was up to 10 times higher in the rat kidney than either the mouse or human kidney (Green et al., 1990, as reported in ECETOC, 1990). Although only 11 human kidney samples were used in this study, the variation in β-lyase activity was remarkably small—rates ranged from 0.1 to 0.56 nmol/minute/mg protein.

Acute Toxicity

The LD_{50}/LC_{50} values for PCE in mice and rats show that the chemical does not have marked acute toxicity. A 4-hour inhalation LC_{50} of 5,200 ppm (35.3 mg/L) for female albino mice was established in an earlier study (ATSDR, 1993). In an NTP (1986, as cited in ATSDR, 1993) study, the highest concentration for a 4-hour exposure that did not produce death in B6C3F1 mice or F344 rats was 2,445 ppm; the lowest concentrations producing mortality were 2,613 ppm in mice and 3,786 ppm in rats. Single oral LD_{50} values of 3,835 and 3,005 mg/kg were determined for male and female rats treated by gavage. Death occurred within 24 hours after dosing and was preceded by tremors, ataxia, and central nervous

system depression (ATSDR, 1993). In other studies (Regulatory Toxicology and Pharmacology, 1994), oral LD_{50} values ranged from 8,800 to 10,800 mg/kg for mice.

Death has been reported in humans following unmeasured, but likely high, levels of exposure (Lukaszewski, 1979; Levine et al., 1981, both as reported in ATSDR, 1993).

Irritation/Sensitization

No data have been located regarding the irritation/sensitization potential of PCE exposure in humans or animals.

Subchronic/Chronic Toxicity

Kidney

In rodents, renal toxicity has been demonstrated after short-term and chronic inhalation exposures. Male rats exposed to 1,000 ppm for 10 days developed hyaline droplets in proximal tubules, but no lesions were present after exposure to 400 ppm for 28 days. Renal tubular karyomegaly occurred in both sexes of mice exposed to 200, 400, 800, and 1,600 ppm for 13 weeks, but did not occur in mice exposed to 100 ppm. Kidney lesions did not occur in rats similarly exposed to 1,600 ppm (NTP, 1986, as cited in ATSDR, 1993). In the chronic inhalation study, both sexes of F344 rats and B6C3F1 mice developed renal tubular cell karyomegaly at all exposure concentrations. This alteration was accompanied by low incidence of renal tubular cell hyperplasia in male rats. Thus, a no-observed-adverse-effect level (NOAEL) for renal toxicity was not established in a lifetime bioassay.

Compound related kidney damage has been reported in animals after oral exposure. Daily administration of 1,000 mg/kg by gavage to male F344 rats for 10 days produced an increase in protein droplets correlated with an increased amount of α-2μ-globulin and peroxisomal proliferation; these effects were not seen in female rats. Male rats exposed to 1,500 mg/kg by gavage for 42 days developed male-specific nephropathy. Male B6C3F1 mice exposed to 1,000 mg/kg by gavage for 10 days had peroxisomal proliferation in the kidneys. Osborne-Mendel rats and B6C3F1 mice of each sex were exposed by gavage for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice) in a carcinogenicity bioassay (NCI, 1977, as cited in USEPA, 1985). Average 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. Toxic nephropathy occurred at all dose levels in both sexes. The nephropathy was characterized by degenerative changes in the proximal convoluted tubules with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium and hyalin intraluminal casts. Thus, the lowest dose levels in this study (386 to 536 mg/kg/day for mice and 471 to 474 mg/kg/day for rats) produced nephrotoxicity.

Symptoms of renal dysfunction, including proteinuria and hematuria, have been associated with accidental exposure of humans to anesthetic concentrations of PCE vapor. Weak or no renal effects, depending on the parameters evaluated, were reported in people with chronic occupational exposure (average exposures of 10 to 21 ppm). No studies were found regarding renal effects in humans after oral exposure (ATSDR, 1993).

Mutti et al. (1992) recently evaluated a variety of parameters in blood (4) and urine (19) potentially indicative of kidney damage in PCE-exposed drycleaning workers (n=50) versus matched controls. PCE exposure was evaluated by measuring PCE in the workplace air (ranging from trace to 85 ppm, median = 15 ppm) and concomitant analysis of PCE in blood. Results showed significant differences between exposed and control groups for 2/4 blood parameters and 9/19 urinary parameters; however, the authors noted a lack of association between kidney dysfunction and duration of PCE exposure.

Liver

The hepatotoxic effects of PCE have been characterized in a number of laboratory studies. In general, fatty degeneration, enlargement, cellular vacuolization, and necrosis have been observed in rodents following inhalation or oral exposure for about 90 days or longer. Mice appear to be more susceptible to hepatotoxic effects than rats. In a 14-day inhalation study, male B6C3F1 mice exposed to 875 or 1,750 ppm had hepatocellular vacuolization; females exposed to the highest dose also showed this lesion. Liver lesions differed markedly between mice and rats after longer duration exposure. In a 13-week study (6 hours/day, 5 days/week), 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, 800, and 1,600 ppm. Rats, however, had liver congestion at 200 ppm but no other lesions at any exposure concentration. Hepatocellular degeneration and necrosis occurred in male mice exposed to 100 and 200 ppm for 103 weeks and in females exposed to 200 ppm. Liver lesions were not reported in rats chronically exposed to these concentrations (NTP, 1986, as cited in ATSDR, 1993). The hepatic lesions in male mice were dose-dependent, and no NOAEL was established for the hepatotoxic effects.

Another shorter-term (30-day) inhalation study with NMRI mice showed liver effects at the lowest concentration, 9 ppm. Mice continuously (24 hours/day) exposed to 37, 75, or 150 ppm developed hepatocellular vacuolization and enlargement. Absolute liver weights were significantly elevated at exposure concentrations of 9 ppm and higher. Liver weights were still increased (10%) 120 days after exposure to the highest concentration. In another study with mice and rats, light microscopic and ultra-structural liver lesions were correlated with levels of cyanide-insensitive palmitoyl CoA oxidase, a marker for peroxisomal β-oxidation (ATSDR, 1993). Animals were exposed to 200 ppm for 28 days or 400 ppm for 14, 21, or 28 days. In all exposed mice, centrilobular hepatocellular vacuolization corresponded to lipid accumulation, and cytoplasmic eosinophilia corresponded to peroxisomal proliferation with a significant increase in the marker enzyme. Exposed male rats in both dosage groups and female rats at 400 ppm had hepatocellular hypertrophy but no increase in peroxisomes (ATSDR, 1993).

The lowest effective doses in the chronic exposure study and the shorter-term (30 day) inhalation study differ by approximately an order of magnitude. Nine ppm may be close to a NOAEL since no microscopic lesions were observed at this dose. The quantitative differences in the lowest effective dose between the two studies may be related to the length of exposure each day (6 versus 24 hours) and/or the strain of mice.

The liver is also a target organ in rodents after oral administration of PCE (ATSDR, 1993). Gavage doses of 1,000 mg/kg/day for 10 days to male B6C3F1 mice increased relative liver weights and elevated cyanide-insensitive palmitoyl CoA oxidase levels. The same dose given to F344 rats did not increase enzyme levels above controls, although relative liver weights increased. Toxic effects induced in male Swiss Cox mice by oral gavage at doses of 20, 100, 200, 500, 1,000, 1,500, or 2,000 mg/kg/day, 5

days/week, for 6 weeks, were increased relative liver weights and triglycerides beginning at 100 mg/kg/day, decreased glucose-6-phosphate and increased serum alanine aminotransferase at 500 mg/kg/day, and hepatic lesions. Lesions consisted of hepatocellular hypertrophy, karyorrhexis, necrosis, polyploidy, and vacuolization. The NOAEL for this study was 20 mg/kg/day.

The liver is a target organ in humans, particularly in those exposed in occupational settings. There have been two recent occupational exposure studies that reported subtle liver effects in PCE-exposed drycleaning workers (Gennari et al., 1992, and Brodkin et al., 1995). Gennari et al. found a statistically significant increase in total serum gamma glutamyltransferase (GGT) in PCE-exposed workers (n=141) versus controls (n=130) drawn from unexposed university staff/students with a similar age/sex composition. A similar difference was not observed in other enzyme levels measured (alkaline phosphatase [ALP], lactic acid dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and 5'-nucleotidase [5'-NU]). Also, none of the workers showed any clinical signs of liver disease. The reported levels of PCE in the workplace air on the day the blood samples were drawn was 11.3 ppm $\pm$ 4.0 ppm.

Brodkin et al. (1995) report a new technique (ultrasonography) to assess subclinical liver toxicity in PCE-exposed workers. The authors compared the ultrasonographic results with the results of traditional liver function tests (serum measurements of ALT, GGT, AST, and ALP). Results suggest that ultrasonography, in which parenchymal changes were noted, was more sensitive than the serum liver enzyme levels in showing a difference between exposed drycleaning operators (n=29, mean PCE exposure = 16 ppm) and non-exposed laundry workers (n=29).

Saland (1967) reported on nine firemen who were exposed to high concentrations of PCE fumes for approximately 3 minutes in the cellar of a drycleaning facility. Transient increases in SGOT (8/9), decreases in white blood count (3/9), and hepatomegaly (1/9) were observed.

There is only one report of adverse effects on the liver from oral ingestion in humans; obstructive jaundice and hepatomegaly were reported in an infant exposed via breast milk (ATSDR, 1993). The concentrations that produced hepatotoxic effects in the infant are not known.

Other Effects

Osborne-Mendel rats received PCE 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, as cited in ATSDR, 1993). In a 14-day inhalation exposure study, mortality occurred in rats exposed to 1,750 ppm but not in mice. Compound related mortality did not occur in either species at exposure concentrations of 875 ppm or lower. In a 13-week inhalation study, mortality occurred in rats and mice exposed to 1,600 ppm but not to concentrations of 800 ppm or lower (NTP, 1986, as cited in ATSDR, 1993).

There have been case reports of cardiovascular, immunologic, or respiratory toxic effects in humans. For the first two systems, alternative explanations preclude evaluating the significance of the findings in the case reports. Respiratory irritation appears to occur in humans exposed to concentrations of PCE as low as 216 ppm for 45 minutes to 2 hours (ATSDR, 1993).

Neurotoxicity

The brain is a major target organ in humans exposed to PCE by inhalation. It is generally agreed that acute exposure to high concentrations can result in narcosis (Regulatory Toxicology and Pharmacology, 1994) and other reversible mood and behavioral changes, (Coler and Rossmiller, 1953; Lob, 1957; Eberhardt and Freundt, 1966; Gold, 1969; Stewart, 1969; Bagnell and Ellenberger, 1977, all as reported in USEPA, 1985). No behavioral effects were reported in humans after exposure to 106 ppm for 1 hour, and symptoms of dizziness and drowsiness were reported after exposure to 216 ppm for 45 minutes to 2 hours. Coordination was impaired after exposure to 280 ppm for 2 hours or 600 ppm for 10 minutes (see USEPA, 1985).

More recent human studies have supported earlier findings with animals indicating that chronic exposure to low doses of PCE may have adverse effects on the nervous system. Stewart et al. (1981) and Hake and Stewart (1977, as cited in ATSDR, 1993) found that electroencephalogram (EEG) responses reflect a very sensitive measure of central nervous system depression. These controlled studies in healthy human adults indicate significant EEG effects following PCE exposures of 100 ppm for 7.5 hours/day over 5 days; and no effects following PCE exposures of 20 ppm for 7.5 hours/day over 5 days. In a clinical study of 65 drycleaning personnel, Echeverria et al. (1995) reported neurobehavioral deficits after 3 or more years of exposure to concentrations below 50 ppm. Deficits were seen on behavioral tasks designed to measure frontal and limbic lobe functions of the brain.

Concentrations between 216 and 1,000 ppm PCE over varying exposure durations result in reports of dizziness, faintness, headache and nausea (see ATSDR, 1993). Collapse, coma, and seizures have occurred following exposure to higher concentrations of PCE fumes, such as 2,000 ppm after as little as 5 to 7 minutes (Carpenter, 1937; Hake and Stewart, 1977; Morgan, 1969; all as cited in ATSDR, 1993).

Animal studies have reported similar neurological effects of inhaled PCE. At high concentrations (greater than 1,750 ppm), effects of hyperactivity, ataxia, hypoactivity, and loss of consciousness have been reported in rodents (Friberg et al., 1953; NTP, 1986; Rowe et al., 1952, all as reported in ATSDR, 1993).

Developmental/Reproductive Toxicity

Most of the information presented in this section was obtained from review documents prepared by USEPA (USEPA, 1985, 1988) and other organizations (ATSDR, 1993). This report focuses on the effects of PCE via inhalation, as this route is of primary concern for human exposure.

Available human data have been inconclusive with regard to the potential of PCE exposure to cause developmental and reproductive toxicity. In animals, however, PCE was shown to be developmentally toxic by causing decreased fetal body weights in mice (altered growth) and increased resorptions in rats (death of the developing organism) exposed by inhalation at the only dose tested, 300 ppm.

Human Data

Some of the available human data suggest that occupational exposure to PCE in the drycleaning industry may be associated with adverse developmental/reproductive effects (e.g., an increase in spontaneous abortions and menstrual disorders). Other studies have been unable to find any such association. Due to the discrepancy in findings and the numerous limitations associated with these studies (i.e., small sample populations, failure to account for confounding factors, poor or no exposure data, inadequate study methodology, etc.) no definitive conclusions can be drawn.

Eskenazi et al. (1991a) compared the reproductive outcomes of wives of men exposed to PCE in the drycleaning industry with wives of laundry workers. The numbers of pregnancies, the standardized fertility ratios, and the rates of spontaneous abortions were similar for both groups, after consideration of a variety of possible contributing factors. Wives of drycleaners did have a slightly longer time to conception compared with the wives of laundry workers, but inadequate sample size and broad exposure indices prevent definite conclusions from being drawn. Sallmen et al. (1995) reported a similar effect, defined as the number of menstrual cycles that occurred prior to a desired pregnancy, in women exposed to drycleaning solvents, including PCE.

