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June 25, 1996

TSCA SECTION 4 FINDINGS

FOR 21 HAZARDOUS AIR POLLUTANTS

A Supporting Document for Proposed Hazardous Air Pollutants (HAPs) Test Rule

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The testing proposed in the HAPs rule is based on the authority of section 4(a) of the Toxic Substances Control Act (TSCA), 15 U.S.C. 2601 et seq. The U.S. Environmental Protection Agency (EPA) interprets TSCA section 4(a) to mean that EPA's authority to require testing under TSCA section 4(a)(1)(A) and (B) is predicated on the "data insufficiency" and "testing is necessary" findings required under TSCA section 4(a)(1)(A)(ii) and (iii) and 4(a)(1)(B)(ii) and (iii). Discussions of the statutory framework for TSCA section 4(a) findings are provided in EPA's first and second proposed test rules, which were published in the Federal Register notices of July 18, 1980 (45 FR 48524) and June 5, 1981 (46 FR 30300). Thus once EPA has made a finding under TSCA section 4(a)(1)(A)(i) that a chemical substance may present an unreasonable risk of injury to health or the environment or a finding under section 4(a)(1)(B)(i) that a chemical substance is or will be produced in substantial quantities, and either it may enter the environment in substantial quantities or there may be substantial or significant human exposure to the chemical substance, EPA may require any type of health or environmental effects testing necessary to address unanswered questions about the effects of the chemical substance. EPA need not limit the scope of testing required to the factual basis for the section 4(a)(1)(A)(i) or (B)(i) findings. As explained in EPA's statement of policy for making findings under TSCA section 4(a)(1)(B) in the Federal Register of May 14, 1993 (EPA, 1993a, pp. 28736, 28738):

> Essentially, under TSCA section 4(a)(1)(B)(i), EPA may require health effects testing even if it has only made a

finding that there is or may be substantial entry into the environment of a substance, or require environmental effects testing even if it has only made a finding that there is or may be substantial or significant human exposure to a substance. Clauses (I) and (II) of section 4(a)(1)(B)(i) can be interpreted as mutually exclusive. . . . Either finding is sufficient to require testing, so long as EPA finds that data relevant to a determination of whether a substance does or does not present an unreasonable risk of injury to health or the environment are insufficient and that testing is necessary to develop such data.

In articulating the policy for making findings under section TSCA 4(a)(1)(B) (frequently described as the "B policy"), EPA has defined "substantial production" as annual aggregate production of 1 million pounds or more and "substantial release" as an annual release into the environment of 1 million pounds or 10% of production, whichever is lower. Id. at 28746. These definitions apply to the terms "substantial production" and "substantial release" as used in this document. (As explained in Unit III.C. of the preamble to the proposed rule, all chemical substances proposed for testing in this proposed rule are emitted into the atmosphere in the amount of 50 tons per year or more according to the Toxics Release Inventory (TRI).)

In its final B policy statement, EPA defined "substantial human exposure" as an annual exposure of 100,000 members of the general population, 10,000 consumers, or 1,000 workers. Id. In proposing the B policy on July 15, 1991 (EPA, 1991a pp. 32294, 32297), EPA explained its use of different exposure levels in this way:

> EPA believes that the different numerical thresholds for workers, consumers, and the general population are necessary

to reflect the inherent differences in each probable exposure scenario (e.g., workers generally are exposed on a more routine or direct basis than consumers, and consumers are generally exposed on a more direct basis than the general public).

As a general matter, EPA has found that workers tend to be subject to routine or episodic exposure over a long period of time. Thus, exposure, to be considered substantial, does not have to be as widespread for workers as for consumers or the general population. . . .

Under TSCA, EPA has generally interpreted the term "significant" as relating to the nature or importance of exposure. EPA therefore is proposing to interpret "significant" as referring to the nature of the exposure. EPA believes that if the nature of some exposure is sufficiently direct, large or prolonged, even if the number of people exposed is not "substantial", there is a need to develop data on the chemical because, on the basis of the data, EPA may take some risk management action to control the exposure.

Consistent with this policy, the findings below regarding substantial human exposure use different numerical thresholds for workers, consumers, and the general population.

A. 1,1'-Biphenyl (92-52-4)

EPA is proposing testing of 1,1'-biphenyl under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of 1,1'-biphenyl may present an unreasonable risk of injury to human health. Rats were fed 0.01%, 0.1%, and 1% 1,1'-biphenyl for three generations in a study on reproductive effects. Decreased fertility, litter size,

and growth rate were noted at the high dose level (Dow Chemical Company, 1983). A subchronic inhalation study of 1,1'-biphenyl (mice dosed at 25 and 50 ppm for 13 weeks) showed hyperplasia of the tracheal epithelium and hyperactivity (Sun Company Inc., 1983a; Sun Company Inc., 1983b). Neurotoxicity is suggested in a study of 33 exposed workers (Hakkinen et al., 1973).

Based on the exposure discussed below and these concerns, EPA finds that 1,1'-biphenyl may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that 1,1'-biphenyl is produced in substantial quantities. Sales of 1,1'-biphenyl were 17.9 million pounds in 1991. In 1990, there were sales of 23.4 million pounds out of a production of 53.5 million pounds (USITC, 1991).

(ii) EPA believes that there is or may be substantial human exposure to 1,1'-biphenyl. According to the TRI, 1,1'-biphenyl is produced at 37 locations mainly as an impurity or byproduct from the hydrodealkylation of toluene (EPA, 1992; Thompson, 1992). 1,1'-biphenyl is used as a heat transfer agent, a dye carrier for polyesters, a feedstock for the production of alkylbiphenyls, and a citrus fruit wrapping impregnate to reduce spoilage (ACS, 1994; Paetz, 1989; Thompson, 1992). Alkylated biphenyls are used as heat transfer agents and dielectrics in condensers (Thompson, 1992). NIOSH estimates that 20,351 workers are exposed to 1,1'-biphenyl (NIOSH, 1989). 1,1'-Biphenyl was measured at 10.1 to 19 ppm in the air of a Finnish paper impregnation plant (Hakkinen et al., 1973). Workers were exposed

to Dowtherm A, a mixture of 1,1'-biphenyl and diphenyl ether, in a nylon production plant as indicated by hydroxybiphenyl in their urine (Dorgelo et al., 1985).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are insufficient data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of 1,1'-biphenyl. Sun Oil Co. conducted an acute inhalation study of 1,1'-biphenyl in mice at 14, 38, and 43 ppm for 4 hours (Sun Company Inc., 1983b). Although respiratory discomfort was noted, organ histopathology was not conducted. Sun also evaluated 1,1'-biphenyl at 25 and 55 ppm in mice for 2 weeks (Sun Company Inc., 1983c) and conducted a 90-day inhalation study in mice at 25 and 50 ppm (Sun Company Inc., 1983a). These studies were deficient in that only two dose levels were used and a no-observed-adverse-effect-level (NOAEL) was not identified; however, testing at higher exposures in the vapor phase is not possible given the low vapor pressure of this compound. Given the limitation of vapor pressure exposure and EPA's concern for aerosol or particulate exposures and the higher exposures that can result from them, EPA is proposing subchronic testing by an aerosol exposure route (see Unit IV.B. of the preamble to the proposed HAPs test rule).

Dow Chemical Company conducted a three-generation reproductive feeding study that reported effects on fertility, litter size, and growth rate at the high-dose level. The study, however, used only 3 male and 9 female rats per dose level (Dow Chemical Company, 1983). This is less than half of the number of

animals called for in the EPA test guidelines and as a result, this study has poor statistical power to detect effects.

An oral developmental toxicity study in rats exists for 1,1'-biphenyl that is considered acceptable (Khera et al., 1979). A developmental toxicity study in a second mammalian species is needed in order to adequately assess the risk for developmental toxicity as indicated in the developmental toxicity risk assessment guidelines (EPA, 1991b). Only poorly characterized case reports were found for neurotoxicity (Hakkinen et al., 1973). No data were located for immunotoxicity or respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of 1,1'-biphenyl is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine whether the manufacture, processing, and use of 1,1'-biphenyl does or does not present an unreasonable risk of injury to human health as a result of inhalation exposure.

B. Carbonyl Sulfide (463-58-1)

EPA is proposing testing of carbonyl sulfide (CS) under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of CS may present an unreasonable risk of injury to health. There is a neurotoxic concern for CS. An acute toxicity study in rats via inhalation for 4 hours showed central nervous system effects at 1,062 and 1,189 ppm (Monsanto Company, 1991). An inhalation study in rabbits at 54 ppm for 7 weeks also reported neurological disorders (Kamstrup and Hugod, 1979).

There is concern for the carcinogenic potential of CS by inhalation because it is chemically reactive and is expected to react with tissues of the respiratory tract. Furthermore, CS is the oxidation product of carbon disulfide which has been shown to be positive in the strain A mouse lung tumor bioassay. Significant increases in the incidence (tumors per tumor-bearing mouse) and frequency (tumors per mouse) of lung adenomas was observed in A/J mice exposed to carbon disulfide for 6 months by inhalation (Adkins et al., 1986). A study in which treated males were mated with untreated females suggests that carbonyl sulfide reduces male fertility (Monsanto Company, 1990).

Based on these concerns, EPA finds that CS may present an unreasonable risk of injury to health or the environment.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that CS is produced in substantial quantities. Since most CS is produced as an unwanted byproduct, EPA is using the 1993 TRI release estimate of 12.8 million pounds as a low end estimate of production volume (EPA, 1995).

(ii) EPA believes that CS is released to the environment in

substantial quantities. The TRI indicates that 12.8 million pounds of CS were released to the atmosphere in 1993 (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of CS. A one-generation reproductive toxicity study (Monsanto Company, 1990) conducted in rats at 10, 60, and 180 ppm was found to be inadequate because matings between both treated males and treated females were not tested and the dosing period for males (7 days prior to mating) was too short to assess the potential effects on the full spermatogenic process. Moreover, a two-generation study is needed to assess the effects on lactation and the reproductive performance of the second generation that was exposed during development.

An acute study in rats at 804, 993, 1,062, 1,096, 1,147, and 1,189 ppm for 4 hours indicates adverse central nervous system effects (Monsanto Company, 1991). This study is inadequate to characterize acute inhalation risk because it was not intended to provide an evaluation of appropriate parameters for neurotoxicity. No histopathological evaluation was conducted for the respiratory tract or extra-respiratory organs.

No information was located on the carcinogenicity of CS. However, as noted above, CS is expected to react with tissues of the respiratory tract and is the oxidation product of carbon disulfide, which produced positive results in the mouse lung tumor bioassay. Therefore, CS should be tested for its

carcinogenic potential.

No data were located for subchronic toxicity, developmental toxicity, genetic toxicity, immunotoxicity, or respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of CS is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, carcinogenicity, immunotoxicity, genetic toxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of CS does or does not present an unreasonable risk of injury to human health from inhalation exposure.

C. Chlorine (7782-50-5)

EPA is proposing testing chlorine under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of chlorine may present an unreasonable risk of injury to human health. Chlorine has been shown to cause changes in the respiratory tract of mice, rats, and monkeys over a range of exposure durations from 5 weeks to 2 years. Mice and rats exposed to 9 ppm for 5 days showed severe exfoliation, erosion, ulceration, and necrosis in the respiratory and olfactory epithelium of the upper respiratory tract (Buckley et al., 1984; Jiang et al., 1983). Moderate terminal

bronchiolitis was also observed in the lower respiratory tract. A 6-week study exposing rats (6 hours/day, 5 days/week) to chlorine gas at 1, 3, and 9 ppm produced respiratory tract lesions at all concentration levels, and hepatic and renal effects at 3 and 9 ppm (Shell Oil Company, 1992). Kutzman reported upper respiratory tract irritation in rats exposed to the two highest concentrations exposed to 0.5, 1.5, and 5.0 ppm for 90 days (Kutzman, 1983). Biochemical changes and pulmonary function tests also indicated changes in the lower respiratory tract at both 1.5 and 5 ppm (Kutzman, 1983). Rhesus monkeys exposed to 0.1, 0.5, and 2.3 ppm showed mild nasal mucosal lesions at all concentrations and focal epithelial hyperplasia with loss of cilia and goblet cells in the trachea at 2.3 ppm (Klonne et al., 1987). Inflammatory, degenerative, and hyperplastic changes of the nasal cavity showed a concentration-response for incidence and severity in both rats and mice exposed to 0.4, 1.0, and 2.3 ppm (CIIT, 1993). Mice also showed septal fenestration (CIIT, 1993).

Based on the exposure discussed below and these concerns, EPA finds that chlorine may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that chlorine is produced in substantial quantities. In 1992, 22.28 billion pounds of chlorine were produced in the United States (Reisch, 1993).

(ii) EPA believes that there is or may be substantial human exposure to chlorine. The major use of chlorine is in the

manufacture of vinyl chloride that is used to make polyvinyl chloride. It is used in the production of polyurethanes, solvents, other organics, inorganics, and titanium dioxide. Chlorine is also used to bleach pulp and paper and in water treatment (CMR, 1992d). Chlorine is a slimicide and is used as a sanitizing and disinfecting agent for municipal water supplies and swimming pools (Curlin et al., 1991).

NIOSH estimates that 170,000 workers are exposed to chlorine in the United States (NIOSH, 1989). During a respiratory health survey conducted in 1988, 78 of 316 pulp mill workers had at least one chlorine exposure incident in their work histories (Salisbury et al., 1991). High concentrations were detected in generator buildings of pulp and paper industries with concentrations ranging up to 1.59 ppm in workplace air in a pulp bleaching facility (Bjorkholm et al., 1988; Schoultz et al., 1983). Accidental chlorine gas exposures have been measured as high as 15 ppm in a pulp mill (Kennedy et al., 1991). The general population has also been exposed to chlorine gas following accidental discharges or spills such as the tank car derailment in Youngstown, Florida, on February 26, 1978 (Jones et al., 1986).

Lifeguards and the public are exposed to chlorine in the air of indoor swimming pools during periods of high crowding and poor ventilation (Shaw, 1986). Chlorine is in equilibrium with sodium hypochlorite in liquid chlorine bleaches. Commercial strength bleach contains 12%-15% chlorine; household bleach used by consumers contains about 5% chlorine (Curlin et al., 1991; Farr

et al., 1992).

(iii) EPA believes that chlorine is released to the environment in substantial quantities. The TRI indicates that in 1993, 75 million pounds of chlorine were released to the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are insufficient data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of chlorine. Upper airway lesions appear to increase in both incidence and severity at comparable concentrations from short-term (5 days and 6-8 weeks) to chronic (2 years) exposure durations, but the nature of the investigations of the respiratory tract lesions in the available short-term data was not equivalent to that of the more recent, longer-term studies (Leininger et al., 1994). Differences between species in the nature and distribution of lesions may be due to interspecies differences in regional chlorine dosimetry and/or numbers and distribution of susceptible cell populations (Leininger et al., 1994). Thus, due to the insufficient information provided in the short term studies on concentration, duration, and degree of response, these data are considered inadequate for characterizing the acute effects of chlorine in the respiratory tract.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of chlorine is necessary to develop data for acute respiratory effects. EPA believes that this testing is needed to determine whether the manufacture,

processing, and use of chlorine does or does not present an unreasonable risk of injury to human health from inhalation exposure.

Subchronic and chronic studies exist that demonstrate that the critical effect of long-term exposure is toxicity to the respiratory tract (CIIT, 1993; Klonne et al., 1987; Kutzman, 1983; Shell Oil Company, 1992). No remote site or organ toxicities were found in the CIIT study. Thus, even though data do not exist for toxicity at remote sites, EPA is not requiring such testing at this time because, based on available data, chlorine, a water soluble and highly reactive gas, appears to produce toxicity only at the portal of entry.

D. Chlorobenzene (108-90-7)

EPA is proposing testing chlorobenzene under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of chlorobenzene may present an unreasonable risk of injury to human health. Chlorobenzene is toxic to the liver, kidney, and lungs. Deichmann observed liver, kidney, and lung lesions in guinea pigs exposed to chlorobenzene by inhalation at 475 ppm for 44 days (Deichmann, 1981). Microscopic kidney lesions were also observed in rats exposed to 73 and 248 ppm of chlorobenzene for 7 hours/day, 5 days/week for 24 weeks (Dilley, 1977). Hepatocellular hypertrophy and renal degeneration were observed in a two-generation reproductive effects study at 150 and 450 ppm (Nair et al., 1987).

Chlorobenzene also causes reproductive and developmental effects in animals. In a two-generation reproduction study in the rat, degeneration of the testicular germinal epithelium was observed (Nair et al., 1987). John et al. observed skeletal abnormalities (delayed ossification, bilobed centra, and cervical spurs) in the offspring of Fischer 344 rats exposed to 590 ppm in a developmental toxicity study (John et al., 1984). Rabbits also showed developmental effects at 590 ppm (John et al., 1984).

Chlorobenzene is also considered to present a potential neurotoxic risk. Classic solvent effects are cited in Anger and Johnson (Anger and Johnson, 1985), and ototoxicity was observed in rats (Pryor and Rebert, 1993).

Based on the exposure discussed below and these concerns, EPA finds that chlorobenzene may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that chlorobenzene is produced in substantial quantities. The United States production of chlorobenzene in 1991 was 210 million pounds (USITC, 1993).

(ii) EPA believes that there is or may be substantial human exposure to chlorobenzene. NIOSH estimates that 17,056 workers are exposed to chlorobenzene. Chlorobenzene is used in the production of nitrochlorobenzene (41%), which is used in the manufacture of dyes and pigments, rubber processing chemicals, pesticides, and pharmaceuticals. Chlorobenzene is also used as a solvent especially in herbicide formulations and other agricultural products (NIOSH, 1989).

There may be chlorobenzene exposure for the general population. Chlorobenzene has been detected in the air of some United States cities. Typical concentrations ranged up to 0.8 ppb, but a maximum of 12 ppb has been observed. In a study of three New Jersey cities in summer and winter, chlorobenzene was detected in 91% to 100% of atmospheric samples with mean levels of 0.07 to 0.22 ppb (Harkov et al., 1984). Chlorobenzene was also found in 9 out of 10 finished drinking water supplies surveyed by the EPA, but because chlorobenzene can be formed from the chlorination of water, it is not clear that these concentrations result from industrial release. Drinking water in Terrebonne Parish in Louisiana and New York City contained 5.6 and 4.7 ppb, respectively (NAS, 1977). Chlorobenzene would be expected to partition to air (EPA, 1994).

(iii) EPA believes that chlorobenzene is released to the environment in substantial quantities. The TRI indicates that in 1993, 2 million pounds of chlorobenzene were released to the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are insufficient data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of chlorobenzene. Several subchronic studies have been performed on chlorobenzene, but all were significantly flawed. Deichmann administered chlorobenzene to rats, rabbits, and guinea pigs at 475 and 1,000 ppm for 44 days (Deichmann, 1981). The number of animals exposed was not reported and the study used only two exposure concentrations for

44 days instead of the generally accepted 90-day exposure period for a subchronic study. Dilley studied only male rats and rabbits and used only two exposure concentrations (Dilley, 1977). Zub studied 5 male and 5 female mice for 3 months at only a single exposure level (22 ppm) and did not perform complete histopathology (Zub, 1978). Chlorobenzene has not been studied for acute effects using adequate methods of studying respiratory tract effects despite evidence of respiratory tract toxicity (Utah Biomedical Laboratory, 1991). No studies of neurotoxicity per se were found. Existing data suggest, but do not adequately define, the potential for chlorobenzene to cause neurotoxicity (Utah Biomedical Laboratory, 1991). NTP reported that mice exposed by gavage to ≥250 mg/kg/day for 13 weeks showed thymic necrosis and lymphoid or myeloid depletion of bone marrow, spleen, or thymus (NTP, 1985). However, immune function tests were not conducted.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of chlorobenzene is necessary to develop data for acute toxicity, subchronic toxicity, neurotoxicity, and immunotoxicity. EPA believes that this testing is needed to determine whether the manufacture, processing, and use of chlorobenzene does or does not present an unreasonable risk of injury to human health from inhalation exposure.

E. Chloroprene (126-99-8)

EPA is proposing testing of chloroprene under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture and processing of chloroprene may present an unreasonable risk of injury to health. Effects on the hematopoietic system and degeneration of hepatocytes were reported in a subchronic study in rats at 200 ppm. Degeneration of the olfactory epithelium was reported at 32 ppm and higher (Battelle Pacific Northwest, 1988). Increased lymphoid aggregates in lungs and hepatocellular alterations were noted in a chronic study in rats at 50 ppm (Reuzel et al., 1985). In an acute inhalation rat study conducted at exposures ranging from 1.95 to 13.30 mg/L, pulmonary and liver damage was reported (DuPont, 1985a).