Subtle changes in semen quality were noted in specimens from drycleaning workers compared with those from laundry workers (Eskenazi et al., 1991b). On average, standard clinical measurements showed that the drycleaners' semen was within normal limits. However, sperm of drycleaners were significantly more likely to be round and less likely to be narrow. These effects were related to expired air levels of PCE and to an exposure index based on job tasks. Also, sperm of drycleaners tended to swim with greater amplitude of lateral head displacement (a finding that correlated with expired air levels of PCE). The authors concluded that additional studies are required to determine whether these changes are associated with changes in fertility.

A small scale exploratory study described menstrual disorders in drycleaning workers (Zielhuis et al., 1989, as cited in ATSDR, 1993). Limitations of the study include lack of exposure measurement data, methodological 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 female drycleaning workers in Nordic countries suggest that these women had an increased risk of spontaneous abortion (Ahlborg, 1990; Kyyroenen et al., 1989; both as cited in ATSDR, 1993). 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 (Kyyroenen et al., 1989).

Olsen et al. (1990) conducted a combined analysis of data from Norway, Sweden, Denmark, and Finland, which includes data from the Ahlborg and Kyyroenen et al. studies mentioned above. They used meta-analysis (a statistical procedure which combines quantitative results across studies) and other statistical procedures to evaluate the data. Practical problems, however, caused several differences in the study design and precluded use of a common Nordic study protocol. Risks for reproductive failures in relation to births (congenital malformations, still births, and low birth weights) showed no elevated risk related to exposure in the studies from Sweden, Norway, or Finland when analyzed together. The relative

risk (odds ratio) was significantly elevated for all types of reproductive failures combined (reproductive failures in relation to births plus spontaneous abortions) for the high exposure group (drycleaning plus spot removal at least 1 hour/day) for Sweden, Denmark, and Finland combined, and for spontaneous abortions in the high exposure group for Finland only. Because of the low plant participation rate for Sweden, Norway and Finland combined (54%), inability to control for various lifestyle factors known to influence pregnancy outcome, and the questionable utility of combining data sets in the meta-analysis (i.e., heterogeneity of the studies with respect to their design, methodology, cohort selection, exposure criteria, endpoints, sample sizes, etc.), interpretations of these findings should be viewed with caution.

Spontaneous abortions and birth defects occurred at a higher incidence in Italian drycleaning workers than in housewives, but this difference was not statistically significant (Bosco et al., 1987, as cited in ATSDR, 1993). No increase in spontaneous abortion rates for laundry and drycleaning workers in Canada was detected in a cross-sectional study (McDonald et al., 1986, as cited in ATSDR, 1993).

Animal Data

Several studies on the developmental and reproductive toxicity of perchloroethylene (PCE) have been found. In one of these studies, PCE caused a statistically significant decrease in fetal body weights in mice, and increased resorptions in pregnant rats exposed to 300 ppm PCE for 7 hours/day on gestation days 6-15 (Schwetz et al., 1975). Although this is a single-dose study, the slight maternal toxicity (slightly reduced body weight gain) seen indicates that the dose was not excessively high.

Another developmental toxicity study in rats showed, in the absence of maternal toxicity, a statistically significant reduction of body weight plus excess skeletal and soft tissue variations in fetuses of dams exposed to 1,000 ppm (Tepe et al., 1982, as cited in USEPA, 1985).

Hardin et al. (1981, as cited in ATSDR, 1993) evaluated the developmental toxicity for a selected group of chemicals using a single concentration of 500 ppm PCE in Sprague Dawley rats and New Zealand white rabbits, exposed 6-7 hours/day on gestation days 1-19 and 1-24, respectively. There was no evidence of feto/maternal toxicity; however, the study had limitations. It used only one dose level, and portions of the study were done in different laboratories.

Narotsky and Kavlock (1995) tested nine pesticides, solvents, and industrial chemicals, in timed-pregnant Fischer 344 rats given PCE once daily by gavage at doses of 0, 900, or 1,200 mg/kg/day on gestation day 6-19. Litters delivered by dams were examined on postnatal day 1, 3, and 6. All compounds exhibited dose-related maternal toxicity as manifested by alterations in weight gain. Observed developmental effects for PCE consisted of micro-/anophthalmia (eye defects), dose-related full-litter resorption, delayed parturition, increased post-natal losses, and reductions in fetal weights. The authors state this is the first report of developmental malformations for PCE, although previously reported studies used doses not shown to be maternally toxic. In this study, PCE produced developmental toxicity at doses that were also maternally toxic. However, full-litter resorption was not observed with other chemicals tested in the presence of maternal toxicity, and therefore the authors suggest there may not be a causal relationship, for PCE, between maternal and developmental effects.

Moreover, the data are consistent with effects observed in Long Evans rats when trichloroacetic acid, a metabolite of PCE, was administered by gavage at doses of 0, 330, 800, 1,200, and 1,800 mg/kg/day

(Smith et al., 1989, as cited in Davidson and Beliles, 1991). In that study, the authors concluded the lowest-observed-adverse-effect level (LOAEL) for developmental toxicity to be 300 mg/kg/day, based on effects such as full-litter resorption, cardiac malformations, and micro-/anophthalmia. Given this, Narotsky and Kavlock (1995) suggested that trichloroacetic acid may be the primary developmental toxicant associated with PCE exposure.

Two studies on the reproductive toxicity of PCE have been found. Carpenter (1937), as cited in ATSDR (1993), exposed rats to 70, 230, and 470 ppm PCE by inhalation for 28 weeks. Although this study has numerous limitations, including nonstandard protocols and inadequate controls, no adverse effects on reproductive performance, as measured by the number of pregnancies, numbers of litters conceived, and number of offspring per litter, were observed.

The second study is a reproductive toxicity study of PCE by the inhalation route (Tinston, 1995). Initially, groups of 24 male and female F_0 parental Sprague Dawley rats were exposed for 6 hours/day to 0, 100, 300, or 1,000 ppm PCE vapor. Prior to being housed for mating, the rats were exposed to these dosages 5 days/week for 11 weeks and were then exposed daily for up to 21 days. Following mating, males and females were exposed daily until termination and gestation day 20, respectively. An F_1A litter was produced from the first generation by daily exposure of dams and their litters to the dosages on post-partum day 6-29, at which time a second generation of parents, F_1, was selected and then subsequently exposed to the same dosages of PCE 5 days/week for 11 more weeks prior to mating.

Three additional litters were produced from the F_1 parental matings, F_2A, F_2B, and F_2C. Each of these three litters were exposed to different dosing regimes. Dams and litters from the F_2A litter were exposed during lactation on post-partum day 6-29 to 0 and100 ppm or on post partum day 7-20 to 300 ppm. No exposure was conducted at the 1,000 ppm dose level. The F_2B dams and their litters, which were obtained from mating the control, 300, and 1,000 ppm dose groups of the F_1, were not exposed to PCE during lactation. The F_2C litter was produced by mating males in both the control and 1,000 ppm dose groups with unexposed females.

A LOAEL of 300 ppm for adult toxicity was established based on central nervous system depression, decreased respiration rate during or immediately following exposure, decreased parental body weight gain, increased kidney weight with associated histopathological effects, and increased absolute liver weight. In addition, the effect on kidney and liver weights was more pronounced in adult males.

A LOAEL of 300 ppm was indicated for reproductive toxicity based on statistically significant reductions in number of live births, litter sizes, post-natal survival indices, and pup and testis weight.

Mutagenicity

Available data on PCE have not clearly demonstrated it to be mutagenic (USEPA, 1985, 1991). Most of those data indicate that it is not mutagenic, or at most weakly mutagenic. It is believed that certain commercial or technical preparations of PCE may contain mutagenic impurities and/or stabilizers that contribute to the mutagenicity of PCE under test conditions.

However, available data on metabolites (perchloroethylene epoxide, trichloroacetaldehyde, dichloroacetaldehyde, monochloroacetaldehyde, trichloroacetic acid, S-(1,2,2-trichlorovinyl) glutathione) of PCE indicate that these metabolites are mutagenic.

Carcinogenicity

Human Data

A variety of epidemiologic studies have been carried out in occupational and residential populations. Most of these studies have been conducted in populations exposed to a mixture of solvents, making it difficult to ascribe the results to PCE alone. In addition, limitations in the study designs, exposure characterization, impact of potential confounding factors (e.g., smoking, alcohol consumption, ethnicity, and socioeconomic status) and statistical considerations (e.g., having multiple endpoints) make these studies inadequate overall for establishing a causal relationship between PCE exposure and cancer in humans.

Occupational Studies

USEPA (1985) reviewed a number of occupational studies (Blair et al., 1979; Duh and Asal, 1984; Kaplan, 1980; Katz and Jowett, 1981; and Lin and Kessler, 1981; all as cited in USEPA, 1985); however, only the Kaplan (1980) study could verify exposure to PCE. The 1985 USEPA review acknowledged an association between cancer and employment in the drycleaning industry, but the lack of PCE-specific exposure information precluded identifying PCE as a causative agent. A more recent review of the epidemiologic studies of PCE also concluded that they provide inadequate evidence for an increased cancer risk associated with PCE (ATSDR, 1993).

Since the ATSDR review was completed, at least one epidemiologic study has been updated. In the original report, its overall cohort (i.e., 1,690 drycleaning workers exposed to PCE as well as other solvents) had a significant excess of mortality from bladder, kidney, and cervical cancer, the latter being attributed to the low socioeconomic status of the cohort (Brown and Kaplan, 1987, as reported in ATSDR, 1993). A subcohort of 615 workers employed only in shops where PCE was the primary solvent (referred to as the PCE-only cohort), were not found to be at any increased risk for cancer mortality at any site analyzed. In an 8-year follow-up (Ruder et al., 1994), statistically significant excesses of bladder, esophageal, and intestinal cancer deaths were observed in the overall cohort. In the PCE-only subcohort, no increases in mortality were identified for any cancer site. When duration (greater than or equal to five years' employment) and latency (greater than or equal to 20 years from first exposure to diagnosis of disease) were considered in the analysis, however, a significant excess of esophageal cancer was noted in the subcohort (Ruder et al., 1994). Although smoking and alcohol are both potential risk factors for esophageal cancer, the investigators failed to determine the smoking and alcohol habits of the cohort. The authors indirectly explored the possible influence of these confounding factors and concluded that they were not important, based largely on the low lung cancer mortality rates and the low liver cirrhosis rates; both of which would have been expected to be higher if either heavy smoking or heavy alcohol use were involved. Coupled with other study weaknesses, such as the lack of quantitative exposure information, these confounding factors limit the interpretation of the findings.

Finally, IARC (1995) recently reviewed the cancer epidemiology on PCE alone, and the drycleaning industry as an occupation. IARC concluded there was limited evidence in humans for the carcinogenicity of PCE, based on studies showing elevated risks for esophageal cancer, non-Hodgkin's lymphoma, and cervical cancer (IARC, 1995).

Residential Studies

A study conducted among Upper Cape Cod, Massachusetts, residents exposed to PCE-contaminated well water (Aschengrau et al., 1993) explored the relationship between exposure and the incidence of bladder and kidney cancers and leukemia. The authors noted an elevated relative risk for both leukemia (with and without consideration of latency) and bladder cancer (without consideration of latency) among "ever-exposed" subjects as compared to a control group. However, these results are difficult to interpret due to poor exposure measurements/modeling and the lack of substantial differences in exposure between the cases and controls.

Animal Data

The evidence of carcinogenicity of PCE is based primarily on the results of two long-term bioassays in rodents. An earlier study conducted by NCI (1977, as cited in USEPA, 1985) reported increased hepatocellular carcinomas in male and female mice following PCE exposure by gavage. In a more recent bioassay by inhalation (NTP, 1986, as cited in ATSDR, 1993), there were also significantly increased incidences of liver tumors in male and female mice exposed to PCE. In addition, marginally increased incidences of mononuclear cell leukemia were found in male and female rats; low incidences of kidney tumors occurred in treated male rats.

In the gavage study (NCI, 1977), groups of 50 Osborne-Mendel rats and 50 B6C3F1 mice of each sex were exposed to PCE in corn oil 5 days/week for 78 weeks, followed by observation periods of 32 weeks (rats) and 12 weeks (mice). Time weighted average (TWA) doses were 471 or 941 mg/kg/day for male rats, 474 or 949 mg/kg/day for female rats, 536 or 1,072 mg/kg/day for male mice, and 386 or 772 mg/kg/day for female mice. Groups of 20 untreated and vehicle-treated rats and mice of each sex served as controls. PCE induced a statistically significant increase in the incidence of hepatocellular carcinomas in both high- and low-dose male and female mice. Incidences in the untreated control, vehicle control, low-dose, and high-dose groups were 2/17, 2/20, 32/49, and 27/48, respectively, in male mice, and 2/20, 0/20, 19/48, and 19/48, respectively, in female mice. No increases in tumor incidences were observed in treated rats. However, the rat study was deemed inconclusive because of high mortality of the animals.

In the inhalation study (NTP, 1986), groups of 50 F344/N rats of each sex were exposed to 0, 200, or 400 ppm PCE, and groups of 50 B6C3F1 mice of each sex were exposed to 0, 100, or 200 ppm PCE. Exposures were 6 hours/day, 5 days/week, for 103 weeks. Increased incidences of mononuclear cell leukemia were found in the treated male rats (28/50 in controls, 37/50 at low dose, 37/50 at high dose) and female rats (18/50 in controls, 30/50 at low dose, and 29/50 at high dose). The increased incidences in the males were borderline significant; the increases in females were clearly significant. Low incidences of renal tubular cell adenomas or adenocarcinomas (1/49, 3/49, 4/50) occurred in male rats. The kidney tumor incidence was not statistically significant; however, such tumors are rare in control F344/N rats. In mice, there were significantly increased incidences of hepatocellular carcinomas in males (7/49, 25/49, 26/50, respectively) and in females (1/48, 13/50, 36/50, respectively).