Chloroprene is toxic to the reproductive system. Sanotskii reported testicular atrophy and desquamation of the germinal epithelium in a subchronic toxicity study at exposure levels of 0.15 and 1.69 mg/m^3 in rats and at 0.32 mg/m^3 and higher in mice (Sanotskii, 1976). Developmental toxicity has been reported in rats exposed to 73.5 and 171 ppm of chloroprene (DuPont, 1985b). In addition, disturbances in spermatogenesis, increased incidence of spontaneous abortions in workers' wives, and sexual impotency were reported in a study of 143 male workers exposed to chloroprene for 6 to 10 years (NIOSH, 1977).

Battelle also reported evidence of neurotoxicity. Chloroprene caused a concentration-related increase in neurological excitability in male rats and significant damage to

the olfactory epithelium, which is a nervous system tissue (Battelle Pacific Northwest, 1988).

Based on the exposure discussed below and these concerns, EPA finds that chloroprene may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that chloroprene is produced in substantial quantities. United States production of chloroprene is approximately 300 million pounds per year (Stewart, 1993).

(ii) EPA believes that there is or may be substantial human exposure to chloroprene. Chloroprene is almost entirely used in the production of polychloroprene synthetic rubbers (Stewart, 1993). NIOSH estimates that 17,749 workers are exposed to chloroprene in the United States (NIOSH, 1989). In a survey of a chloroprene production facility in 1979, chloroprene concentrations ranged up to 1,200 ppm, with 53% of the samples exceeding 1 ppm (Harkov et al., 1981). In two other production facilities, levels were below 1 ppm (Brodzinsky and Singh, 1982). Air levels of chloroprene in a polymerization plant ranged from 6 to 6,760 ppm (Shackelford, 1983).

There is evidence of general population exposure to chloroprene. Chloroprene has been detected in the atmosphere near production and processing facilities. Mean and maximum concentrations in six New Jersey cities were 0.097 ppb and 4.0 ppb, respectively (Harkov et al., 1981). Concentrations in Houston, Texas were reported to be 0.59 ppb (Brodzinsky and

Singh, 1982). The half-life of chloroprene in the atmosphere is estimated to be 18.5 hours (Meylan and Howard, 1993).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of chloroprene. Data suggesting that chloroprene causes acute, neurotoxic, and reproductive effects were not adequate for their characterization. Reproductive effects were observed in human epidemiology studies (NIOSH, 1977; Sanotskii, 1976). In a study of 143 male workers exposed over a 6- to 10-year period and 118 unexposed male workers, disturbance of spermatogenesis, increased incidence of spontaneous abortion in exposed workers' wives, and sexual impotency were observed. As is typical of many such studies, too little information on exposure limited the utility of the study to evaluate and characterize human risk.

Battelle conducted a subchronic study in rats at 5, 12, 32, 80, and 200 ppm that included a number of neurological parameters, i.e., residential maze, grip strength, tail flick, startle response, and some neuropathology (Battelle Pacific Northwest, 1988). Neurotoxic effects (increased excitability in males and damage to the olfactory epithelium) were suggested. However, the lack of reporting of raw data or group means limited the utility of this study, and an additional study is needed to adequately characterize these effects.

DuPont conducted an acute inhalation study in rats (4 hour exposures to 1.95, 6.24, 8.42, 13.04, and 13.30 mg/L) (DuPont,

1985a). This study, reporting pulmonary and liver damage, was limited in that it did not include females or histopathology evaluation. Studies done by Plugge and Jaeger tested only male rats by inhalation at 100, 150, 225, and 300 ppm for 4 hours and did not evaluate respiratory tract effects (Plugge and Jaeger, 1979). No studies of immunotoxicity or respiratory sensory irritation were located. NTP has selected chloroprene for an inhalation chronic bioassay (NTP, 1996).

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of chloroprene is necessary to develop data for acute toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of chloroprene does or does not present an unreasonable risk of injury to human health from inhalation exposure.

F. Cresols

EPA is proposing testing cresols under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture and processing of cresols may present an unreasonable risk of injury to health. Existing data suggest that exposure to cresols results in adverse respiratory tract, neurological, and developmental effects. Mice exposed to an ortho-cresol (CAS No. 95-48-7) and water aerosol experienced swelling of the alveolar

region of the lung and macrophage proliferation (Uzhdavini et al., 1972). Oral administration of a meta/para-cresol mixture in feed to rats at 1,880, 3,750, 7,500, 15,000, and 30,000 ppm for 13 weeks caused hyperplasia of the nasal respiratory epithelium in nasal turbinates at all dose levels (NTP, 1992a).

Neuroexcitation was caused by the intravenous administration of ortho-cresol to Fischer 344 rats (Mattsson et al., 1989). In an oral subchronic neurotoxicity study in rats (50, 175, and 600 mg/kg/day for 13 weeks), time- and concentration-dependent effects on a number of neurologically relevant clinical signs were observed for all 3 isomers at 50 mg/kg/day and higher. Convulsions were observed at 600 mg/kg/day (Toxic Research Laboratories, Ltd., 1986).

CMA reported developmental toxicity (increased incidence of minor skeletal variations and dilated lateral ventricles) in rats exposed to 450 mg/kg/day for both ortho- and para-cresol. Poorly ossified sternebrae and increased ecchymosis of the head were seen in rabbits exposed to 100 mg/kg/day of ortho-cresol (CMA, 1988).

Based on the exposure discussed below and these concerns, EPA finds that cresols may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that cresols are produced in substantial quantities. Production data on the three individual cresol isomers is claimed to be confidential business information (CBI), but exceeds 1 million pounds for each. In 1990, the United States production of cresol

and cresylics, excluding that from coke and gas-retort ovens, was 84.3 million pounds (USITC, 1991).

(ii) EPA believes that there is or may be substantial human exposure to cresols. NIOSH has estimated statistically that 132,742 workers are potentially exposed to the cresol mixture (CAS No. 1319-77-3) in the United States; 10, 985, 5,615, and 21,313 workers are potentially exposed to the ortho-, meta-, and para- isomers, respectively, in the United States (NIOSH, 1993).

Cresylics are used in antioxidants (20%), phenolic-epoxy and novolak resins (15%), wire enamel solvents (12%), phosphate esters (5%), other chemical intermediates (5%), and miscellaneous uses. The uses of the different cresol isomers varies somewhat from the general pattern (CMR, 1990a). Mixtures of meta-cresol (CAS No. 108-39-4) and para-cresol (CAS No. 106-44-5) often serve as disinfectants and preservatives (Budavari et al., 1989a). para-Cresol is used in the production of antioxidants such as BHT (2,6-di-tert-butyl-para-cresol). It also has applications in the fragrance and dye industries (Fiege, 1987; Sax and Lewis, 1987). Occupational exposure to para-cresol may occur through inhalation or dermal contact. Exposure has been reported in laboratories, coal gasification facilities, wood preserving facilities, application of insulation lacquers to copper wire, and during paint and varnish application (Henriks-Eckerman et al., 1990; Moseley and Handke, 1985; Needham et al., 1984; Nieminen and Heikkila, 1986).

Consumers may be exposed to cresols through their use in perfumes, antiseptics, disinfectants, pharmaceuticals, paints,

varnishes, and soaps. Exposure may be via dermal contact or inhalation (Angerer and Wulf, 1985; Fiege, 1987; Sax and Lewis, 1987).

General population exposure can occur from automobile exhaust, coal combustion, diesel fuel, and municipal solid waste combustion (Graedel et al., 1986; James et al., 1984).

(iii) EPA believes that cresols are released to the environment in substantial quantities. The TRI reports that 1.5 million pounds of cresols were released to the environment in 1991. Approximately half of this amount was discharged to the air (EPA, 1992). Cresols are released from emissions from paint, turbines, automobile exhaust, forest fires, coal combustion, diesel fuel, municipal waste combustion, animal waste, wood pulping, vegetation, and tobacco smoke (Graedel et al., 1986). Cresols may also be formed from the photochemical oxidation of toluene (Leone et al., 1985).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of cresols. Studies conducted to date have suggested that cresols may cause respiratory tract toxicity but are inadequate to characterize that effect. The study by Uzhdavini et al. (1972) was poorly reported and can only be relied on as suggestive evidence. No information is available on the numbers of animals exposed or on other details of the protocol (Uzhdavini et al., 1972). The NTP study was by the oral route, and while it showed some effects on the nasal epithelium,

acute and subchronic inhalation studies are necessary to characterize portal of entry effects (NTP, 1992a). NTP plans a 2-year dose-feed study for carcinogenicity and chronic effects on all three cresol isomers (Olden, 1994).

Although subchronic neurotoxicity has been studied (Toxic Research Laboratories, Ltd., 1986), acute neurotoxicity has not been adequately examined. Neither the Uzhdavini et al. study nor the Mattsson et al. study was designed to measure the recommended range of parameters (i.e., functional observational battery, neuropathology, and motor activity) for a study of neurotoxicity (Mattsson et al., 1989; Uzhdavini et al., 1972). No studies were found for respiratory sensory irritation. Hornshaw et al. reported that spleen weights were unaffected by 28-day oral exposure to ortho-cresol for ferrets at doses of 4,500 ppm and for mink at doses up to 2,500 ppm (Hornshaw et al., 1986). Absolute spleen weights were reduced approximately 18% in a study in which male rats were exposed to 600 mg/kg/day para-cresol for 13 weeks; no changes were noted when ortho- or meta-cresol were tested (MBA, 1988a; MBA, 1988b; MBA, 1988c). These studies are deficient in that immune function was not evaluated.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of cresols is necessary to develop data for acute toxicity, subchronic toxicity, acute neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of cresols does or does not present an unreasonable risk of injury to human

health from inhalation exposure.

G. Diethanolamine (111-42-2)

EPA is proposing testing of diethanolamine (DEA) under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of DEA may present an unreasonable risk of injury to health. Neurotoxic and reproductive effects were reported in an oral rat subchronic study conducted at 0.16, 0.32, 0.63, 1.25, 2.5, and 5 mg/ml for 13 weeks. Demyelination of the spinal cord and brain, atrophy of the seminal vesicle, hypospermia, and spermatic arrest were observed at drinking water concentrations of 2.5 and 5.0 mg/ml, and atrophy of the prostate occurred at 5.0 mg/ml (Battelle Columbus, 1989). Decreased numbers of viable litters and decreased pup growth and survival were observed in an oral mouse developmental toxicity screening study conducted by gavage at 450 mg/kg/day (NIOSH, 1987; Union Carbide Corporation, 1990). Based on the exposure discussed below and these concerns, EPA finds that DEA may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that DEA is produced in substantial quantities. The United States production of DEA in 1991 was 198 million pounds per year (USITC, 1993).

(ii) EPA believes that there is or may be substantial human

exposure to DEA. DEA is used as a chemical intermediate in a wide variety of personal care products such as creams, lotions, shampoos, soaps, and cosmetics, and in detergents. There may be consumer exposure to small amounts of residual DEA in some of these products. It is used in adhesives, cleaners, coatings, corrosion inhibitors for ferrous metals in applications such as coolant systems, lubricating oils, metal working fluids, petroleum antifouling and drilling fluids, and electroplating baths (CMR, 1992e). NIOSH has estimated that 573,000 workers are exposed to DEA (NIOSH, 1989). According to the 1993 TRI, 301,437 pounds of DEA were released to the air to air (EPA, 1995). This may result in general population exposure.

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of DEA. Although oral subchronic data indicate that DEA may cause neurotoxicity (Battelle Columbus, 1989), no study of neurotoxicity per se has been performed on DEA. Although serious toxic effects were observed in oral studies (demyelination of the spinal cord and brain, atrophy of the seminal vesicle and prostate, hypospermia, and spermatic arrest; Battelle Columbus, 1989), inhalation subchronic studies conducted at 0.5 ppm for 9 weeks and 0.26 ppm for 13 weeks showed no effects presumably because they were performed at relatively low exposure levels (Eastman Kodak Company, 1989). Only equivocal evidence of slight lung effects in rats could be detected (Eastman Kodak Company, 1989).

Although NTP has conducted an oral subchronic study, an inhalation study is needed to determine portal of entry and extra-respiratory effects. Given the low vapor pressure of DEA (2.8×10^{-4} mm Hg at 20°C), it may not be possible to reach a maximally tolerated dose in a vapor study; thus, EPA is proposing that DEA be tested by aerosol exposure.

An acute rat study that noted respiratory tract effects was described only in an abstract and thus, was too poorly reported to determine adequacy (Hartung et al., 1970).

No studies on the reproductive effects of DEA has been conducted, despite some evidence in an oral subchronic study that DEA is toxic to the male reproductive system (Battelle Columbus, 1989).

Screening-level developmental toxicity data indicate the potential for DEA to be a developmental toxicant (Union Carbide Corporation, 1990). These screening-level tests are inadequate to evaluate the developmental toxicity of chemical substances. No data were located for immunotoxicity or respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of DEA is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of DEA does or does not present an unreasonable risk of injury to human health from inhalation

exposure.

H. Ethylbenzene (100-41-4)

EPA is proposing testing of ethylbenzene under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of ethylbenzene may present an unreasonable risk of injury to health. Ethylbenzene is considered to present a neurotoxic risk. Classic solvent effects are cited in Anger and Johnson, and ototoxicity was observed in rats (Anger and Johnson, 1985; Pryor and Rebert, 1993). A dose-related increase in the incidence and severity of regeneration of renal tubules was observed in a 90-day inhalation study in rats at 500 ppm and higher (NTP, 1992c). Developmental toxicity (resorbed fetuses and skeletal retardation) was seen in rats exposed to 600 mg/m^3 and higher of ethylbenzene (Ungvary and Tatrai, 1985). Mice tested at a single exposure level (500 mg/m^3) for developmental toxicity showed an increased incidence of anomalies of the uropoietic apparatus (Ungvary and Tatrai, 1985).

Based on the exposure discussed below and these concerns, EPA finds that ethylbenzene may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that ethylbenzene is produced in substantial quantities. Ethylbenzene production in 1992 was 11.4 billion pounds (CMR, 1992a).

(ii) EPA believes that there is or may be substantial human exposure to ethylbenzene. Over 99% of ethylbenzene is used captively in the manufacture of styrene that is used to produce polystyrene and other plastics, but the bulk of exposure to ethylbenzene is found in its other uses. Ethylbenzene is used as a solvent in paint and in the production of acetophenone, diethylbenzene, and ethyl anthraquinone (CMR, 1992a; Coty et al., 1987). Ethylbenzene is a component of gasoline (API, 1991). NIOSH estimates that 80,726 workers are exposed to ethylbenzene in the United States (NIOSH, 1989). Spray painters were exposed to time-weighted average exposures of 1.2 to 4.4 ppm of ethylbenzene (Ahrenholz, 1980). The mean and maximum exposures to ethylbenzene while loading a top-loading gasoline tank truck are 0.42 and 2.2 ppm, respectively (Kawai et al., 1991).

There is widespread consumer exposure to ethylbenzene. Ethylbenzene was found in 157 of 658 household products surveyed from 65 product categories (Sack and Steele, 1991; Sack et al., 1992). Products likely to contain ethylbenzene are paints and paint-related products, fabric and leather treatments, automotive products, cleaners for electronic equipment, and household cleaners and polishes (Sack et al., 1992). Based on the occurrence of ethylbenzene in spray paints (64%) and the use of spray paints in the United States, it is estimated that 55 million consumers are exposed to ethylbenzene each year through spray paints alone (DOC, 1987; Sack and Steele, 1991; Westat Incorporated, 1987). Consumers are also exposed to ethylbenzene during refueling of their vehicles. A study of six service

stations showed ethylbenzene levels of 0.1 ppm (API, 1991).

The general population is exposed to ethylbenzene. The average level of ethylbenzene in air in 15 United States cities studied from 1979 to 1984 was 0.6 to 4.6 ppb, with a maximum concentration of 31.5 ppb (Singh et al., 1985). Ethylbenzene concentrations in major western United States cities ranged from 0.1 to 27.7 ppb, with a mean of 2.68 ppb (Singh et al., 1980). Ethylbenzene has also been found in United States municipal water supplies (Cotruvo, 1985). Ethylbenzene has also been found in human blood and adipose tissue. Blood concentrations ranged up to 59 ppb, with a mean of 1 ppb (Antoine et al., 1986). In the United States Human Adipose Tissue Survey, 96% of samples were positive with a maximum concentration of 280 ppb (Stanley, 1986).

(iii) EPA believes that there is substantial environmental release of ethylbenzene. The 1993 TRI indicates that 10.3 million pounds of ethylbenzene were released to air (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of ethylbenzene. Two studies related to the neurotoxicity of ethylbenzene were found. One was a study of effects on brain chemistry that suggested that dopamine metabolism is a toxicity target for ethylbenzene (Mutti et al., 1988; Romanelli et al., 1986). This study was a brain chemistry assay, not a standard neurotoxicity study, and thus is not adequate to evaluate the neurotoxicity of ethylbenzene. Similarly, the study discussed in Pryor and Rebert assessed only

one function, ototoxicity (Pryor and Rebert, 1993). Ototoxicity is an indicator of neurotoxicity, but a full study of neurotoxicity including a functional observational battery, motor activity assessment, and neuropathology is needed to adequately characterize the neurotoxicity of ethylbenzene.

Although an adequate inhalation developmental toxicity study is available for rats (Andrew et al., 1981), the studies in other species are inadequate. In a mouse inhalation study in which results were only presented in a summary form, only a single exposure at 500 mg/m^3 was used (Ungvary and Tatrai, 1985). In this study, no maternal toxicity was noted, but increases in anomalies were seen. Inhalation studies in rabbits were conducted at 500 and 1,000 mg/m^3 (Ungvary and Tatrai, 1985) and at 100 and 1,000 ppm (Andrew et al., 1981). Although malformations were not reported, other developmental effects were seen in these studies (decreases in numbers of live fetuses and fetal body weight). Results of maternal toxicity were inconsistent in the rabbits. In the Ungvary and Tatrai (1985) study, all dams aborted at 1,000 mg/m^3. In the Andrew et al. (1981) study, no maternal toxicity was seen at 1,000 ppm.

Although a short-term inhalation study was conducted in several species for 4 days by Biodynamics, the respiratory tract and other organs were not studied using histopathology (Biodynamics, 1987). Nielsen and Alarie examined mice at inhalation exposures ranging from 410 to 9,640 ppm for 30 minutes and found a decrease in respiration rate at all concentrations (Nielsen and Alarie, 1982). Although this study indicates a

respiratory effect, it is not an adequate evaluation of the respiratory tract for acute exposures given that histopathology was not performed. In addition, both the Nielsen and Alarie (Nielsen and Alarie, 1982) and Biodynamics (Biodynamics, 1987) studies were conducted on males only and used too few animals. No data were located on the reproductive effects of ethylbenzene. NTP reported no effects on the thymus and spleen of rats and mice with 90-day exposures up to 1,000 ppm (NTP, 1992c), but an evaluation of immune function was not performed. NTP has conducted an inhalation chronic assay, but the final report is not yet available (NTP, 1996). No data were located on the respiratory sensory irritation of ethylbenzene.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of ethylbenzene is necessary to develop data for acute toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, use, and disposal of ethylbenzene does or does not present an unreasonable risk of injury to human health from inhalation exposure.

I. Ethylene Dichloride (107-06-2)

EPA is proposing testing of ethylene dichloride (EDC) under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the

manufacture, processing, and use of EDC may present an unreasonable risk of injury to health. Several studies indicated high mortality rates following inhalation exposure. Hofmann et al. exposed rats, guinea pigs, rabbits, and cats to 100 and 500 ppm of EDC for 6 hours/day, 5 days per week for 6 weeks. Mortality was high in all species exposed to 500 ppm. Necropsy revealed lesions in the liver, kidney, adrenals, heart, and lungs (Hofmann et al., 1971). Maltoni et al. reported a high incidence of mortality of rats exposed to 250 ppm of EDC in an carcinogenicity study, forcing him to reduce the high exposure to 150 ppm after 10 weeks (Maltoni et al., 1980). Mortality was reported at 300 ppm in a study of developmental toxicity (Shell Oil Company, 1979).

The carcinogenicity of EDC has been demonstrated in rats and mice by gavage exposure (NCI, 1978a), but not by inhalation (Maltoni et al., 1980). Male rats had a significantly increased incidence of forestomach squamous-cell carcinomas and circulatory system hemangiosarcomas in the NCI study. Female rats and mice were observed to have significant increases in mammary adenocarcinoma incidence. Mice of both sexes developed alveolar/bronchiolar adenomas, females developed endometrial stromal polyps and sarcomas, and males developed hepatocellular carcinomas (NCI, 1978a). Based on the exposure discussed below and these concerns, EPA finds that EDC may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that EDC is produced in substantial quantities. EDC production in

1992 was 14.3 billion pounds (CMR, 1992f).