Overall Evidence

Based on these bioassay data, which show increased incidences of tumors at three different sites and in two animal species, together with its evaluation of several epidemiological studies including Ruder et al. (1994), IARC (1995) classified PCE as a group 2A carcinogen; i.e., probably carcinogenic to humans.

Although PCE increased the incidence of tumors at three different sites and in two rodent species, controversy surrounds each of the tumor endpoints regarding their relevance to humans. Mononuclear cell leukemia is a common tumor that occurs spontaneously in F344/N rats. Furthermore, mononuclear cell leukemia is a rodent-specific tumor with no human correlate. Therefore, the biological significance of the marginally increased incidences of mononuclear cell leukemia observed in rats is considered by some to be questionable. Subsequent studies on the mechanisms of PCE carcinogenesis have suggested that the mouse liver tumors and male rat kidney tumors observed in the bioassays may be species specific; uncertainties exist regarding their relevance to humans.

In both carcinogenicity bioassays of PCE, a significant increase in hepatocellular carcinoma was observed in male and female mice but not rats. Based on species differences in metabolism of PCE to trichloroacetic acid and in hepatic peroxisome proliferation between rats and mice, it has been suggested that PCE-induced hepatic carcinogenesis may be related to peroxisome proliferation and toxicity of trichloroacetic acid (Odum et al., 1988, as cited in ECETOC, 1990). As human liver cells are even less efficient metabolizers of PCE (to trichloroacetic acid) than rats and are generally unresponsive to peroxisome proliferating agents, it would be unlikely that PCE exposure could lead to liver cancer in humans if this is the mechanism of action in mice.

Several studies have sought an explanation for the kidney tumors seen in male rats exposed to PCE. Male rats given high doses of PCE by gavage have been found to accumulate the protein α-2μ-globulin in renal proximal tubular cells and to exhibit the features of protein droplet nephropathy. The strong correlation between this toxic effect and kidney tumor formation specifically in male rats has led to the suggestion that this is the mechanism responsible (Goldsworthy et al., 1988, as cited in USEPA, 1991). Evidence of a minor metabolic pathway for PCE, which may be related to the development of kidney tumors, has also been reported. A glutathione-β-lyase conjugation pathway of PCE metabolism has been discovered in rodents. This minor pathway leads to the formation of a cytotoxic/mutagenic metabolite, 1,2,2-trichlorovinylcysteine (TCVC). The detection of low levels of TCVC in the urine of workers exposed to PCE in a recent study (Birner, 1996) appears to indicate that this glutathione-dependent bioactivation of PCE is operative in humans.

While there is some evidence to support each of the proposed mechanisms, there are also quantitative and qualitative gaps in the supporting data (USEPA, 1991). Several other mechanisms may contribute to the carcinogenicity of PCE. Although mutagenicity data are predominantly negative for the parent compound, the possibility that there may be mutagenic metabolite(s) of PCE in the development of tumors cannot be entirely ruled out. Since the mechanisms of PCE carcinogenesis are not clearly understood, USEPA has considered the inclusive animal data for PCE, taken as a whole, to be sufficient evidence for classifying PCE as a group B2 substance (probable human carcinogen) (USEPA, 1991).

The Health Assessment Document for PCE (USEPA, 1985) and its Addendum (USEPA, 1986) were reviewed by USEPA's Science Advisory Board (SAB), which subsequently also considered USEPA's response to the mechanistic data and issues of PCE (USEPA, 1991). The SAB expressed the view that the PCE evidence falls on the continuum from group C (possible human carcinogen) to group B2 (probable human carcinogen). These positions were expressed prior to the publication of epidemiological studies (particularly, Anttila et al., 1995; Ruder et al., 1994; both as cited in IARC, 1995) that IARC (1995) recently reviewed. Anttila et al. (1995) does not appear to add statistically significant elevations to the evidence; while Ruder et al. (1994), as discussed earlier in this section, saw significant duration and latency-related incidence of esophageal cancer, limitations remained in their conclusions. IARC, however, considered the pattern of endpoints to be important, despite the individual lack of statistical significance of some of them. Meanwhile, the view of USEPA's SAB was framed to encompass a concern for high PCE exposures, which is consistent with the uncertainties regarding the modes of action associated with the several tumor types.

C.1.2 Hydrocarbon Solvents

A variety of hydrocarbon solvents (e.g., Stoddard solvent, 140°F solvent, naphtha, and DF-2000, to name a few) may be used as drycleaning agents. Each solvent is a unique mixture of carbon and hydrogen molecules that co-exist as linear and branched chains, as well as in cyclic forms. In this CTSA, hazard data are presented on Stoddard solvent, which is assumed to qualitatively represent the hazard of the other, similar solvents used in drycleaning.

Summary

The information presented on Stoddard solvent is based primarily on ATSDR (1995). In humans, Stoddard solvent has been shown to be an irritant to eyes, skin, and mucous membranes (the membranes lining all bodily channels that communicate with the air, such as the nose and throat). Neurological effects (i.e., headaches, the feeling of euphoria, color blindness, cerebral atrophy, memory deficits, and fatigue) have been observed in humans occupationally exposed to Stoddard solvent either by breathing or skin contact; however, these studies contain poor exposure information and multiple solvent exposures, making it difficult to draw any definitive conclusions.

Limited information prevents any conclusions regarding developmental/reproductive toxicity. A study of individuals with prostate cancer, lung cancer, and Hodgkin's lymphoma suggested associations of those cancers with chronic inhalation exposure to mineral spirit, an often used synonym for Stoddard solvent. Interpretation of these findings is limited, however, and no other studies of human experience have been located.

The primary toxic effects following acute exposures to high concentrations of Stoddard solvent in animals (observed variously in rats, dogs, and cats) consist of eye irritation, irritation to the upper membranes of the respiratory tract, salivation, loss of coordination, muscle spasms, tremors, convulsions, and death. Skin contact has been associated with skin irritation in rabbits and guinea pigs.

One study in which Stoddard solvent together with two other components was applied to the skin of mice repeatedly over their lifetime showed some skin cancers. This result can not be attributed solely to the Stoddard solvent. Stoddard solvent does not appear to be mutagenic in bacteria or in mammalian

systems. Kidney effects were observed in exposed male rats but were not considered to be clinically relevant to humans.

Absorption/Metabolism

Very limited data are available concerning the pharmacokinetics of Stoddard solvent. Stoddard solvent is readily absorbed by inhalation based on the results of two studies dealing with the kinetics of Stoddard solvent in human volunteers (Pedersen et al., 1984, 1987, both as cited in ATSDR, 1995). The calculated pulmonary uptake from humans (eight males) exposed to 600 mg/m^3 (about 100 ppm) for 3 hours was approximately 400 mg (133 mg/hour) (Pedersen et al., 1984). Stoddard solvent was detected in the blood and subcutaneous fat. The estimated mean half-life in fat, associated with this single short-term exposure, was 2 days. Using a multi-compartmental analysis (simulated model) of the data obtained from blood and fat samples of seven male volunteers exposed to 600 mg/m^3 Stoddard solvent 6 hours/day for 5 consecutive days, the authors estimated minimum and maximum steady-state concentrations of Stoddard solvent in the brain to be 0.6 and 5-11 mg/kg, respectively (Pedersen et al., 1984, 1987). The half-life was estimated to be 18-19 hours in the brain and 7 days in fat (Pedersen et al., 1984).

Although there are no data on the oral absorption rate of Stoddard solvent, it is known that other petroleum distillates with longer carbon chains, such as kerosene (C_{10}-C_{16}), are very poorly absorbed from the gastrointestinal tract (Dice et al., 1982; Mann et al., 1977; Wolfsdorf and Kundig, 1972, all as cited in USEPA, 1993), whereas gasoline, a smaller chain petroleum distillate (C_4-C_{12}), appears to be relatively completely absorbed (NESCAUM, 1989). The smaller (C_9-C_{11}), alkane or aromatic hydrocarbons (10-20% in Stoddard solvent) may be absorbed readily (Litovitz and Greene, 1988). The rate and extent of gastrointestinal absorption of Stoddard solvent would, therefore, likely be dependent on the lipophilicity and size of various components and the amount of food in the stomach (USEPA, 1993).

No information on the absorption following dermal exposure was located. However, Stoddard solvent (absorbed dose of 210 mg) applied to the tails of rats daily for 6 weeks was associated with axonal prenodal swelling, an indication that dermal absorption had occurred (Verkkala et al., 1984).

Elevated levels of dimethylbenzoic acid (a marker of exposure) were found in the urine of men occupationally exposed to Stoddard solvent mist (Pfaffli et al., 1985), and in rats dermally exposed by daily applications to their tails for 6 weeks (Verkkala et al., 1984), showing that this solvent is indeed metabolized.

Acute Toxicity

An acute inhalation LC_{50} greater than 5,500 mg/m^3 and an acute oral LD_{50} greater than 5 g/kg have been estimated for rats (Vernot et al., 1990, as cited in ATSDR, 1995). An acute dermal LD_{50} in rabbits was reported to be greater than 3 g/kg (Vernot et al., 1990, as cited in ATSDR, 1995). The primary symptoms observed in animals consist of eye irritation, irritation to the upper membranes of the respiratory tract, salivation, loss of coordination, clonic spasms, tremors, convulsions, and death. No additional data have been located pertaining to the potential oral or dermal toxicity of Stoddard solvent in animals.

Groups of 15 rats inhaled various concentrations (420 to 1,400 ppm) of Stoddard solvent for single 8 hour periods followed by either immediate necropsy (n=5) or necropsy after 14 days of observation

(n=10) (Carpenter et al., 1975a, 1975b). Effects observed in rats exposed to 1,400 ppm (8,000 mg/m^3) included loss of coordination, eye irritation, and bloody exudate around the nostrils. Similar signs, without loss of coordination, were observed at 800 ppm (4,600 mg/m^3). No effects were observed during or after exposure at 420 ppm (2,400 mg/m^3). A female dog exposed to 1,400 ppm (8,000 mg/m^3) Stoddard solvent for 8 hours displayed eye irritation at 1 hour, increased salivation at 3 hours, tremors at 4 hours, and clonic spasms at 5 hours, whereas a second female dog exposed to the same level under the same conditions was asymptomatic during and after exposure (Carpenter et al., 1975a, 1975b).

Histopathological changes in the nasal cavity, trachea, and larynx were observed in three rats exposed to atmospheric levels of 214 mg/m^3 Stoddard solvent (a level selected to represent one half the TLV of 525 mg/m^3 for Stoddard solvent) 4 hours/day for 4 days compared to no changes in the control (Riley et al., 1984, as cited in ATSDR, 1995).

Irritation/Sensitization

In humans, Stoddard solvent is an irritant to the eyes, mucous membranes, and skin. One of six human volunteers exposed to 850 mg/m^3 (150 ppm) Stoddard solvent vapors for 15 minutes/day for 3 days experienced slight eye irritation (Carpenter et al., 1975a, 1975b); all subjects experienced eye irritation following exposure to 2,700 mg/m^3 (470 ppm). Additionally, one subject exposed to 2700 mg/m^3 showed throat irritation; two volunteers experienced slight dizziness at this concentration. No eye or throat irritation was seen in the subjects after exposure to 140 mg/m^3 (24 ppm). Minor irritation was reported in 50 male volunteers exposed to 600 mg/m^3 Stoddard solvent; however, there was no observable difference between cases and controls with respect to eye-blink rate, swallowing rate, or respiration rate (Hastings et al., 1984).

One man working with Stoddard solvent in a drycleaning factory, who had his forearms and hands wetted with or immersed in the solvent, developed follicular dermatitis of the exposed skin after 2 weeks (Braunstein, 1940), and a positive skin sensitization response to Stoddard solvent was observed. Five men wearing coveralls damp from drycleaning with Stoddard solvent developed sores on their genitals and buttocks (Nethercott et al., 1980, as cited in ATSDR, 1995). The limited information makes it impossible to determine whether Stoddard solvent is a cause of contact dermatitis in humans.

Stoddard solvent has been classified as a moderate irritant to the skin in rabbits (Vernot et al., 1990, as cited in ATSDR, 1995). Dermal exposure to Stoddard solvent, three times daily for 3 days, resulted in skin irritation in guinea pigs as evidenced by an increase in mean epidermal thickness, visible redness, palpable induration, and evident swelling (Anderson et al., 1986, as cited in ATSDR, 1995). A dermal sensitization study in guinea pigs did not show positive results (Vernot et al., 1990, as cited in ATSDR, 1995); the details of this study are not clear.

Subchronic/Chronic Toxicity

There have been a few case reports associating occupational exposure to Stoddard solvent (boiling point 150-200°C) and other higher-boiling-point petroleum distillates with the development of aplastic anemia (Prager and Peters, 1970, and Scott et al., 1959, both as cited in ATSDR, 1995), but no epidemiological studies appear to have been done.

A young man (29 years old), exposed to direct dermal contact and inhalation of Stoddard solvent 6 hours a day for 1 year, developed glomerulonephritis (Daniell et al., 1988, as cited in ATSDR, 1995). Exposure concentrations were not reported. This isolated case report is inadequate for assessing the risk of kidney effects.

No hepatic effects were observed in a laboratory study of 12 men exposed to 610 mg/m^3 of vaporized Stoddard solvents for 6 hours (Pedersen et al., 1984, as cited in ATSDR, 1995), or among a group of house painters compared to controls (Hane et al., 1977, as cited in ATSDR, 1995).

No statistically significant differences were observed in dogs exposed to 480, 1,100 or 1,900 mg/m^3 (84, 190, and 330 ppm, respectively) of Stoddard solvent for 6 hours/day, 5 days/week for 13 weeks compared to controls (Carpenter et al., 1975a, 1975b). Nephropathic effects (i.e., kidney damage) have been observed in groups of 25 male rats exposed to up to 1,900 mg/m^3 (330 ppm) of Stoddard solvent for 13 weeks (Carpenter et al., 1975a, 1975b). This type of "hydrocarbon nephropathy" appears to be unique to the male rat (Alden, 1986, and Rothman and Emmett, 1988, both as cited in ATSDR, 1995).

Neurotoxicity

A number of studies have reported neurological findings in humans who have been chronically exposed to Stoddard solvent via the inhalation or dermal routes at the workplace; however, details of exposure concentrations and/or exposure duration were not reported. In addition, workers were often exposed to other solvents, making it difficult to identify which solvent (or combination of solvents) may be responsible for the neurological effects. Neurological effects that have been reported include bifrontal headaches and the feeling of euphoria (Daniell et al., 1988, as cited in ATSDR, 1995), color blindness (Mergler et al., 1988, as cited in ATSDR, 1995), cerebral atrophy (Mikkelsen et al., 1988, as cited in ATSDR, 1995), memory deficits, and fatigue (Arlien-Soberg, et al. 1979; Flodin et al., 1984; Gregersen et al., 1984; and Hane et al., 1977, all as cited in ATSDR, 1995; Olson, 1982). Gregersen (1988) has also reported significantly more symptoms of chronic encephalopathy, in particular memory and concentration impairment in a group of solvent-exposed workers (n=59) compared to controls (n=30).

Exposure of eight male volunteers to 4,000 mg/m^3 (about 698 ppm) Stoddard solvent vapor for 50 minutes resulted in a prolonged reaction time and a possible impairment of short-term memory in performance tests (Gamberale et al., 1975). These men (plus six others) remained unaffected by exposure to 625, 1,250, 1,850 and 2,500 mg/m^3. Human subjects exposed to 2,400 mg/m^3 (419 ppm) Stoddard solvent for 30 minutes displayed no problems with visual-motor tasks (Hastings et al., 1984). No adverse systemic, immunological, or neurological effects were observed in human subjects exposed to 570 mg/m^3 (about 100 ppm) Stoddard solvent for 6 hours/day for 5 days (Pedersen et al., 1987, as cited in ATSDR, 1995).

Incoordination at 8,200 mg/m^3, and tremors and convulsions at 8,000 mg/m^3 were observed in rats and dogs, respectively, exposed for 8 hours (Carpenter et al., 1975a, 1975b; for more details see acute section above). Exposure of cats to 10,000 mg/m^3 (1,700 ppm) Stoddard solvent for 2.5 to 7.5 hours resulted in slowed reaction to light at 20 minutes, tremors at 26 to 74 minutes, clonic convulsions at 1.75 to 7.5 hours, and deaths at 2.5 to 7.5 hours (Carpenter et al., 1975a, 1975b); only one concentration was examined.

Developmental/Reproductive Toxicity

Sperm counts, motility, and morphology measured over a period of 2 months were normal in 11 men occupationally exposed to a mixture of organic solvents, including 50 ppm Stoddard solvent, in a printing factory (Tuohimaa and Wichmann, 1981, as cited in ATSDR, 1995).

No signs of toxicity were exhibited in fetuses of three groups of 20 to 27 female rats exposed from day 6 to 15 of gestation, 6 hours/day, to Stoddard solvent at concentrations from zero to 2,356 mg/m^3 (400 ppm) (API, 1977, as cited in ATSDR, 1995). No embryonic or teratogenic effects were seen in mated female rats exposed to 100 or 300 ppm Stoddard solvents 6 hours/day by inhalation from day 6 to day 15 of gestation (Phillips and Egan, 1981). Pregnancy rates, implantation efficiency and rates, and fetal deaths for female rats mated to fertile male rats exposed to 100 or 300 ppm Stoddard solvent 6 hours/day, 5 days/week for 8 consecutive weeks prior to mating, were comparable to those of controls (Phillips and Egan, 1981). No further information is available regarding exposures to Stoddard solvent and reproductive/developmental effects in animals or humans.

Mutagenicity

Based on data derived from several types of assays, Stoddard solvent does not appear to be mutagenic in bacteria or in mammalian systems. Stoddard solvent has been tested for genotoxic potential in several *in vitro* assays (two Ames tests, two mouse lymphoma tests, and a chromosomal aberration assay using human peripheral lymphocytes), and *in vivo* assays (mouse micronucleus test, mouse and rat dominant lethal tests, and chromosomal aberration test using rat bone marrow) (Conaway et al., 1984; Gochet et al., 1984; API, 1982; API, 1987). No significant increase in sister chromatid exchange in human peripheral lymphocytes was observed. No chromosomal aberrations were found in bone marrow cells. Negative results were obtained in the dominant lethal assays. The Ames and lymphoma tests support the negative results observed in the mammalian *in vivo* and human *in vitro* studies.

Carcinogenicity

There is limited information available regarding the potential carcinogenic effects of Stoddard solvent in humans and animals. Although lung cancer, prostate cancer, and Hodgkin's lymphoma were observed in humans exposed to mineral spirits and skin cancer in mice exposed to Stoddard solvent, limitations of these studies preclude their usefulness in assessing risk. Therefore, no conclusions regarding the carcinogenic potential of Stoddard solvent can be drawn at this time.

In a case-referent study of 3,762 cancer patients, associations of prostate cancer, lung cancer, or Hodgkin's lymphoma with chronic inhalation exposure to mineral spirit (a common synonym for Stoddard solvent) were seen (Siemiatycki et al., 1987). The absence of exposure information, multiple comparisons, lack of control for confounding factors, use of other cancer patients as referents, and other limitations of this study make it unsuitable for risk determinations.

In a lifetime (864 days) skin-painting study, squamous cell carcinomas were observed in 6 of 50 mice exposed to a mixture of 90% Stoddard solvent, 7% calcium petroleum sulfonate, and 3% ethylene glycol monobutyl ether compared to none of the 50 controls (USEPA, 1984); this is a statistically significant increased incidence. It is not possible, however, to assess the carcinogenic potential of

Stoddard solvent in this study because the test substance contained additional components that could have contributed to the result, and only one dose level was used. No inhalation or oral animal studies appear to be available.

C.2 MACHINE WETCLEANING EXAMPLE DETERGENT CHEMICALS

Wetcleaning detergent formulations are complex mixtures typically containing water plus several chemicals. Most formulations are trade secrets, and the concentrations of the individual chemicals are unknown to all but the manufacturer. Hazard summaries are presented for 10 constituents of the two sample detergents used in the exposure assessment (see Chapter 4 and Appendix E) portion of this CTSA[1]. They are meant to provide illustrative information on the types of hazards that could be related to chemicals potentially found in machine wetcleaning detergent formulations. It is not known how representative these effects are of the chemicals that may be found in actual detergent formulation.

The detergents considered in this hazard assessment are grouped into surfactants and surfactant aids. It should be noted that especially for surfactants (e.g., CAPB and lauramide DEA), the substances discussed herein are rarely used by themselves, and the variety of formulations makes it difficult to establish general toxicity conclusions.

C.2.1 Surfactants

Cellulose Gum (CG)

A number of studies in both animals and humans have been conducted by the manufacturers of products containing cellulose gum in concentrations of less than or equal to 0.1% to up to 10% (concentrations most frequently used range between 0.1 and 1.0%). Results of these studies have been voluntarily submitted to the Cosmetic, Toiletry and Fragrance Association (CTFA) and reviewed by the Cosmetic Ingredient Review (CIR, 1986a) panel. The following information (studies and conclusions) used to compile this health hazard review was adapted from the published materials of the CIR panel, unless otherwise cited.

Summary

Cellulose gum (CG) is used as a thickener, suspending agent, film former, stabilizer, emulsifier, emollient, and binder or water retention agent in a wide variety of cosmetic and toiletry products, and is one of a number of water-soluble cellulose ethers (carboxymethyl cellulose [CMC], methylcellulose [MC], hydroxypropylmethylcellulose [HPMC], hydroxyethylcellulose [HEC], and hydroxypropylcellulose [HPC]). All of these ethers have been reported to be nonirritating and nonsensitizing, exhibiting very low oral toxicity, and no neurologic, reproductive, or mutagenic effects have been reported. Cellulose gums are largely negative for developmental effects. Rat oral LD_{50} values ranging from greater than 3.0 to 27 g/kg have been reported. NOAELS of 20 and 10 g/kg were reported in rats and guinea pigs, respectively.

[1]Hazard summaries are not provided for lauryl polyglucose, Aveda's fragrance, cocamphocarboxyproprionate, diazolidinyl urea, and methyl-2-sulfolaurate

Absorption/Metabolism

Cellulose gum does not appear to be absorbed by humans, rats, or dogs and so is excreted unchanged. The lack of absorption is also inferred from wide use in concentrations from less than 0.1% to 1% as bulk laxative, protective colloid, surgical and dental adhesive, and binder in dietary supplements. Some CGs are soluble in water and organic solvents, and some are not; thus, solubility does not help infer humans' susceptibility (Clayton and Clayton 1982; CIR, 1986a).

Acute Toxicity

Oral LD_{50} values in rats range from 3 to 27 g/kg. Acute toxicity studies have not been identified for dermal exposure routes.

Irritation/Sensitization

Cellulose gum, as well as the other cellulose polymers tested, was found to be non-irritating or slightly irritating to the skin and eyes of humans and animals (rabbits).

Humans

CG and MC were evaluated for irritation and sensitization in groups of 200 volunteers by patch test and/or challenge tests. All results were negative. Twenty-four-hour patches containing 100% or 5.0% HEC, or 10% HPC, applied every other day to the skin of 50 subjects, for a total of 10 exposures, produced no irritation or sensitization. Of the 48 studies presented in the CIR review assessing the irritancy and sensitization potential of the various cellulose derivatives, only five studies showed any indication of an effect, which was classified as mild at worst.

No irritation occurred to the eyes of 10 volunteers given four artificial tear drops (5 minutes apart) containing a 2.0% concentration of HPMC or HEC or to an unspecified number of individuals administered an eye lotion containing 0.5% CG.

Animals

Following applications of 23- and 24-hour occlusive patches, no or slight skin irritation was observed in rabbits exposed to various cosmetic products containing CG, CMC, HEC, HPC, and HPMC ranging in concentrations from 0.3 to 3.0%, and to 2.0% aqueous solutions of HEC, HPC, and MC. A single occlusive patch containing 5.0 g/kg HPC (a dermal dose 500 times the expected human exposure), applied to each of six rabbits, resulted in no deaths, no irritation, and no gross effects.

Repeated application (5 days/week for 4 or 6 weeks) of CG (1.0, 4.0, or 10% in aqueous solution) to the shaved backs of rabbits was observed to be either nonirritating or "slightly irritating and relatively well tolerated" (CIR, 1986a).

No or minimal eye irritation was seen in rabbits exposed to various cosmetic products containing CG or CMC ranging in concentrations from 0.3 to 3.0%. The majority of tests, using a variety of different

protocols, showed no eye irritation following exposures of rabbits to various levels of HEC, HPC, MC, CMC, HPMC, and CG, although some showed slight irritancy.

Subchronic/Chronic Toxicity

The CIR panel found oral exposures to cellulose derivatives in both humans and animals (rats, chicken, dogs, rabbits, mice, and guinea pigs) to be basically non-toxic. Only two dermal studies were reported, both 13 weeks in rats; neither showed significant adverse systemic or dermal toxicity.

Humans

Humans ingesting 10 g CG daily over a 6-month period exhibited no hematological or other toxic effects and no mucosal irritation. Cellulose gum given as a laxative to 250 subjects in twice-daily doses of 2.0-18 g over a period of 3 years produced no toxic effects.

Although no clinical inhalation studies have been conducted, occupational long-term exposure to the dust of cellulose ether generated in manufacturing operations has not led to any known adverse effects.

Animals

No effects with reference to survival rates, body weights, hematological endpoints, urinary function analysis, or gross or microscopic examination of tissues were noted in rats receiving daily applications of 886 mg/kg of a 3% CG product in a vehicle containing sodium silicate (groups of 15) or receiving daily applications of a 1.1% CG lotion, 2,900 mg/kg (male and female groups of 10) for 13 weeks. As cited by Clayton and Clayton (1982) no evidence of toxicity was seen in either rats or dogs (unspecified numbers) fed 6.0% MC or 10% HPMC for 90 days.

Neurotoxicity

No behavioral or other toxic effects were observed in rats fed 0.2, 1.0, or 5.0% HPC (three groups of 10) or HEC (three groups of 20) for 90 days. No other information has been located regarding the neurotoxicity of cellulose derivatives in animals or humans.

Developmental/Reproductive Toxicity

No significant developmental or reproductive effects were found in studies in which cellulose derivatives were administered orally to rats, rabbits, mice, and hamsters.

Mutagenicity

Cellulose gum and its derivatives have not been found to be mutagenic. In a series of short-term tests for CG using several strains of *Salmonella*, *Bacillus*, and silkworm for assessing mutations, and hamster lung fibroblast cells (without metabolic activation) for assessing chromosomal aberrations, all results were negative. Carboxymethyl cellulose gave negative results in several strains of *Salmonella,* with and without metabolic activation. Using the dominant lethal assay, MC was non-mutagenic in rats dosed with up to 5,000 mg/kg.

Carcinogenicity

No animal studies on the carcinogenicity of CG were reported.