(ii) EPA believes that there is or may be substantial human exposure to EDC. EDC is currently used as a chemical intermediate principally in the synthesis of vinyl chloride monomer, as a solvent in closed systems, and in the synthesis of vinylidene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, aziridines, and ethylene diamines (ATSDR, 1992). NIOSH estimated that 77,111 workers were potentially exposed to EDC in 1980 in the apparel and textile industries, chemical and allied products industries, business services, and petroleum and coal products industries (NIOSH, 1989).

The greatest source of exposure to EDC for the general population is inhalation of contaminated air. Atmospheric exposure to EDC varies greatly from one location to another. Mean levels as high as 27.5 ppb have been monitored near production and use facilities in Lake Charles, Louisiana. Most locations have EDC concentrations of 0.5 ppb or less (EPA, 1985).

(iii) EPA believes that there is substantial environmental release of EDC. The 1993 TRI indicates 2.3 million pounds of EDC were released to the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of EDC. An inhalation developmental toxicity study was conducted in rabbits at 100 and 300 ppm (Shell Oil Company, 1979). Despite the use of only two exposure levels, EPA regards this study as acceptable. Maternal

toxicity was observed at both treatment levels. No developmental effects were noted. However, the inhalation developmental toxicity test in rats is inadequate (Shell Oil Company, 1979). Again, only two exposure levels were used (100 and 300 ppm). However, maternal toxicity was so severe at the highest dose level that many females died and no pups were born to the surviving dams. Although no maternal or developmental effects were seen at 100 ppm, too few pregnant animals were used at this dose level to conclude that this was an acceptable negative study. A one-generation reproductive inhalation study was conducted in rats at 25, 75, and 150 ppm (Murray et al., 1980) and a multi-generation drinking water test in mice was conducted at 30, 90, and 290 mg/L (Lane et al., 1982). Both studies are deficient, however, in that neither identified an effect level.

The acute tests are not adequate to determine portal of entry effects and extra-respiratory effects. The respiratory irritation study by DuPont was conducted in rats at inhalation exposures ranging from 640 to 12,000 ppm for only 10 minutes, exposed only males, did not evaluate histopathology, and used too few animals (DuPont, 1982). Union Carbide exposed rats, mice, and rabbits to 200 ppm of EDC for 1 hour (Union Carbide Corporation, 1987). This study was inadequate because it was conducted at only one dose level and only limited endpoints were evaluated. Similarly, Carpenter et al. exposed rats by inhalation to 1,000 ppm of EDC for 4 hours (Carpenter et al., 1949). Spencer et al. exposed rats by inhalation to six different concentrations ranging from 300 to 3,000 ppm over a

0.5- to 8-hour period (Spencer et al., 1951). The lack of adequate reporting precludes the further evaluation or use of this study. Heppel et al. exposed rats, mice, guinea pigs, rabbits, cats, hogs, and raccoons by inhalation at 1,500 and 3,000 ppm over a range of times varying between 1.5 and 7 hours (Heppel et al., 1945). The Heppel et al. study was also reported as a summary that precludes its full evaluation and use. Several inadequate subchronic studies were found in the literature. Lioia and Elmino exposed rabbits to 3,000 ppm of EDC by inhalation for 90 days (Lioia and Elmino, 1959). This study was conducted at only one exposure level and does not report the use of controls. Hofmann et al. exposed rats, guinea pigs, rabbits, and cats to 100 and 500 ppm of EDC for 6 hours/day, 5 days/week for 6 weeks (Hofmann et al., 1971). This study exposed animals to only two concentrations for only 6 weeks. High mortality was found at the high exposure level and no toxic effects were reported at the low exposure level. Intermediate exposure levels should be studied to determine the effects of sublethal concentrations. A second study by Hofmann exposing rats, guinea pigs, rabbits, and cats to 500 ppm of EDC for 13 weeks followed by exposure to 1,000 ppm EDC for an additional 13 weeks produced results (no toxicity at 500 ppm) that appear at odds with those of his first study (Hofmann et al., 1971). This study is not a standard subchronic study.

Although acute studies indicate neurological effects, these studies are inadequate because they did not evaluate the appropriate neurological endpoints: functional observational

battery, neuropathology, and motor activity (Spencer et al., 1951). No subchronic neurotoxicity studies were found. No data were located for respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of EDC is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of EDC does or does not present an unreasonable risk of injury to human health from inhalation exposure.

J. Ethylene Glycol (107-21-1)

EPA is proposing testing of ethylene glycol under the authority of TSCA section 4(a)(1)(B).

1. Section 4(a)(1)(B)(i) findings. (i) EPA believes that ethylene glycol is produced in substantial quantities. Ethylene glycol production in 1992 was 7.4 billion pounds (CMR, 1993a).

(ii) EPA believes that there is or may be substantial human exposure to ethylene glycol. Ethylene glycol is widely used as an antifreeze in heating and cooling systems, a de-icing agent on bridges and airport runways, and a solvent in the paints and plastics industry. It is also used in hydraulic brake fluids, printer's inks, and inks for stamp pads and ballpoint pens (Budavari et al., 1989b; Hawley, 1981). NIOSH has estimated that 1.1 million workers are exposed to ethylene glycol (NIOSH, 1989).

The highest concentrations of ethylene glycol aerosol and vapor found in the breathing zone of workers spraying 50% ethylene glycol on bridges were 2.33 and 3.36 mg/m^3, respectively. The maximum vapor concentration collected from bridges was 10.34 mg/m^3 (Abdelghani et al., 1990). Fajen reported a time-weighted average concentration of 6.67 mg/m^3 during plastics processing (Fajen, 1982).

(iii) EPA believes that there is substantial environmental release of ethylene glycol. The 1993 TRI indicates that 10.1 million pounds of ethylene glycol were released to the air (EPA, 1995). Ethylene glycol may enter the environment through its use in de-icing runways and from spills and improper disposal of antifreeze, coolant, and solvents containing ethylene glycol (Lovell et al., 1980). Despite its release to air, modeling shows that most ethylene glycol (99.9%) will partition to the aqueous compartment (EPA, 1994).

2. Section 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of ethylene glycol. Several subchronic inhalation studies have been conducted showing portal of entry effects, but none have adequately characterized the respiratory tract toxicity and extra-respiratory organ effects of ethylene glycol. Coon et al. exposed rats, guinea pigs, and rabbits to 12 mg/m^3 for 90 days (Coon et al., 1970). The study is inadequate because it was carried out at only one dose level and looked at only a few endpoints. A second study by Coon was carried out at 10 and 57

mg/m^3,but also only looked at a limited number of endpoints. No data were found for neurotoxicity. Limited human inhalation data were found on acute toxicity (Wills et al., 1974); no animal acute inhalation studies were found. No data were located for respiratory sensory irritation.

Rats immunized with trinitrophenyl/lipopolysaccharide were administered ethylene glycol by gavage at 50 to 400 mg/kg for 2 days (Smialowicz et al., 1992). This represents an inadequate study of immune function because the antigen challenge was administered prior to exposure to ethylene glycol.

3. Section 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of ethylene glycol is necessary to develop data for acute toxicity, subchronic toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, use, and disposal of ethylene glycol does or does not present an unreasonable risk of injury to human health from inhalation exposure.

K. Hydrochloric Acid (7647-01-0)

EPA is proposing testing of hydrochloric acid (hydrogen chloride, HCl) under the authority of section 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of HCl may present an unreasonable risk of injury to health. Acute studies on HCl

showed a concentration-dependent response for pulmonary irritation, morphological injury in the alveolar region, and decreased pulmonary performance in guinea pigs at exposures ranging from 320 to 1,380 ppm for 30 minutes (Burleigh-Flayer et al., 1985). A subchronic inhalation study in rats showed dose-related respiratory tract effects (rhinitis) at exposures ranging from 10 to 50 ppm for 90 days (CIIT, 1985). Based on the exposure discussed below and these concerns, EPA finds that HCl may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that HCl is produced in substantial quantities. In 1992, 5.75 billion pounds of HCl were produced in the United States (Reisch, 1993).

(ii) EPA believes that there is or may be substantial human exposure to HCl. HCl is one of the most important basic industrial chemical substances and the largest proportion of it is used by the producer (Austin and Glowacki, 1989). A substantial amount of HCl is produced as a byproduct from the manufacture of vinyl chloride from 1,2-dichloroethane (Reisch, 1993). HCl is used in the manufacture of a variety of chemical substances including pharmaceutical hydrochlorides, vinyl chloride from acetylene, alkyl chlorides, and arsenious chloride (Budavari et al., 1989c). HCl is also used to dissolve minerals; pickle and etch metals; regenerate ion-exchange resins for water treatment; neutralize alkaline products or waste materials; acidify brine in electrolysis; control pH; catalyze isomerization, polymerization, and alkylation reactions; and hydrolyze starch, proteins, and a variety of other substances.

It is also used in the production of tin and tantalum, as an analytical reagent, deliming agent for hides, and coagulation agent for latex, in the desulfurization of petroleum, in cleaning boilers, and as a gastric acidifier (Austin and Glowacki, 1989; Budavari et al., 1989c; Curlin et al., 1991).

NIOSH estimates 1.1 million workers are exposed to HCl (NIOSH, 1989). Workers in the finishing room of a polytetrafluoroethylene plant were exposed to an atmosphere containing 35 ppm HCl outside the oven where polytetrafluoroethylene is heated above normal drying temperatures (Adams, 1963). Laboratory workers, high school and college students in chemistry laboratories, and swimming pool operators are exposed to HCl (Austin and Glowacki, 1989).

Persons living downwind from coal combustion sources may be exposed to HCl. Up to 98% of the chlorine in coal is emitted as HCl (Crummet, 1982).

(iii) EPA believes that there is substantial environmental release of HCl. According to the 1993 TRI, 79 million pounds of HCl were released to the air (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of HCl. Two studies were located on the acute respiratory toxicity of HCl. Burleigh-Flayer et al. exposed guinea pigs to 320, 680, 1,040, and 1,380 ppm HCl for 30 minutes. This study showed concentration-related effects but was only conducted for 30 minutes (Burleigh-Flayer et

al., 1985). The study of baboons by Kaplan et al. was conducted for only 15 minutes (Kaplan et al., 1988). Neither study contained histopathology.

Existing subchronic data indicate that the respiratory tract is the only critical target tissue (CIIT, 1985). EPA believes that available data indicate that HCl produces toxicity only at the site of contact because, as a strong acid, it completely dissociates in an aqueous medium to hydronium and chloride ions. Thus, no testing for systemic or remote site toxicity is being required at this time.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of HCl is necessary to develop data for acute respiratory effects. EPA believes that this testing is needed to determine if the manufacture, processing, and use of HCl does or does not present an unreasonable risk of injury to human health from inhalation exposure.