Cocamidopropyl Betaine (CAPB)

The CIR panel (CIR, 1991) concluded, based on the data available at the time of its report, that CAPB is safe for use in rinse-off cosmetic products at the current levels of use. They recommended that the concentration of use for products designed to remain on the skin for prolonged periods of time should not exceed 3.0%. The latter is expressed as 10% dilution of a full-strength cocamidopropyl betaine solution that has an activity of 30%. The main toxic effect by dermal application or ingestion is irritation.

A number of studies in both animals and humans have been conducted by the manufacturers of products containing cocamidopropyl betaine in concentrations as high as 50% of full strength (which is considered to be 30% activity). Results of these studies have been voluntarily submitted to the CTFA and reviewed by the CIR panel. The following information (studies and conclusions) used to compile this health hazard review was adapted from the published materials of the CIR panel, unless otherwise cited.

Summary

CAPB, primarily used in hair shampoos but also in formulations used as hair conditioners, hair dyes and colors, bath soaps/detergents, skin cleansing preparations, and bubble baths, is reported as a potentially irritating substance. Concentrations of CAPB in these formulations range from 0.1 to 50% (expressed as a percent dilution of commercially supplied CAPB that is 30% active). CAPB does not appear to have undergone any studies of reproductive or developmental toxicity or neurotoxicity or chronic studies of systemic effects. The single carcinogenicity study employed CAPB in a formulation. Without any remarkable response, its results suggest that CAPB does not increase systemic tumors above background, but are not enough to be conclusive. Although no dermal subchronic toxicity testing appears to have been performed, results of a 28-day oral test suggest a CAPB potential for irritation, which is consistent with outcomes from a collection of patch and ocular animal tests.

Absorption/Metabolism

No studies were found on the absorption, distribution, metabolism, and excretion of CAPB. It is unclear whether the amide bond of CAPB can be hydrolyzed to yield the fatty acids and 3-aminopropylbetaine. No metabolism data are available on the latter compound.

Acute Toxicity

Humans

No studies have been located discussing acute effects of CAPB in humans by any route of administration.

Animals

All reported studies are by gavage or intubation, in mice or rats. An oral LD_{50} of 6.45 ml/kg was calculated for mice from a study of a full-strength CAPB solution, 30% active, administered by gastric intubation. For rats, the acute oral LD_{50} for full-strength CAPB was 4.91 g/kg. Gross necropsy findings in rats showed redness of the stomach and intestinal mucosa, suggesting irritation.

Irritation/Sensitization

Responses of humans to dermal exposure have ranged from none to moderate in voluntary test and case report contexts. More recently than CIR (1991), there have been several reports of apparent contact dermatitis, but these instances are not necessarily exclusively the result of CAPB exposure, and the amounts of any compound that may have sensitized the individuals are uncertain. Consequently, while irritation occurs at certain levels of exposure, sensitization initially attributed to CAPB has since been identified with another chemical in the same surfactant.

Humans

A 1.0% aqueous dilution of a product formulation containing 6.0% active CAPB was tested for skin irritation using a single insult occlusive patch and 19 panelists. The formulation was considered "practically nonirritating."

Daily doses of 0.2 ml of an 8% aqueous dilution of a liquid soap formulation containing 6.5% active CAPB were applied via occlusive patches to the forearms of 12 subjects for 5 days. An erythema score of 0.48 (scale 0-4) was calculated.

In a study of cumulative irritation, 0.3 ml of two soap formulations, described as "cream colored" or "white liquid," were applied to skin sites on the backs of 10 panelists using occlusive patches. Each contained 1.9% active CAPB. Daily 23-hour patches were applied for 21 consecutive days. Across all applications, the total irritation scores for all subjects were 588 and 581, respectively, of a maximum of 630. The average irritation times were 1.48 and 1.69 days, with medians of 2 days.

A repeated open application procedure was performed with a 10% aqueous dilution of a shampoo containing 18.7% active CAPB using 30 volunteers to determine skin sensitization. The same procedures were performed on additional subjects with another test substance containing an identical concentration of CAPB. No sensitization was seen in any of the 88 subjects exposed to the test materials in a shampoo base under any open patching conditions in both the induction and challenge applications.

Other skin sensitization potential studies similar to the above study were performed. Induction applications generally were repeated to the same site and scored following a 48-hour period. An alternate site was used for the challenge test and was scored after 48 and 96 hours. In one study, a 0.9% active aqueous solution of CAPB was tested on 93 volunteers who had slight responses to the test material. These responses were attributed to primary irritation, rather than sensitization, during both the induction and challenge tests. In another similar study, the skin sensitization potential of a formulation containing 10% active CAPB was tested on 100 volunteers. No evidence of sensitization was observed with the test material.

An investigation of the potential of CAPB to induce contact skin sensitization was conducted using 141 subjects. All applications initially contained a concentration of 1.5% active CAPB in distilled water, until a protocol modification changed the concentration to 3.0% active CAPB. Subjects who began the study a week earlier received two applications at a concentration of 1.5%, and all other applications of the test material at a concentration of 3.0%. Induction applications were made to the same, previously untreated site on the back three times per week for 3 successive weeks. Gauze patches were applied and then removed after 24 hours. A challenge application was applied to a previously untreated site for 24 hours 10-15 days later, and the site was scored 24 and 72 hours after patch removal. No responses were observed during either the induction or challenge tests.

Subsequent to CIR (1991), several case studies of individuals apparently presenting with contact dermatitis based on exposure to CAPB were reported (Korting et al., 1992, 1% aqueous, activity unspecified, standard patch; Fowler, 1993, 1% aqueous, activity unspecified, standard patch; Peter and Hoting, 1992, standard patch, and 5% aqueous, 0.1-0.2% active; Cameli et al., 1991, 1% aqueous patches; and Ross and White, 1991, standard patch). Several instances were initiated by contact lens solution exposure, others were in hairdressers or recipients of shampoo exposure over extended periods (Taniguchi et al., 1992). Peter and Hoting (1992) used their findings to hypothesize that the increased apparent allergenic activity could be attributed to some recent manufacturing process change that introduced impurities. Subsequently, it has been confirmed that the major allergen is the impurity dimethylaminopropylamine used in the synthesis of CAPB (Angelini et al., 1995; Pigatto et al., 1995).

In another study, five dilutions (0.15, 0.30, 0.75, 1.5, and 3.0% w/v) of three quality levels of CAPB (ranging from 29.5 to 29.8% active) were applied simultaneously to separate dorsal locations of up to 67 volunteers using a 48-hour occlusive patch (Vilaplana et al., 1992). The study's purpose was to examine three different noninvasive evaluative methods. The qualities were based on amounts of free amidoamine and sodium monochloro-acetate. None showed excessive irritant response, but the formulation with greatest free amidoamine content showed a statistically significantly greater preponderance of higher responses at 0.75% w/v and above. The authors concluded that the response "can be described as an irritant contact dermatitis but not as an allergic contact dermatitis."

An additional study investigated the potential of a 3.0% active solution of CAPB to induce contact photoallergy. There was no response to the challenge tests except for those exposed to both UVA and UVB radiation, who had mild to moderate erythemic responses that were not uncommon and were said to have resulted from the sunburn derived from UVB exposure (CIR, 1991).

Animals

Six studies applied occlusive patches with CAPB solutions of various activity (7.5% to 30%) to intact and abraded sites on the backs or abdomens of groups of rabbits. The responses ranged from no irritation (7.5% active) to a Primary Irritation Index of 3.75 (scale 0-8) with eschar (scab) formation (30% active).

Ten ocular irritation studies in rabbits, employing concentrations ranging from 2.0% to 30% active in water or in soap formulations, showed mostly conjunctival irritation and mild to moderate corneal irritation to treated, unrinsed eyes.

Two studies in guinea pigs followed intradermal injections with topical induction and challenge applications to identify the potential for skin sensitization. Fifteen male guinea pigs were injected (at three separate sites) with 0.1 ml of 0.5% (v/v) CAPB dilution in saline, 0.1 ml in saline and Freund's complete adjuvant, and 0.1 ml of 50% Freund's complete adjuvant in water, followed by a 48-hour occlusive patch on each site of 60% (v/v) CAPB 1 week later (induction). Five control animals received the treatment series without CAPB content. Two weeks following induction, a 10% (v/v) CAPB challenge patch showed no evidence of delayed contact hypersensitivity.

In another similar test, 20 guinea pigs (sex unspecified) received a 10% aqueous dilution of a 30% active CAPB sample in a 48-hour patch, following a 0.1% dilution injection. The challenge was a 10% aqueous dilution. Microscopic changes in the treated skin indicated slight delayed-type contact sensitization.

Subchronic/Chronic Toxicity

In a 28-day gavage short-term study in rats, with full-strength solution (30% CAPB), treatment-induced lesions were produced in the nonglandular portion of the stomach in the high-dose group but not in the low-dose group.

No other studies discussing subchronic effects of CAPB in humans or animals have been located.

Neurotoxicity

No studies have been located discussing neurotoxic effects of CAPB in humans or animals.

Developmental/Reproductive Toxicity

No studies have been located discussing reproductive or developmental effects of CAPB in humans or animals.

Mutagenicity

The mutagenic potential of a 31% active CAPB formulation was tested in five strains of the *Salmonella*/mammalian microsome mutagenicity assay, with and without activation, and the L5178Y TK +/- mouse lymphoma assay. CAPB was nonmutagenic in these assays.

Carcinogenicity

CAPB was not carcinogenic in a skin-painting study in mice. An aqueous preparation of a non-oxidative hair dye formulation containing an unspecified grade of CAPB at a concentration of 0.09% active CAPB was tested for carcinogenicity using groups of 60 male and female mice. The formulation also contained 5% propylene glycol, 4% benzyl alcohol, 0.6% Kelzan, 0.9% lactic acid, and less than 0.5% or each of fragrance and the disperse brown, red, yellow, and blue dyes. A dose of 0.05 ml per mouse was applied three times weekly for 20 months to clipped, shaven interscapular skin. Mortality, behavior, and physical appearance of the mice were observed daily. Dermal changes in particular were noted. Body

weights were recorded weekly. Ten males and 10 females from each group were killed at 9 months for a hematological study and necropsy. Urinalysis was also performed.

At termination, all mice were necropsied, and the tissues were examined microscopically. No adverse effects were noted on average body weight gains, survival, hematological, or urinalysis values in any group. Varying degrees of chronic inflammation of the skin were seen in all groups, including controls. Other lesions occurred, but were considered unrelated to treatment. Pulmonary adenomas, hepatic hemangiomas, and malignant lymphomas were observed in the 60 treated female mice and in the 59 treated male mice (no information was given on whether any were observed in the early sacrifice). However, the incidences of these systemic neoplasms did not differ statistically significantly from those in the two control groups (numbers unspecified) that were shaved and received no topical treatment.

Ethoxylated Sorbitan Monodecanoate (Polysorbate 20 or P-20)

The information (studies and conclusions) used in preparing this health hazard section has been adapted from a report issued by the CIR panel (CIR, 1984), unless cited otherwise.

Summary

Polysorbates are commonly used as surfactants in a variety of cosmetic products at concentrations ranging from less than or equal to 0.1% to greater than 50% for polysorbate 20 (P-20). The majority of product formulations (95%) fall into the range of less than 0.1% to 5.0% P-20. In both animals and humans P-20 has been found to be essentially nontoxic following acute and long-term oral ingestion and to exhibit little or no potential for skin irritation or sensitization. No inhalation studies are available; however, this is not an expected route of exposure. LD_{50}s in animals range from 18 to 36.7 ml/kg and greater than 5.0 to 38.9 g/kg following oral exposure, and from 0.7 to 3.5 ml/kg and 1.45 to 3.85 g/kg following injection routes of exposure. By analogy to other polysorbates, P-20 is not expected to be mutagenic. While not carcinogenic itself, P-20 has been shown to enhance the activity of known chemical carcinogens, and to inhibit tumor growth activity under certain conditions. No animal or human data regarding reproductive, developmental, or neurotoxic effects associated with P-20 exposures were located.

Absorption/Metabolism

The most common routes of exposure are oral and dermal. There is little likelihood of inhalation exposure of this substance. P-20 is one of a series of polyoxyethylenated sorbitan esters. It is hydrolyzed by enzymes in the pancreas and blood. The fatty acid moiety (the ester portion of the molecule) is readily absorbed and metabolized, whereas the other portion of the molecule (the polyoxyethylenated sorbitan moiety) is very poorly absorbed and excreted unchanged. Clinical tests have shown essentially the same pattern in humans as in rats.

Acute Toxicity

No acute toxicity data are available on dermal exposures.

Humans

For therapeutic reasons, 13 premature and 2 full-term infants with steatorrhea (abnormal fecal fat loss) were given four daily doses of 200 mg undiluted P-20. Although no increase in fat absorption was observed, it was noted that P-20 produced no adverse effects with respect to anorexia, vomiting, defecation, or growth.

Animals

A 24-hour occlusive patch containing 3.0 g/kg of P-20 was applied to the clipped intact or abraded skin of the back and flank of six albino guinea pigs and observed for 7 days. No deaths occurred and no adverse effects were observed before and after necropsy.

Oral LD_{50}s for rats, mice, and hamsters range from greater than 5.0 to 38.9 g/kg.

Irritation/Sensitization

There is no evidence of sensitization in humans following P-20 exposures. No dermal irritation was observed in humans exposed to a 100% concentration of P-20, whereas some product formulations containing P-20 produced a range of irritancy, but no sensitization. It is impossible to interpret the meaning of these results, however, without knowledge of the other ingredients in the formulations. P-20 produced no or mild eye irritation and no to moderate skin irritation in rabbits, depending on the length of the study, and moderate or strong skin sensitization in guinea pigs.

Humans

No evidence of irritation or sensitization was observed in several human studies: 50 persons administered two 72-hour occlusive patches containing undiluted P-20 (applied 7 days apart); two groups of 10 persons receiving two 48-hour occlusive patches containing undiluted or 30% aqueous concentrations of P-20; or among 19 persons tested in 24-hour single insult patch tests exposed to 40% aqueous dilutions of P-20. In three separate tests, no to mild irritation was observed in subjects (18, 19, or 20) tested with a 24-hour single insult patch of unspecified product formulation containing 2.0, 6.0, or 8.4% P-20. Cumulative irritancy tests (daily 23-hour occlusive patches applied for 21 days), in 10 to 12 subjects, of a bubble bath containing 6.0% P-20 produced moderately to highly irritating results. CIR (1984) concluded that these results cannot be interpreted due to the absence of information regarding other ingredients in the formulations.

No photosensitization reactions were observed in 103 persons exposed (open and closed 48-hour patches, repeated after 2 weeks) to a bubble bath containing 0.3% P-20.

Animals

In three separate studies, undiluted (100% concentration) 0.5 ml patches of P-20 occluded for 24 hours produced no or only minimal skin irritation in the one, six, or nine rabbits tested. The same results were seen for rabbits (one to six) receiving 0.1 ml sample of 100% P-20 instilled in the eye either with or

without a water wash and observed for 7 days. No inflammation was seen when P-20 was applied to the cheek pouch mucosa of hamsters (unspecified number of animals, volume, and concentration of P-20).

Polysorbates 20, 60, 80, and 85 were applied undiluted or diluted in water, petrolatum, or a hydrophilic ointment (1.0, 5.0, or 10%) daily to the backs of rabbits (unspecified number) for 30 days. For the undiluted P-20, erythema was observed by day 3, skin thickening by day 10 accompanied by minimal to mild irritation, and mild to moderate inflammation with acanthosis by day 30. At all dilutions, the polysorbates tested induced erythema and minimal irritation by day 10 and minimal to marked irritation at day 30, depending on the polysorbate.

To determine the sensitization potential of P-20, five guinea pig assays (unspecified number of animals per assay) were performed with three different batches of P-20. Following one to three challenge(s) with undiluted P-20, four of the five assays evoked responses indicative of moderate sensitization, and one batch of P-20 produced strong sensitization under the test conditions.

Subchronic/Chronic Toxicity

Humans

No dermal studies are available. There have been a number of long-term human feeding studies evaluating the use of polysorbates for therapy in liquid malabsorption syndromes (CIR, 1984). Many studies are reviewed in CIR (1984), and CIR concluded that long-term use (up to several years) of polysorbate 20 or polysorbate 80 for this purpose was not harmful to humans.

Animals

No dermal studies are available. In several long-term studies (7 weeks to 2 years), levels from less than 1 up to 25% P-20 in the diet were fed to chickens, rats, monkeys, and hamsters, in some cases over multiple generations. No adverse effects were seen in chickens, monkeys, or rats with the exception of a single fatality in rats (1/10) fed 25% P-20 for 21 weeks. Hamsters, on the other hand, fed diets containing 15% P-20, showed numerous gross and histopathologic findings in the bladder, kidney, spleen, and gastrointestinal tract. Results of these and other studies led the FOA/WHO Committee on Food Additives to conclude that polysorbates cause no toxicological effects in the animals at daily dietary levels of 5.0% (CIR, 1984).

Neurotoxicity

No data have been located discussing the neurotoxic potential of P-20 in either humans or animals.

Developmental/Reproductive Toxicity

No data have been located in humans or animals regarding developmental/reproductive toxicity associated with P-20 exposures.

Mutagenicity

While there are no data available for P-20, polysorbate 80 was negative in both the micronucleus and Ames assays for mutagenicity.

Carcinogenicity

From studies of limited duration, there was no evidence of carcinogenic activity following oral exposure to P-20. In one study, benign tumors with a tendency to regression were reported following dermal exposure; however, the overall evidence suggests that P-20 is not carcinogenic when applied to the skin. On the other hand, polysorbates have been shown to be both tumor enhancers (i.e., involved in tumor promotion and cocarcinogenesis) and, under certain experimental conditions, tumor growth inhibitors. Thus, they are able to enhance the activity of known chemical carcinogens although they may not be carcinogenic themselves.

No tumors were observed in rats (groups of 10 or 14) or hamsters (groups of 10 or 36) fed diets containing 5.0 to 25.0% P-20 for periods ranging from 8 to 21 weeks. In two separate studies, groups of 50 mice received dermal applications of 100% P-20 (unspecified dose) 6 days/week for 24 or 52 weeks. In the 24-week study, no tumors were produced. In the 52-week study, one mouse developed a benign skin tumor at 36 weeks. Both studies, however, are of short duration for determining cancer effects. After reviewing these results, as well as those of several other studies, Setala (1960, as cited in CIR, 1984) concluded that polysorbates are not carcinogenic when applied to the skin.

Dermal application of 0.125 mg 1,2-dimethylbenz[a]anthracene (DMBA), a carcinogenic agent, followed by repeated applications of 0.2 ml 0.3-3.0% P-20 (duration not provided) in ICR Swiss mice (no number given) resulted in weak tumor promotion. In another study of Wistar rats (no number given) given drinking water containing 50 mg/L of the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and 0.4% P-20 for 26 to 30 weeks, an increased incidence of stomach tumors as compared to MNNG controls was observed.

In vitro tests with P-20 on mouse carcinoma cells showed tumor growth inhibition activity, whereas *in vivo* tests with P-20 did not exhibit tumor growth inhibition activity when tested on the same mouse cancer cells.

Lauric Acid Diethanolamide (Lauramide DEA)

There is limited information available on the toxicity of lauramide DEA. A number of formulations (soaps, shampoos and bubble baths) containing concentrations ranging from 4.5 to greater than 50% lauramide DEA have been tested by the manufacturers in both animals and humans. Results of these tests have been voluntarily submitted to the CTFA and reviewed by the CIR panel (CIR, 1986b), which was used to compile this health hazard section, unless otherwise cited.

Summary

Acute dermal exposures of humans to various concentrations (4.0 to 10%) of lauramide DEA were found to result in no to moderate skin irritation depending on the formulation. No evidence of dermal

sensitization, regardless of the formulation or dose, was observed. No human studies were located regarding the potential toxicity of lauramide DEA following oral or inhalation exposure. In rats, LD_{50}s ranging from 2.7 to 9.63 g/kg were identified following single oral dose exposures; and NOAELs of 50 and 250 mg/kg/day were reported following subchronic exposure to lauramide DEA. No systemic effects were observed following dermal exposures in animals, although a dose-related increase in both skin and eye irritancy was reported in animals following exposure to solutions containing 1.0 to 25% lauramide DEA. Lauramide DEA was not found to be mutagenic. The carcinogenic potential of lauramide DEA is currently being investigated (NTP, 1998). No data were located regarding reproductive, developmental or neurological effects of lauramide DEA in animals or humans.

Absorption/Metabolism

No human or animal studies were located discussing absorption or metabolism of lauramide DEA by any route of exposure.

Acute Toxicity

Humans

No studies have been located discussing acute effects of lauramide DEA in humans.

Animals

A 24-hour patch containing 6.0 ml/kg of 50% lauramide DEA in a corn oil vehicle was applied to the shaved backs of six guinea pigs. Body weights, apparently reduced on day 7, were back to, or above, expected values by day 14 (CTFA, 1978b). Authors concluded that lauramide DEA was nontoxic by percutaneous absorption, following skin patch testing in guinea pigs.

In a series of acute studies (CTFA, 1977a, 1978a, 1979a,b,c), groups of five rats each were administered a single oral (gavage) dose ranging from 0.252 to 15 g/kg of lauramide DEA (0.25% in corn oil, 10% aqueous solution, or formulations containing 6.0 to 8.0%). LD_{50}s of 2.7, 9.63, and greater than 15 g/kg were reported. Based on their findings, investigators concluded that lauramide DEA was nontoxic or slightly toxic, depending on the dose.

Irritation/Sensitization

Humans

Compared to an equal number of controls, human subjects (17, 18 or 19) exposed to products containing 5.0, 6.0, or 8.0% lauramide DEA (tested as a 1.0 or 1.25% aqueous solution below an occlusive patch) were found to have mild to minimal skin irritation (CTFA, 1977c, 1979d, 1981a).

Each of three soaps containing 10% lauramide DEA (tested at 8% aqueous solutions) were applied to the forearms of groups of 12 or 15 subjects for 5 consecutive days (CTFA, 1980b, 1982b,c). Two soaps were determined to be mild skin irritants, and the third was non-irritating.

In a 21-day cumulative irritation study, a 25% solution of a soap containing 5% lauramide DEA applied daily under an occlusive patch was found to be moderately irritating in the seven persons tested (CTFA, 1977d).

Several products containing 4.0 to 10% lauramide DEA were tested for sensitization in humans (41, 52, 86, or 159 subjects) using multiple 24- to 72-hour occlusive patches over 6 weeks, followed by a 48-hour challenge. No products were shown to be sensitizers (CTFA, 1977d, 1979e, 1980c,d; RTL, 1978, 1980).

Animals

Concentrations of 1.0, 5.0, and 25% lauramide DEA in water were applied (5.0 ml each) to the shaved abdominal area (at one intact and one abraded site) of rabbits (number not specified). A dose-related increase in severity (i.e., no, moderate or severe irritation for 1.0, 5.0, and 25% lauramide DEA, respectively) was observed following 10 or 3 applications over a period of 14 days to the intact sites and abraded areas, respectively. A similar dose-related increase in severity (practically non-irritating to slightly irritating to markedly irritating) was observed in five groups of rabbits (nine per group) administered a single 24-hour occlusive patch containing 1.25, 10, or 20% aqueous lauramide DEA (CTFA, 1976, 1977b, 1979e) and observed 2 and 24 hours following patch removal.

Aqueous emulsions of 1.0, 5.0, and 25% lauramide DEA in the unwashed compared to washed eyes of rabbits (three/group) showed no to slight effects (some conjunctival irritation), disappearing within 24 hours following exposure to the 1.0% emulsion; slight to moderate effects (appreciable conjunctival irritation and superficial corneal injury with no vision loss) disappearing within a week following exposure to the 5.0% emulsion; and moderate to severe corneal and conjunctival injury with some vision impairment after exposure to the 25% emulsion.

Subchronic/Chronic Toxicity

Humans

No studies have been located discussing chronic effects of lauramide DEA in humans.

Animals

NOAELs of 50 mg/kg/day (equivalent to 0.1% lauramide DEA) and 250 mg/kg/day were identified for rats orally exposed to lauramide DEA for 90 days in the following studies, respectively. In the first study, groups of 15 male and 15 female rats were fed diets containing 0 (controls), 0.1, 0.5, 1.0, or 2.0% lauramide DEA for 90 days. Growth was normal in the 0.1% group, slightly reduced in the 0.5% group, and moderately reduced in the 1.0 and 2.0% groups. Growth retardation associated with a decrease in food intake and some hematological differences was observed at and above the 0.5% level (statistical significance not provided). Test animals were comparable to controls for bone marrow cytological values, kidney function tests, and gross and microscopic findings. In the second study, groups of 20 male and 20 female rats were fed diets containing 0 (controls), 25, 80 or 250 mg/kg/day lauramide DEA for 13 weeks. With the exception of a transient increase in blood glucose concentrations noted at 6 weeks in male rats fed 250 mg/kg/day, all other endpoints measured were comparable to controls (general health, body

weight, food consumption, hematologic values, organ weights, mortality (no deaths), and gross and microscopic findings) (CIR, 1986b).

In the first of two subchronic dermal studies, a medicated cleanser containing 5.0% lauramide DEA (2.0 ml/kg applied as a 4.8% aqueous solution) was applied to the shaved backs of 10 male and 10 female rats 5 days/week for 13 weeks (CTFA, 1980a). With the exception of minimal skin irritation in females during the first week only, all other indices measured were reported comparable to controls (e.g., body weight, appearance, behavior, survival, gross necropsy, and histology). Blood and urine samples, analyzed at 7 and 10 weeks, were within the normal range. In the second study, 15 female rats received a daily 2.0 ml/kg dose of a cream cleanser containing 4.0% lauramide DEA administered as a 0.45 aqueous solution, 5 days/week for 13 weeks (CTFA, 1982a). No deaths occurred. As in the previous study, gross and histopathologic findings were reported comparable to the untreated controls, and blood and urine levels were within normal limits. The investigators concluded that there was no evidence of dermal or cumulative, systemic toxicity associated with either of these products.

Neurotoxicity

No studies have been located discussing the neurotoxic effects of lauramide DEA in either humans or animals.

Developmental/Reproductive Toxicity

No studies have been located discussing developmental or reproductive effects of lauramide DEA in humans or animals.

Mutagenicity

Lauramide DEA was not found to be mutagenic in four separate Ames-type *Salmonella* assays, a DNA-damage assay or in two studies on *in vitro* transformation of hamster embryo cells. In a spot test performed with and without metabolic activation in five strains of bacteria, 50 µg lauramide DEA was judged to be mutagenic in two of five strains without metabolic activations, but quantitative results were not provided.

Carcinogenicity

The National Toxicology Program has recently completed a 2-year skin painting bioassay using rats and mice to determine the carcinogenicity of lauramide DEA condensate (NTP, 1998). Although the technical report is not yet published, NTP (1998) reports that post-peer review results indicate no evidence of carcinogenicity in either mice or rats. No other carcinogenicity studies were located in the published literature.

Sodium Laureth Sulfate

There is limited information available on the toxicity of sodium laureth sulfate. A number of studies in both animals and humans have been conducted by the manufacturers of products containing sodium laureth sulfate ranging from concentrations of less than or equal to 0.1% to greater than 50%.