L. Hydrogen Fluoride (7664-39-3)

EPA is proposing testing of hydrogen fluoride (HF) under the authority of section 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of hydrogen fluoride may present an unreasonable risk of injury to health. Acute exposure of rats to hydrogen fluoride for 30 to 60 minutes followed by an observation period is reported to result in respiratory distress;

severe changes in nasal, tracheal, and bronchial histopathology; necrotic lesions of the eyes, face, and ears; corneal opacity; and severe weight loss (Haskell Laboratory, 1988; Stavert et al., 1991).

Studies of repeated administration of HF show emphysema, necrosis of the liver, and inhibition of certain enzymes relating to lipid metabolism (Dousset et al., 1984; Humiczewska et al., 1989; Philibert et al., 1991). Battelle conducted an inhalation subchronic study of HF in rats (5 males and females per exposure level) at 1 to 100 ppm (Battelle, 1990). There were no effects observed at 1 ppm (except for a slight increase in lung to body weight ratio), whereas at 25 ppm and above, animals manifested severe clinical signs and died. This suggests an extremely steep exposure-response curve.

An accidental release of HF occurred in 1991. Eye and skin irritation, sore throat, chest pain, shortness of breath, cough, vomiting, dizziness, hypoxemia, hypocalcemia, and headache were observed in residents of a nearby community (Wing et al., 1991).

Based on the exposure discussed below and these concerns, EPA finds that HF may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that hydrogen fluoride is produced in substantial quantities. In 1991, 322 million pounds of HF were produced in the United States (CMR, 1991b).

(ii) EPA believes that there is or may be substantial human exposure to hydrogen fluoride. HF is primarily used in the

production of fluorocarbons. Other major uses include aluminum manufacture, petroleum alkylation catalysis, and stainless steel pickling. Miscellaneous uses include glass etching, herbicide manufacture, preparation of fluoride salts, and production of uranium tetrafluoride (CMR, 1991b). NIOSH estimates that 182,589 workers are exposed in the United States (NIOSH, 1989). HF concentrations ranged from 0.34 to 3.0 mg/m^3 in the air of the etching department of a glass company (Burr et al., 1990). From 1961 to 1971, the estimated amount of HF in the atmosphere surrounding an alkylation unit at an oil refinery was over 25 ppm during acid tank gauging, 25 to 200 ppm during shutdown and repair, and 3 ppm during normal service (Waldbott, 1978). HF concentrations of 2.0 and 1.1 mg/m^3 have been measured around the acid line of a hard chrome plating production shop (Sheehy, 1982).

Based on information on HF use and release to the atmosphere, general population exposure to HF would be expected near facilities using HF (NAS, 1971). HF exposure may also result from the atmospheric breakdown of formylfluoride formed from the oxidation of hydrofluorocarbons HFC-134a and HFC-41 (Wallington and Hurley, 1993).

(iii) <u>EPA believes that there is substantial environmental release of hydrogen fluoride</u>. The 1993 TRI shows that 7.7 million pounds of HF were released to the air (EPA, 1995). HF may be released to the atmosphere during its production and from manufacturing aluminum, brick, glass, pottery, ceramics, electronics, fertilizers, lacquers, fluorocarbons, phosphoric

acid, and steel (Graedel et al., 1986; NAS, 1971).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of hydrogen fluoride. Stavert et al. conducted an acute study at a single high-exposure level (1,300 ppm for 30 minutes) using only male rats (Stavert et al., 1991). Only a limited number of endpoints were examined. No data were available concerning the exposure levels used in the Haskell study that assessed a limited number of endpoints in male rats after only a 1-hour exposure (Haskell Laboratory, 1988).

Battelle conducted a 14-day inhalation subchronic study of HF in rats (5 males and females per exposure level) at 1 to 100 ppm. There were no effects observed at 1 ppm, whereas rats died manifesting severe clinical signs at 25 ppm and above, suggesting a steep exposure-response curve (Battelle, 1990). The Battelle study is limited in that neither the cause of death nor a LOAEL was identified. The sufficiency of the subchronic study by Humiczewska et al. could not be determined because the study was inadequately reported (Humiczewska et al., 1989). The other repeat-dose studies do not meet the criteria for adequate subchronic toxicity studies. The studies by Philibert et al. were only of several days duration and only a narrow range of endpoints was assessed (Philibert et al., 1991). Although a chronic study in guinea pigs was poorly translated from French, this study only used one dose level (Bourbon et al., 1979).

Drozdz et al. exposed rats to 2.75 or 4.99 mg/m^3 HF prior to

mating and during pregnancy and lactation, followed by exposure of offspring for 1-6 months (Drozdz et al., 1981). This study evaluated the metabolism of collagen and was not designed to be a reproductive toxicity study. Oral treatment of rabbits with 4.5 mg fluoride/kg/day (as sodium fluoride) for 18 months resulted in a decrease in antibody titer (Jain and Susheela, 1987).

A study in humans for 10 to 50 days reported only irritation. Only five subjects were evaluated and it is not known to what extent indicators of systemic toxicity were assessed (Largent, 1960; Largent, 1961). No data were located on the developmental toxicity, neurotoxicity, respiratory sensory irritation, and immunotoxicity for HF.

There is a suggestion that HF does not act toxicologically as other hydrohalic acids. Acute toxicity of the other hydrohalic acids occurs primarily at the portal of entry, and results in the typical burn associated with acids. HF also results in destruction of tissues, but this may not be observed for as long as 24 hours after an acute exposure. It was reported that following dermal exposure, there is deep penetration into the tissue, which is not typical of a highly ionized compound, and that the observed effect of extreme pain may be delayed for up to 6 hours.

The unique toxicology of HF may be explained by its unusual chemistry. In contrast to other hydrohalic acids, hydrogen fluoride is a relatively weak acid in dilute aqueous solutions; however, pure HF is one of the strongest acids known and is classified as a super acid. The rationale for this apparent

discrepancy is due to high electronegativity of fluorine, the resulting strength of the hydrogen-fluorine bond, and in all but very dilute solutions, the strong polymeric association of hydrogen fluoride. Hydrogen fluoride is one of the most stable diatomic molecules known; it has a dissociation energy similar to nitrogen. It takes so much energy to break HF into hydrogen and fluoride ions that dissociation is a slow event. It is postulated that the slow rate of dissociation gives HF time to penetrate tissues, thus giving rise to delayed systemic effects rather than toxicity confined to the portal of entry (Syracuse Research Corporation, 1994).

Given the chemical characteristics of HF, the potential for HF to be absorbed and distributed to remote tissue sites in its undissociated form, and its observed extra-respiratory effects (liver necrosis, changes in enzyme level in liver, heart, and stomach), EPA believes more studies are needed to characterize HF's reproductive and developmental toxicity and neurotoxicity despite the highly irritating properties of HF at the portal of entry.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of hydrogen fluoride is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of HF does or does not present an unreasonable risk of injury to human health

from inhalation exposure.

M. Maleic Anhydride (108-31-6)

EPA is proposing testing of maleic anhydride under the authority of section 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of maleic anhydride may present an unreasonable risk of injury to health. Studies of maleic anhydride in several species indicate respiratory tract effects. An inhalation study in which rats were exposed for approximately 4 weeks to 12, 32, and 86 mg/m^3 of maleic anhydride showed numerous upper respiratory tract lesions at all concentrations and lung lesions at the two highest concentrations (Goldenthal et al., 1984a). Rats, hamsters, and monkeys were exposed to 1, 3, or 10 mg/m^3 maleic anhydride for 6 months (Short et al., 1988). Nasal and ocular irritation was observed in all dose groups. Ulrich et al. also observed nasal discharge, ocular irritation, dyspnea, and other respiratory disturbances in studies with rats, hamsters, and monkeys exposed to 0.010 mg/L for 6 months (Ulrich et al., 1984). In a study of reproductive toxicity, Monsanto found reduced weight gain and renal cortical necrosis in dams and reduced growth in pups of dams orally dosed with 150 mg/kg of maleic anhydride (Monsanto Company, 1984).

Humans were exposed to concentrations up to 30 ppm maleic anhydride for 5 minutes, 6 ppm for 1 hour, and 5 ppm for 4 hours (Chevron Chemical Company, 1984). Eye and nose irritation and

pulmonary discomfort were observed. Based on the exposure discussed below and these concerns, EPA finds that maleic anhydride may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that maleic anhydride is produced in substantial quantities. United States production of maleic anhydride was 382 million pounds in 1991 (CMR, 1992b).

(ii) EPA believes that there is or may be substantial human exposure to maleic anhydride. Maleic anhydride is used primarily in the production of unsaturated polyester resins. It is also used to make lubricating oil additives, copolymers, fumaric acid, agricultural chemicals, maleic acid, sulfosuccinic acid esters, and alkenyl succinic anhydrides (CMR, 1992b). Polyester and alkyd resins are used to make fiberglass-reinforced plastics in the construction and electrical industries and in textile finishing (Lin, 1992). Maleic anhydride is used in the production of the pesticides captan and malathion and is added to drying oils to reduce the drying time and improve the coating qualities of lacquers (Lohbeck et al., 1990). NIOSH has estimated that 37,897 workers are exposed to maleic anhydride in the United States (NIOSH, 1989). Workers are most likely to be exposed via inhalation of dust or vapor or dermal contact in production facilities or factories that produce unsaturated polyester resins, lubricating oils, and other chemicals that use maleic anhydride in their production. Of special concern is loading and unloading maleic anhydride solids and exposure to vapor from

molten material. The 1993 TRI indicates that 372,315 pounds of maleic anhydride were released to the air (EPA, 1995). This may result in general population exposure.

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of maleic anhydride. Data from subchronic studies indicate that the respiratory system is affected by exposure to maleic anhydride (Goldenthal et al., 1984a; Short et al., 1988; Ulrich et al., 1984), but no acute inhalation studies in animals were located.

An oral developmental toxicity study was conducted in which rats were exposed to 30, 90, and 140 mg/kg/day of maleic anhydride (Goldenthal et al., 1984b). Although this study is acceptable and reported no developmental effects, EPA believes that, consistent with its testing and assessment policy for developmental toxicity, testing in a second species is necessary in order to adequately assess risk.

Maleic anhydride is a suspect carcinogen by inhalation because of its potential of being a direct-acting acylating agent. A number of acylating agents are known to be carcinogenic (Van Duuren et al., 1987). No treatment-related increase in tumor incidence was observed in female and male rats exposed to dietary maleic anhydride at doses of 10, 32, and 100 mg/kg/day for 2 years (CIIT, 1983). However, this study may be of limited value in predicting the carcinogenicity of maleic anhydride from inhalation exposure since, if maleic anhydride administered

orally hydrolyzes in the stomach, the substance reaching remote target organs would be the acid or acid salt rather than the anhydride. Furthermore, the study is compromised because of the high incidence of uterine adenocarcinomas and ophthalmological lesions in controls and treated groups. Toxicity data from subchronic inhalation studies have provided evidence that maleic anhydride is, as expected, reactive in tissues of the respiratory tract. Goldenthal et al. conducted a study in rats at 12, 32, and 86 mg/m^3 for only 30 days, but reported numerous upper respiratory tract lesions at all exposure levels and lung lesions at the intermediate and high concentrations (Goldenthal et al., 1984a). On the basis of the carcinogenicity observed in screening tests (Dickens and Jones, 1965) and the lesions observed in the respiratory tract (Goldenthal et al., 1984a), EPA concludes that a chronic bioassay is necessary to characterize the potential of maleic anhydride to cause cancer via inhalation exposure.

Although maleic anhydride is reported to be a respiratory sensitizer in humans (Lee at al., 1991), respiratory sensitization and immune suppression are separate endpoints so this study does not address immune suppression. No data were found for neurotoxicity and respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of maleic anhydride is necessary to develop data for acute toxicity, developmental toxicity, neurotoxicity, carcinogenicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing

is needed to determine if the manufacture, processing, and use of maleic anhydride does or does not present an unreasonable risk of injury to human health from inhalation exposure.

N. Methyl Isobutyl Ketone (108-10-1)

EPA is proposing testing of methyl isobutyl ketone (MIBK) under the authority of section 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of methyl isobutyl ketone may present an unreasonable risk of injury to health. Available data indicate that MIBK may cause neurotoxicity and developmental toxicity. Neurotoxicity (loss of coordination, partial paralysis, muscular weakness in hindlimbs, and negative tail and toe pinch) was seen in dams at the highest dose (3,000 ppm) in developmental toxicity studies conducted by Union Carbide (Union Carbide Corporation, 1984). Humans exposed to MIBK in several studies complained of somnolence, insomnia, nausea, headache, and central nervous system symptoms (Armeli et al., 1968; Hjelm et al., 1990; Linari et al., 1964).

Developmental toxicity in multiple species expressed as increased incidence of unossified skeletal elements and decreased fetal body weight was also observed at 3,000 ppm (Union Carbide Corporation, 1984). Based on the exposure discussed below and these concerns, EPA finds that MIBK may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that

MIBK is produced in substantial quantities. MIBK had a 1992 production volume of 175 million pounds (CMR, 1993b).

(ii) EPA believes that there is or may be substantial human exposure to MIBK. MIBK is an important solvent for vinyl, epoxyacrylic, and natural resins and for nitrocellulose and dyes. It is also used as an extractant (Siegel and Eggersdorfer, 1990). Its solvent uses break out as follows: surface coatings (66%), process solvent for pharmaceuticals, adhesives, and pesticides (15%), chemical production including rubber-processing chemicals (15%), and miscellaneous (4%) (CMR, 1993b). NIOSH estimates that 467,763 workers are exposed to MIBK in the United States. Workers in spray paint booths were exposed to mean levels of 0.6 ppm of MIBK. The highest level recorded in spray booth operations was 45 ppm; the highest time-weighted exposure level was 8.8 ppm (Whitehead et al., 1984). Workers in a custom silk screen wall covering plant had substantially higher exposures measured between 24 and 143 ppm (Almaguer, 1984).

There is widespread consumer exposure to MIBK. MIBK was found in 64 of 1,039 household products surveyed from 65 product categories (Sack and Steele, 1991; Sack et al., 1992). MIBK is found in spray paint, wood stains, paint thinners, paint removers, varnishes, adhesives, carburetor cleaners, fabric and leather treatments, spot removers, oils, greases, lubricants, and tape recorder cleaners (Sack et al., 1992). For 17 consumer products containing MIBK, consumer usage has been estimated to range from 7.2 to 112 million people (EPA, 1993b).

The general population is exposed to MIBK from motor vehicle exhaust and from air in industrial areas (Brodzinsky and Singh, 1982; Hampton et al., 1982). It has been found in the effluent from the following industries: printing and publishing, coal mining, electronics, and organic chemicals (Bursey and Pellazari, 1982). It has been measured in air in industrial areas at a median concentration of 270 ppt (Brodzinsky and Singh, 1982).

(iii) EPA believes that there is substantial environmental release of MIBK. According to the 1993 TRI, 25 million pounds of MIBK were released into the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of MIBK. No data were found on reproductive toxicity, immunotoxicity, or respiratory sensory irritation. The acute toxicity study conducted by DuPont was at extremely high doses for 30 minutes and did not fully characterize the effect of acute exposure by conducting organ histopathology including the respiratory tract (DuPont, 1983).

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of MIBK is necessary to develop data for acute toxicity, reproductive toxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of MIBK does or does not present an unreasonable risk of injury to human health from inhalation exposure.

O. Methyl Methacrylate (80-62-6)

EPA is proposing testing of methyl methacrylate under the authority of section 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of methyl methacrylate may present an unreasonable risk of injury to health. NTP exposed rats and mice by inhalation to 500, 1,000, 2,000, and 5,000 ppm of methyl methacrylate for 14 weeks (NTP, 1986). Lesions of the olfactory epithelium, kidney, and liver were noted in rats and mice at the two highest concentrations in these studies. The olfactory region of the nasal passage was also found to be a key target organ at the two highest exposure levels in chronic rat inhalation studies conducted at 25, 100, and 400 ppm (Rohm and Haas Company, 1989; Rohm and Haas Company, 1992). In an acute study, pulmonary damage (hemorrhage, pulmonary vasodilation, and edema) was reported after a 2-, 3-, or 4-hour exposure of rats to approximately 96.7 ± 0.41 ppm of methyl methacrylate (Raje et al., 1985). In another acute rat study at 13.4 mg/ml and higher, slight irritation of the respiratory tract was noted after 8 hours of exposure (Haskell Laboratory, 1989). Neurotoxicity was observed in studies of methyl methacrylate. Impaired locomotor activity and learning were reported in rats at 500 mg/kg/day administered by gavage for 21 days (Husain et al., 1985). Neurological symptoms have also been reported in humans. A study of dental technicians revealed numbness, coldness, whiteness, and decreased sensory conduction velocities in the fingers

(Rajaniemi, 1986).

Based on the exposure discussed below and these concerns, EPA finds that methyl methacrylate may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that methyl methacrylate is produced in substantial quantities. There were 1.2 billion pounds of methyl methacrylate produced in 1990 (CMR, 1991a).

(ii) EPA believes that there is or may be substantial human exposure to methyl methacrylate. Methyl methacrylate is an acrylic resin monomer that is used for cast and extruded sheet, molded powders and resins, surface coatings, impact modifiers, emulsion polymers, and miscellaneous polymeric applications (CMR, 1991a). NIOSH estimates that 120,778 workers are exposed to methyl methacrylate in the United States (NIOSH, 1989). The time-weighted average exposure level measured in five polymethylmethacrylate sheet manufacturing plants ranged from 4 to 88 ppm. Methyl methacrylate has been found in the urine of dental technicians working with acrylics (Rajaniemi et al., 1989).

Consumers may be exposed from acrylic bone cements and dental devices. Residual methyl methacrylate has been detected in commercial polystyrene plastics at 36 ppm. Residual methyl methacrylate in commercial acrylic bone cements has been reported to have migrated into prepared tissue medium and concentrations of 0.7% to 5.1% by weight have been detected in fatty components of bone marrow (IARC, 1979).

(iii) EPA believes that there is substantial environmental release of methyl methacrylate. The 1993 TRI indicates that 2.3 million pounds of methyl methacrylate were released to the atmosphere (EPA, 1995). Methyl methacrylate has been found in Lake Michigan at 10 ppb (Konasewich et al., 1978).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of methyl methacrylate. The data on neurotoxicity by Husain et al. and Innes and Tansy are limited by the few endpoints that were examined and the fact that only one dose level was used in each study. Husain administered methyl methacrylate by gavage at the rate of 500 mg/kg/day to male rats for 21 days and measured motor activity and learning (Husain et al., 1985). Only male rats were used. The Innes and Tansy study was an acute inhalation study of only 60 minutes duration (Innes and Tansy, 1981). The single exposure level, use of only males, and poor reporting of study parameters make it inadequate for assessing the neurotoxicity of methyl methacrylate.

Raje et al. exposed male rats to 96.7 ± 0.41 ppm of methyl methacrylate for up to 4 hours (Raje et al., 1985). This study showed effects on the lung and may be adequate for screening purposes; however, significant flaws (use of too few animals, males only, and single a exposure) limit its use for assessment of risk to the respiratory tract and other systems. The study by Oberly and Tansy in rats also reported irritation of the

respiratory tract, but was inadequate because it was conducted in males only, used two exposure levels rather than three, and did not report an adequate range of endpoints (Oberly and Tansy, 1985).

Developmental toxicity has been adequately studied in only one species, the rat (Imperial Chemical Industries, 1977; Rohm and Haas Company, 1976; Rohm and Haas Company, 1991). The mouse study by Rohm and Haas was inadequate because the test substance was administered only through day 13, thus running the risk of missing late-stage developmental effects (Rohm and Haas Company, 1976). No data were found on the reproductive toxicity of methyl methacrylate.

Exposure of rats to 116 ppm methyl methacrylate vapor for 8 hours/day for 3-6 months showed a decrease in fat deposits, body, lung, and spleen weight, and altered blood chemistry (Tansy et al., 1976). At three months, spleen weight in controls was 0.41 g and in treated rats, slightly, but significantly less, at 0.39 g. There were no differences in spleen weights in the 6 month study. Santavirta et al. reported a lack of immune response to methyl methacrylate in lymphocyte cultures (Santavirta et al., 1991). These are inadequate studies of the immune system because immune function was not assessed. No data were located for respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of methyl methacrylate is necessary to develop data for acute toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, immunotoxicity,

and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of methyl methacrylate does or does not present an unreasonable risk of injury to human health from inhalation exposure.