Results of these studies have been voluntarily submitted to the CTFA and reviewed by the CIR panel (CIR, 1983). The following information (studies and conclusions) used to compile this health hazard review was adapted from the published materials of the CIR panel, unless otherwise cited.

Summary

Sodium laureth sulfate is a commonly used component in bath and hair preparations. Products containing sodium laureth sulfate may be expected to remain in contact with the skin up to an hour and are likely to be used repeatedly over a period of several years. Sodium laureth sulfate has been shown to produce eye and skin irritation at concentrations above 5% in animals and skin irritation at concentrations as low as 0.7% repeated over 21 days in humans.

Sodium laureth sulfate, following oral exposures, is "moderately to slightly toxic" (CIR, 1983) in acutely exposed animals and virtually non-toxic in chronically exposed animals. The severity of the effect shows a trend to increase with increasing doses, although there are some unexplained inconsistencies in this observation. Oral LD_{50}s range from greater than 0.28 to 3.55 g/kg. A NOAEL of 1000 ppm was identified for a 13-week study in rats fed dietary levels of 24% w/w sodium laureth sulfate. Sodium laureth sulfate does not appear to exhibit any reproductive, developmental or carcinogenic effects in animals. No data were located discussing the neurological or mutagenic effects of sodium laureth sulfate exposure in humans or animals.

Absorption/Metabolism

Sodium laureth sulfate is poorly absorbed through the skin. CIR (1983) suggests that the ingredient's ethoxylation decreases its biological activity. When oral exposures occur, the majority of compound is excreted in the urine, with small amounts appearing in the feces and in expired CO_2. In rats given sodium laureth sulfate by oral intubation or parenteral injection (unspecified length of time), the urine contained high concentrations of the compound, and the carcass retained less than 1% of the dose.

Acute Toxicity

Humans

Acute toxicity studies of sodium laureth sulfate in dilute solution have not been identified for dermal exposure routes.

Animals

In 10 studies of albino rats (groups of 5 or 10) orally exposed to 2.0 to 64 ml/kg test solution (unspecified dosing regime) containing concentrations of 5.6 to 58% sodium laureth sulfate, effects ranged from no effect to moderate effects. At high doses (16-64 g/kg) observed effects included unkempt coats, lethargy, diarrhea, rectal and nasal hemorrhage, and impaired locomotion; however, in all cases, the animals showed no gross or microscopic abnormalities attributable to the test compound. Oral LD_{50}s for sodium laureth sulfate identified from these studies range from greater than 0.28 to 3.55 g/kg.

Irritation/Sensitization

Dermal exposure to sodium laureth sulfate appears to cause mild to severe irritation to both humans and animals (somewhat dependent on the dose), but not sensitization. Eye irritation was observed in animals, but there were no human studies addressing this endpoint.

Humans

In two studies, 24-hour occlusive patches containing a 60% aqueous solution of 30% sodium laureth sulfate (18% active sodium laureth sulfate) produced mild irritation in 2/20 and 11/20 of test subjects. A repeat insult patch test of a dandruff shampoo containing 0.5% sodium laureth sulfate produced minimal irritation and no sensitization in 196 test subjects. No evidence of contact sensitization was seen in 25 persons exposed to a product containing 14.3% sodium laureth sulfate.

In two separate 21-day cumulative irritancy tests, products containing 0.7 or 1.25% active concentrations of sodium laureth sulfate were tested in 10 (although only 4 completed the study) and 13 subjects, respectively. Daily applications of 1.25% sodium laureth sulfate resulted in severe irritation, whereas the 0.7% sodium laureth sulfate produced mild irritation.

Animals

In a number of studies sharing similar protocols, one 0.5 ml sample each of various test solutions containing concentrations of 5.0 to 58.0% sodium laureth sulfate was applied to intact and abraded skin of albino rabbits for a period of 2, 3, or 7 days. No irritation was observed at concentrations of 5.0-5.6%; mild erythema and edema, sometimes transient in nature, were seen at concentrations of 6.0, 7.5, 10, 17.5, and 26%, whereas severe irritation occurred in test solutions containing 15, 25, 28, and 30% sodium laureth sulfate. In the tests using a concentration of 58% sodium laureth sulfate, no irritation occurred. The discrepancy in these findings seen at higher doses (greater than 15%) was not discussed. No deaths were reported at any dose or concentration.

A 0.25 molar solution of sodium laureth sulfate (approximately 5.0-10.0% solution by weight) applied for 3 consecutive days to the shaved skin of weanling rats produced no irritation after 1 day and slight erythema and edema after 3 days.

The ocular toxicity of sodium laureth sulfate was tested in groups of three, six, or nine albino rabbits, using a standardized Draize test. In 18 separate studies, 0.1 ml of test material instilled in the eyes, with or without rinse, and observed for 1 week produced responses ranging from no irritation to severe eye damage independent of the concentration range (1.3 to 58%) of sodium laureth sulfate in the test solution. No discussion was provided for these findings.

To test for skin sensitization, a 0.1% aqueous solution of sodium laureth sulfate was applied topically (3 times/week for 3 weeks) to 10 guinea pigs. Ten days after the final administration, when topically challenged, no skin sensitization was evident; however, when challenged by intradermal injections, the animals showed a positive reaction 1 hour following the challenge, which increased in intensity in three of the animals. At 48 hours six of the animals continued to show a positive reaction, while the other four demonstrated only a slight reaction.

Subchronic/Chronic Toxicity

Humans

No studies of sodium laureth sulfate in solution have been identified for dermal exposure routes.

Animals

A subchronic study on the effect of an anion-active sodium laureth sulfate detergent on the skin and hair cycles of rats was conducted. Various concentrations of the detergent dissolved in tap water were applied daily for 65 days to the shaved backs of five groups (totaling 65) 7- to 8-week-old male rats. Concentrations were as follows: Group-1 received pure detergent (60% sodium laureth sulfate); group-2, 30% sodium laureth sulfate; group-3, 9.0%; group-4, 0.9%; group-5 (controls), 0%. The group exposed to the 60% solution experienced inflammatory changes, epidermal hyperplasia, epidermoid cyst formation, and diffuse hair loss. Seven animals died between days 12 and 15. The 30% solution group had similar, though less severe, skin changes, but had no deaths. No effect was seen for any other concentration.

A NOAEL of 1,000 ppm was identified for a study of rats fed dietary levels of 24% w/w sodium laureth sulfate. Groups of 12 male and 12 female 5-week-old rats were fed diets containing 40, 200, 1,000, or 5,000 ppm of active material for 13 weeks. Compared to controls (18 male and 18 female rats receiving a standard diet), the behavior, body weights, food intake, hematological results, plasma proteins, urinary findings, and urea concentrations were within normal limits. No pathology changes were observed at necropsy. Kidney weights in males, and heart, liver, and kidney weights in females were increased in rats fed 5,000 ppm, but increases in relative organ weights were not found to be statistically significantly elevated.

In a long-term study (105 weeks) in groups of 30 rats fed diets containing 0 (controls), 0.5, or 0.1% sodium laureth sulfate, findings were essentially normal. There were no differences between treated animals and controls with respect to appearance, behavior, organ weights, organ to body ratios, growth rates, food consumption, and survival, with the exception of the male rats who had an unexplained weight loss in the last 8 weeks of the study. Clinical laboratory studies, gross and microscopic pathology, and the appearance of tumors assessed at 52 weeks (10 rats sacrificed from each group) and 105 weeks (the remaining rats were sacrificed) were comparable between treated and control animals.

Neurotoxicity

No data have been located regarding the neurotoxic potential of sodium laureth sulfate exposure in humans or animals.

Developmental/Reproductive Toxicity

Ten male and 10 female rats were fed diets containing 0.1% or no sodium laureth sulfate for 14 weeks, then mated. Their offspring (F_1 generation) were maintained on the same diet as their parents, and mated at approximately 100 days old. Their (F_1) progeny (F_2 generation) were also kept on the same diet for 5 weeks after weaning. No adverse effects on fertility, litter size, lactation, or survival of offspring, no

changes in the blood or urine of the F_1 and F_2 generations, and no gross or microscopic changes that could be attributable to the test compound were observed.

Mutagenicity

No data have been located regarding the mutagenic or genotoxic potential of sodium laureth sulfate exposure in humans or animals.

Carcinogenicity

The carcinogenicity potential of sodium laureth sulfate was tested in mice (two groups of 30 each). A dose of 0.1 ml of 5.0% aqueous solution of sodium laureth sulfate (5.0 mg) was applied twice a week for 105 weeks to the skin of 30 female mice. The total quantity of sodium laureth sulfate applied to each mouse was approximately 1 g. No skin tumors appeared, and the mortality did not differ substantially between the two groups of mice, but sample sizes were too small to detect most elevations.

Additionally, the long-term dietary study described above (see Chronic Toxicity section) found no differences in tumor prevalence at 52 or 105 weeks between treated groups and controls.

Sodium Lauryl Isethionate (SLI)

Summary

The limited information on sodium lauryl isethionate suggests that this chemical may not be a skin irritant and is not mutagenic. No other data were located on any other health endpoints for this compound (CCRIS, 1995).

Absorption/Metabolism

No data have been located regarding the absorption/metabolism potential of SLI exposure in humans or animals.

Acute Toxicity

No data have been located regarding the acute toxicity of SLI in humans or animals.

Irritation/Sensitization

One *in vitro* penetration cell experiment is reported, mentioning the irritancy of several surfactants; no enzymes were released from rat skin slices *(stratum corneum)* following 3-5 hours of exposure to SLI (24 hours incubation). The authors reported this was consistent with their prior knowledge that SLI does not have irritant potential (CCRIS, 1995). No other data are reported regarding any dermal properties or toxicity of SLI.

Subchronic/Chronic Toxicity

No data have been located regarding the subchronic/chronic toxicity of SLI exposure in humans or animals.

Neurotoxicity

No data have been located regarding the neurotoxic potential of SLI exposure in humans or animals.

Developmental/Reproductive Toxicity

No data have been located regarding the developmental/reproductive toxicity of SLI exposure in humans or animals.

Mutagenicity

SLI tested negative in the Ames test using several strains of *Salmonella* with and without metabolic activation at dose ranges of 16 to 2000 µg/plate (CCRIS, 1995).

Carcinogenicity

No data have been located regarding the carcinogenic potential of SLI exposure in humans or animals.

C.2.2 Surfactant Aids

Acetic Acid

Summary

Acetic acid is a common substance added directly at 5% dilution to human food (i.e., baked goods, cheeses, dairy product analogs, chewing gum, condiments, relishes, fats, oils, gravies, sauces, and meat products). It is Generally Recognized As Safe (GRAS) for food use by the Food and Drug Administration (FDA).

All studies reported relate to concentrations at least twice and as much as 16 times as great as acetic acid in vinegar (typically under 6% dilution). Acute exposures to strong solutions (10-20%) of acetic acid resulted in physiologic effects in humans. Splashes of vinegar (4-10% acetic acid solution) have been reported to cause ocular pain and injury. At high concentrations dermal contact with acetic acid, depending on the length of exposure, resulted in severe irritation in both humans and animals. At low concentrations (under 10%) no dermal irritation was seen. Effects such as bronchitis, pharyngitis, erosion of the teeth, conjunctivitis, palpebral edema and conjunctival hyperemia, digestive disorders, dry skin, and blackening and hyperkeratosis of the skin have been reported in workers chronically exposed to high air concentrations of acetic acid. No chronic effect was noted in animals. No neurologic effects were reported in the literature used for this review. There is no evidence of mutagenicity related to acetic acid

exposure. Although no direct information on the carcinogenicity of acetic acid was located, one chronic study in rats that were fed 350 mg/kg sodium acetate found no evidence of tumors. No reproductive studies were located.

Absorption/Metabolism

Undiluted acetic acid is absorbed from the gastrointestinal tract and through the lungs (Clayton and Clayton, 1982). It is readily metabolized by most tissues and may give rise to ketone bodies as intermediates (Clayton and Clayton, 1982). No discussion is available regarding dermal absorption at 5% solution.

Acute Toxicity

Humans

Splashes of vinegar (4-10% acetic acid solution) have been reported to cause ocular pain and injury (HSDB, 1994).

Animals

Data are not reported on results of exposures to solutions of less than 10%.

Irritation/Sensitization

Humans

Acetic acid (undiluted) is caustic to the skin. It can cause dermatitis, ulceration and burns. Based on animal experiments and industrial exposure, it is believed that human exposure (8 hours) to 10 ppm could produce some eye, nose, and throat irritation, and exposure to 100 ppm could produce lung irritation and possible damage to the lung, eyes, and skin (Clayton and Clayton, 1982). Skin sensitization, though rare, has been reported in humans at as low as 1% (HSDB, 1994).

Immediate pain, conjunctival hyperemia, and sometimes injury to the cornea have resulted from a splash of vinegar (4-10% acetic acid) to the eye. Exposures to air concentrations below 10 ppm have resulted in conjunctivitis in some exposed persons (HSDB, 1994). Permanent corneal anesthesia and opacity occurred in two individuals with accidental exposure of glacial (100%) acetic acid to the eyes, even though they were immediately rinsed with water after the exposure occurred (HSDB, 1994).

Animals

No effect was seen following an application of 10% acetic acid to intact or abraded skin patches in guinea pigs or rabbits (unspecified numbers and study length) (Clayton and Clayton, 1982). No discussion is available regarding dermal exposures at 5% solution. Dermal application of 20 mg undilute acetic acid applied to guinea pigs and rabbits (unspecified numbers) for 24 hours produced mild irritation (Clayton and Clayton, 1982). A larger application of 0.5 ml of 525 mg undilute acetic acid in rabbits (unspecified

number) showed no corrosive effects after 4 hours but produced severe irritation (with necrosis) after 24 hours (Clayton and Clayton, 1982).

Subchronic/Chronic Toxicity

Human

All reports relate to high concentrations in the workplace. The principal finding among five workers exposed for 7-12 years to high concentrations (80-200 ppm at peak concentration) of acetic acid was blackening and hyperkeratosis of the skin (HSDB, 1994). In another study, bronchitis, pharyngitis, erosion of the teeth and conjunctivitis were reported among workers (unspecified number) exposed for 7-12 years to concentrations of 60 ppm, plus 1 hour daily to concentrations in the range of 100-200 ppm (HSDB, 1994). Other effects reported among workers (unspecified numbers) exposed for a number of years to air concentrations of up to 200 ppm include palpebral edema, with hypertrophy of lymph nodes, and conjunctival hyperemia (HSDB, 1994). Digestive disorders and dry skin have been reported in workers (unspecified numbers or occupation) following repeated exposures (unspecified levels) (HSDB, 1994).

Animals

No information is reported on dermal exposures to solutions of less than 10%. Rats (unspecified number) receiving daily doses of up to 390 mg/kg acetic acid in their drinking water (up to 5.0%) for 2 to 4 months, were found to experience weight loss (apparently due to anorexia) at the highest dose. The NOAEL was 195 mg/kg/day; no deaths occurred in any dose group. Gastric lesions, forestomach wall thickening, and inflammatory changes were observed in some (proportion unspecified) rats fed 4.5 g/kg/day for 30 days.

Neurotoxicity

No data regarding neurologic effects related to acetic acid exposures in humans or animals were located.

Developmental/Reproductive Toxicity

No studies focusing on reproductive effects were located. Pregnant rats (unspecified number) administered 1.6 g/kg/day apple cider vinegar (5.0% acetic acid) showed no increased mortality or fetal abnormalities compared to sham-treated controls (unspecified study length and number of animals) (Clayton and Clayton, 1982).

Mutagenicity

Acetic acid was not found to be mutagenic in two *in vitro* mutagenicity tests with or without metabolic activation preparations from mice, rats, or monkeys (Clayton and Clayton, 1982).

Carcinogenicity

Male rats (unspecified number) fed 350 mg/kg sodium acetate, a salt of acetic acid, three times/week for 63 weeks, followed by a dose of 140 mg/kg three times/week for 72 days (10+ weeks) showed no histological evidence of tumors (Clayton and Clayton, 1982). This is insufficient to conclude anything about the carcinogenicity of acetic acid.

Citric Acid and Sodium Citrate

Summary

Citric acid is a normal metabolite in humans and occurs naturally in many foods. It is generally considered to be largely innocuous except in the case of ingestion of large quantities (i.e., levels well above 500 mg/kg, the estimated average daily intake) or chronic exposures. Chronic oral exposures in humans may result in tooth erosion, local irritation, and some ulceration. Gastrointestinal irritation has also been observed following ingestion of sodas containing citric acid. Citric acid dust may also be irritating to the nose and throat. Citric acid has been shown to be a mild to moderate skin and eye irritant in humans following inhalation or dermal exposures. Acute high dose exposures in animals have resulted in mild skin and severe eye irritation. Limited animal data suggest that exposure to citric acid does not result in developmental or reproductive effects. No information has been located discussing neurotoxic, mutagenic, or carcinogenic effects associated with citric acid exposures in animals or humans.

The alkaline salt of citric acid, sodium citrate, is expected to behave chemically like the acid systemically. Unlike the acid, however, this alkaline salt may not have irritant properties.

Absorption/Metabolism

Citric acid is a normal metabolite and an intermediate in cellular oxidative metabolism. It is formed in the mitochondrion and successfully degraded to a series of four-carbon acids used in the oxidative process of the cell (Clayton and Clayton, 1982). Sodium citrate is oxidized to bicarbonate in the body and excreted in the urine (HSDB, 1994; no other details provided). No absorption by the skin is expected following dermal exposures (USEPA, 1994).

Acute Toxicity

Humans

No reports relate to dermal exposure.

Animals

No tests reported relate to dermal exposure.

Irritation/Sensitization

Humans

Citric acid, in humans, may be a mild to moderate irritant if inhaled as an aerosol, or if in direct contact with the eyes or skin (HSDB, 1994). Citric acid dust may also be irritating to the nose and throat (HSDB, 1994). Citrate, about 1-2 g/day usually prescribed for ingestion in the form of citric acid and sodium citrate solution, has been reported occasionally to result in gastrointestinal irritation (i.e., irritant effect on the oral mucosa and necrotic and ulcerative lesions) (HSDB, 1994).

Animals

In rabbits (unspecified number), a moderate reaction was observed at 24 hours following a 500 mg application of citric acid to the skin, whereas a severe eye effect was seen after a 750 µg application (relation of amounts in application to potential amounts in formulation unknown) (Clayton and Clayton, 1982). In another study, a single drop of 2.0 to 5.0% solution of citric acid in water caused little or no injury to rabbit eyes (unspecified number); however, irrigation of a 0.5 to 2.0% solution resulted in severe eye injury (HSDB, 1994).

Subchronic/Chronic Toxicity

Humans

Frequent or excessive intake (unspecified) of citric acid in humans may result in tooth erosion and local irritation (Clayton and Clayton, 1982) and some ulceration (HSDB, 1994). These have been seen with lemon juice, about 7% citric acid (Clayton and Clayton, 1982). No dermal exposure responses are discussed in the literature used for this review.

Animals

No dermal exposure studies are discussed in the literature used for this review.

Neurotoxicity

No data have been located regarding the neurotoxic potential of citric acid exposure in humans or animals.

Developmental/Reproductive Toxicity

Citric acid has not been shown to be a reproductive hazard (HSDB, 1994). No studies involving dermal exposure are reported. No reproductive effects were found in a study where two successive generations of rats (unspecified number) were fed diets containing 1.2% citric acid over a 90-week period (Clayton and Clayton, 1982). No effect was detected on litter size or survival up to weaning age in young rats or mice (unspecified numbers) fed diets containing 5.0% citric acid (no study length provided) (Clayton and Clayton, 1982).

Mutagenicity

No data have been located regarding the mutagenic or genotoxic potential of citric acid exposure in humans or animals.

Carcinogenicity

No data have been located regarding the carcinogenic potential of citric acid exposure in humans or animals.

Sodium Carbonate

The information (studies and conclusions) used in this health hazard have been adapted from a report issued by the CIR panel (CIR, 1987), unless otherwise stated.

Summary

Sodium carbonate is a commonly used component in bath, skin, and hair preparations. Products containing sodium carbonate may be expected to remain in contact with the skin up to an hour and are likely to be used repeatedly over a period of several years. Sodium carbonate is also used as a GRAS (generally regarded as safe) direct food ingredient. The CIR panel concluded that due to its alkaline nature, sodium carbonate is a skin and eye irritant. Human skin exposures to products containing 0.0025% active sodium carbonate were not considered to be strong irritants or sensitizers.

Repeated exposure of humans (a dockworker study) to dusts of sodium carbonate resulted in severe skin irritation, as well as upper respiratory irritation. Repeated exposure to high concentrations of aerosols containing sodium carbonate resulted in pathological changes to the lungs and respiratory tract of mice, rats, and guinea pigs. LC_{50}s ranging from 0.8 to 2.3 mg/l (aerosols) were identified in rats, mice, and guinea pigs. Sodium carbonate was not developmentally toxic to mice, rats, or rabbits. No information was available discussing reproductive, neurotoxic, mutagenic, or carcinogenic toxicity following sodium carbonate exposure to humans or animals.

Absorption/Metabolism

Because it is a solid, sodium carbonate is not expected to be absorbed through the skin but is expected to be absorbed (in dissociated form) from the lung. In the stomach, the compound will react with stomach acid to produce carbon dioxide, which is released in expired air (USEPA, 1994). In general, solids such as sodium carbonate with high melting points (851°C) do not penetrate the skin unless present as very fine particles. In addition, inorganic salts, such as sodium carbonate, are generally considered not to penetrate the skin (Schaefer et al., 1982).

Acute Toxicity

Acute toxicity studies of sodium carbonate in dilute solution have not been identified for dermal exposure routes.

Humans

Available acute toxicity data on humans indicate that sodium carbonate may be irritating to mucous membranes. Kamaldinova et al. (1976; as cited in Rom et al., 1983a) report an irritancy threshold (presumably irritation to the upper respiratory tract) of 40 mg/m^3 sodium carbonate in 14 volunteers exposed by inhalation for 1 minute.

Animals

Sodium carbonate aerosols are moderately toxic to rodents (USEPA, 1994). Whole-body inhalation exposure of adult male rats, mice or albino guinea pigs (unspecified numbers) to aerosols of sodium carbonate (91-95% pure) for 2 hours resulted in LC_{50}s of 2.3 mg/l for rats, 1.2 mg/l for mice, and 0.8 mg/l for guinea pigs (Busch et al., 1983, as cited in USEPA, 1992). Immediately after exposure, clinical signs included dyspnea, wheezing, excessive salivation, and distention of the abdomen. Within 3 to 4 hours post exposure, all clinical signs subsided. Animals that died during or shortly after exposure showed accumulation of mucus in, and vesiculation and mucosal edema of, the pharynx and larynx. Edema and vesiculation of the anterior trachea, hemorrhage in the lungs, and severe gastric tympany were also observed. Basal epithelial cells of the posterior pharynx and anterior trachea had enlarged mitochondria following exposures of 1 hour or more. Clinical signs and pathologic changes in all animals were similar regardless of dose level.

Irritation/Sensitization

Humans

The irritancy potential of three bar-soap products containing 0.25% sodium carbonate at a concentration of 1.0% were tested in three groups of 107 to 109 male and female volunteers (CIR, 1987). In all studies, following applications of two occlusive 24-hour patches (induction patch and challenge patch) applied 24 hours apart, investigators concluded that observed reactions indicated weak, nonspecific irritation; thus, this soap was neither a strong irritant nor contact sensitizer. Clayton and Clayton (1982) summarize a human study in which a 50% solution of sodium carbonate was applied to the intact and abraded skins of the volunteers. The solution produced no erythema, edema, or corrosion of intact skin. Abraded skin showed moderate erythema and edema, and one-third of the human volunteers showed tissue destruction at the abraded areas. Rom et al. (1983b, as cited in CIR, 1987) identified no further irritation or sensitization by 10% aqueous sodium carbonate applied to miners suffering pruritic, erythematous lesions from exposure to dust of trona ore (sodium sesquicarbonate, about 45-50% sodium carbonate).

Animals

A 50% (weight/volume) aqueous solution of sodium carbonate was applied to the intact and abraded skin of rabbits and guinea pigs, (CIR, 1987). The sites were examined at 4-, 24-, and 48-hours. The solution produced no erythema, edema, or corrosion of intact skin. Abraded skins of guinea pigs were negligibly affected, but abraded rabbit skins showed moderate erythema and edema.

Sodium carbonate produced ocular irritation in rabbits (two groups of six or more) administered 0.1 ml powdered sodium carbonate, although observed opacities and iritis were transient in the group that received eye rinses after exposure (CIR, 1987). Conjunctivitis persisted in both groups.

Subchronic/Chronic Toxicity

Humans

Kamaldinova et al. (1976, as cited in Rom et al., 1983a) reported that dockworkers exposed to soda ash (sodium carbonate) in ship holds and freight cars at dust levels greater than 300 mg/m^3 exhibited "soda ash burns," a 1.5-fold increase in the incidence (unspecified comparison group) of skin diseases (ulcers, erosion, eczema), and lost work days due to skin inflammation. Rhinitis, pharyngitis, and conjunctivitis were also reported.

Animals

Male rats (number unspecified) were exposed to an aerosol of a 2.0% aqueous solution of sodium carbonate (particles less than 5.0 µm diameter) 4 hours/day, 5 days/week, for 3.5 months. A concentration of 10 to 20 mg/m^3 did not cause any pronounced effect. Histological examination of the lungs of animals exposed to higher doses (approximately 70 mg/m^3) showed thickening of the intra-alveolar walls, hyperemia, lymphoid infiltration, and desquamation (Clayton and Clayton, 1982).

In another study, 10 rats, 20 mice, and 10 guinea pigs were exposed for 2 hours to aerosols consisting predominately of sodium carbonate at the following respective concentration ranges: 800-4,600 mg/m^3, 600-3,000 mg/m^3, and 500-3,000 mg/m^3. For all aerosol concentrations, all animals show clinical sign of toxicity (respiratory impairment, dyspnea, wheezing, excessive salivation, and distention of the abdomen) immediately after exposure, sometimes resulting in death (unspecified number) (CIR, 1987). Respiratory lesions in those that died were observed in the pharynx, larynx, trachea, and lungs. For animals that survived the study, respiratory lesions were limited to the laryngeal mucosa.

Neurotoxicity

There are no data on the neurotoxicity of sodium carbonate.

Developmental/Reproductive Toxicity

Humans

There are no data on the reproductive or developmental toxicity of sodium carbonate in the literature used for this review.

Animals

There are no data on the reproductive toxicity of sodium carbonate. Available data on developmental toxicity in animals indicate that the compound is not a developmental toxicant.

Pregnant mice (number not specified) were dosed daily by oral intubation with aqueous solutions of sodium carbonate at levels of 3.4 to 340 mg/kg during days 6 through 15 of gestation (Clayton and Clayton, 1982; CIR, 1987). There were no effects on implantation or survival of the dams or fetuses. The numbers of abnormalities in soft and skeletal tissues in the experimental group did not differ from those for sham-treated controls. Similar results were observed in rats and rabbits dosed at 245 mg/kg and 179 mg/kg, respectively (CIR, 1987).

Mutagenicity

No data on mutagenicity as it related to sodium carbonate exposure were located in the literature.

Carcinogenicity

No human or animal studies were available to assess the carcinogenic potential of sodium carbonate.

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