P. Naphthalene (91-20-3)

EPA is proposing testing of naphthalene under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of naphthalene may present an unreasonable risk of injury to health. In a chronic inhalation study, the NTP administered 0, 10, and 30 ppm of naphthalene to mice for 6 hours/day, 5 days/week for 104 weeks. Chronic inflammation and metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium was observed at 10 and 30 ppm (NTP, 1992b). Increased pulmonary adenomas also were reported in females at 30 ppm in the NTP study and a study by Adkins et al. (Adkins et al., 1986; NTP, 1992b). Anger and Johnson (1985) also suggested that naphthalene produces depression of the central nervous system, which is consistent with the toxic effects observed in other studies (Anger and Johnson, 1985; Navarro et al., 1991; Pharmakon Research International, 1986). Based on the exposure discussed below and these concerns, EPA finds that naphthalene may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that naphthalene is produced in substantial quantities. There were 235 million pounds of naphthalene produced in the United States in 1989 (CMR, 1990b).

(ii) EPA believes that there is or may be substantial human exposure to naphthalene. Naphthalene is primarily used as a feedstock in the production of other chemical substances. Phthalic anhydride--an intermediate for PVC plasticizers, resins, and insecticides--accounts for 55% of naphthalene production. Naphthalene is also used to make 2-naphthol and naphthalene sulfonic acid, which are used in the synthesis of azo dyes. Naphthalene sulfonate-formaldehyde condensates are used as tanning agents and dispersants for concrete. Hydrogenation of naphthalene produces the solvents tetralin and decalin. Naphthalene is also used as a moth repellant (Collin and Hoke, 1991). NIOSH estimates that 23,092 workers are exposed to naphthalene (NIOSH, 1989). It is estimated that workers may be exposed to up to 220 ppm of naphthalene in the vapor phase and up to 4.4 $\mu g/m^3$ of particulates (EPA, 1980).

Naphthalene is also a component of polycyclic aromatic hydrocarbons (PAHs), which are emitted into the air by many industrial processes involving incomplete combustion of organic materials. Naphthalene was found to be the predominant PAH detected in a study of workplace air exposures to coke oven workers in a Swedish steel mill, accounting for 60% to 95% of PAH exposures, which ranged from 6 to 570 $\mu g/m^3$ (Heikkila et al., 1987). Naphthalene emissions released at a pilot-scale foundry

during aluminum and grey iron casting by the conventional green sand process and the new EPC process ranged up to 9,800 μg/kg of metal produced (Gressel et al., 1988). Naphthalene was the main organic component in vapors in creosote impregnation plants. The mean concentrations of naphthalene in the breathing zone of workers in various categories in two such plants in Finland ranged from 0.2 to 41 mg/m^3 (Heikkila et al., 1987).

Consumers who use naphthalene as a mothproofing agent will be exposed to naphthalene while storing or unpacking clothing in mothballs. Exposures may be relatively high because room or closet ventilation may be poor. Consumers may also be exposed to naphthalene at gasoline stations; the air samples in one survey contained 0.09 ppm (API, 1991).

The general population may also be exposed to naphthalene. Urban air in the United States near naphthalene sources contained a median naphthalene concentration of 400 ppt with a range up to 16 ppb (Brodzinsky and Singh, 1982). Naphthalene levels in air in the Allegheny Tunnel on the Pennsylvania Turnpike ranged up to 10.1 μg/m^3 (Hampton et al., 1983).

(iii) EPA believes that there is substantial environmental release of naphthalene. According to the 1993 TRI, 2.7 million pounds of naphthalene were released to the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of naphthalene. Shopp et al.

conducted two oral gavage studies in mice, one of 14 days duration at 267 mg/kg/day, the other for 90 days at 133 mg/kg/day (Shopp et al., 1984). Neither study qualifies as an adequate study of the reproductive effects of naphthalene because they focused only on the testes and involved no evaluation of reproductive function. Shopp et al. also reported no immunological response to naphthalene except that mitogenic responses to concanavalin A were reduced in females only, and thymic weights were reduced approximately 40% in males and splenic weights were reduced approximately 20% in females (Shopp et al., 1984). The same study reported a 25% decrease in splenic weight in females after oral doses of 133 mg/kg/day for 13 weeks. This study is not an adequate evaluation of immune function.

Respiratory difficulties have been observed in studies of other endpoints, but the respiratory tract and other systems have not been adequately studied by histopathology after acute exposure (NTP, 1992b; Pharmakon Research International, 1985). No data were located for respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of naphthalene is necessary to develop data for acute toxicity, reproductive toxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of naphthalene does or does not present an unreasonable risk of injury to human health from inhalation exposure. NTP will be conducting 90-day subchronic and carcinogenicity studies in the rat (Eastin, 1994) and EPA's

Office of Pesticide Programs is requiring neurotoxicity testing under FIFRA.

O. Phenol (108-95-2)

EPA is proposing testing of phenol under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA. Findings for sections 4(a)(1)(A)(i) and (B)(i) were recently made in the Federal Register (EPA, 1993c pp. 61654, 61659-60). Findings for sections 4(a)(1)(A)(ii), 4(a)(1)(B)(ii), 4(a)(1)(A)(iii), and 4(a)(1)(B)(iii) are made below.

1. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of phenol. Two acute inhalation studies of phenol were located and reviewed. Neither was adequate to assess the acute effects of phenol by inhalation exposure. Dalin and Kristoffersson exposed an unknown number of male and female rats to phenol (26 ppm) for 72 hours (Dalin and Kristoffersson, 1974). No mention was made as to whether respiratory effects and histopathology were assessed. In addition, this study was conducted at only one dose level. DeCeaurriz et al. exposed an male mice (6/group) to four concentrations (levels not reported) of phenol for 5 minutes, reporting a 50% decrease in respiratory rate at 17 ppm and irritation of the upper respiratory tract (DeCeaurriz et al., 1981). While this demonstrates respiratory effects, the lack of

information on dose, duration of exposure, and number of animals exposed as well as the use of a single exposure level make this study inadequate to assess the acute effects of phenol.

Aranyi et al. (1986) reported no infection in mice by pathogenic bacteria following up to 5 days of exposure by inhalation to 5 ppm of phenol (Aranyi et al., 1986). The exposure level was too low and exposure time was too short for this to be considered an adequate study of immunotoxicity.

2. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. EPA believes that the testing of phenol is necessary to develop data for acute toxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of phenol does or does not present an unreasonable risk of injury to human health.

R. Phthalic Anhydride (85-44-9)

EPA is proposing testing of phthalic anhydride under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of phthalic anhydride may present an unreasonable risk of injury to health. Amoco sponsored a study in rats in which phthalic anhydride was administered as a single vapor concentration of 500 $\mu g/m^3$ by inhalation for 6 hours/day for 5 days. A period of 3 weeks without exposure, was then followed with a single 6-hour exposure

to challenge the immune system (Amoco Corporation, 1988). Phthalic anhydride induced hemorrhagic foci in the study, which indicates its potential to induce sensitization in the respiratory tract. Based on the exposure discussed below and these concerns, EPA finds that phthalic anhydride may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that phthalic anhydride is produced in substantial quantities. In 1991, 874 million pounds of phthalic anhydride were produced (CMR, 1992c).

(ii) EPA believes that there is or may be substantial human exposure to phthalic anhydride. Phthalic anhydride is primarily used in the production of plasticizers. It is also used in the production of unsaturated polyester resins and alkyd resins. Miscellaneous uses, which constitute 8% of production, include synthesis of dyes, pigments, and polyester polyols (CMR, 1992c). Phthalic anhydride is used as a curing agent for epoxy resins that have important coating and structural applications (Muskopf and McCollister, 1987). The overwhelming majority of alkyd resins contain phthalic anhydride. NIOSH has estimated that 62,644 workers are exposed to phthalic anhydride (NIOSH, 1989). Time-weighted average concentrations of phthalic anhydride ranged from 0.03 to 10.5 mg/m^3 in a plant that manufactured phthalic anhydride and converted it into unsaturated polyester resins. Urine levels of the hydrolysis product correlated with exposure levels and ranged from 0.03 to 14.0 μmol/mmol creatinine (Pfaffli, 1986a). In another facility that produced and loaded

phthalic anhydride into tank cars for shipment, phthalic anhydride was measured in the range of 4 to 203 $\mu g/m^3$ (Liss et al., 1985). In some facilities, workers may be required to cut open and manually empty bags of phthalic anhydride, a situation with high potential for exposure to the anhydride dust. Exposure to phthalic anhydride vapors and fumes may be caused by heating plastics containing phthalate ester plasticizers (Pfaffli, 1986b). Phthalic anhydride vapors are emitted during heat sealing of plastic films for meat (Bardana et al., 1980; Pauli et al., 1980). The air level of phthalic anhydride vapor in a meat department of a supermarket was reported to be 18.4 ppm (Daniels et al., 1985).

There may also be general population exposure to phthalic anhydride. According to the 1993 TRI, 480,439 pounds of phthalic anhydride were released to the atmosphere (EPA, 1995).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of phthalic anhydride. No data were found for acute toxicity, reproductive toxicity, or neurotoxicity. The pulmonary study conducted by Amoco (in which phthalic anhydride was administered as a single concentration of 500 $\mu g/m^3$ by inhalation to rats for 6 hours per day for 5 days) was designed to detect chemical sensitization (Amoco Corporation, 1988). However, it does not characterize toxicity to the respiratory tract because it was a single exposure study with limited measurements on respiratory tract toxicity. In addition,

the duration of this study was inadequate to assess subchronic toxicity.

The developmental toxicity study conducted by Fabro et al. was inadequately designed and reported (Fabro et al., 1982). It is inadequate because phthalic anhydride was administered intraperitoneally only on days 8 to 10 of gestation. In addition, dose levels and numbers of animals were not reported.

Like maleic anhydride, phthalic anhydride is a suspect carcinogen by inhalation because of its potential of being a direct-acting acylating agent. A number of acylating agents are known to be carcinogenic (Van Duuren et al., 1987).

NTP conducted a carcinogenicity study in rats and mice by the oral route and concluded it was not carcinogenic under these exposure conditions although there was a significant trend in alveolar/bronchiolar adenomas in female rats (NTP, 1979). However, this study may be of limited value in predicting the carcinogenicity of phthalic anhydride from inhalation exposure since, if phthalic anhydride administered orally hydrolyzes in the stomach, the substance reaching remote target organs would be the acid or acid salt rather than the anhydride. Portal of entry effects are suggested by the sensitization study carried out by Amoco (1988). Thus, EPA regards the data inadequate to determine the carcinogenicity of inhaled phthalic anhydride. Phthalic anhydride is reported to be a respiratory sensitizer in humans (Dearman and Kimber, 1992).

Although phthalic anhydride is a respiratory sensitizer in humans (Dearman and Kimber, 1992), respiratory sensitization and

immune suppression are separate endpoints, so this study does not address immune suppression potential. No data were located for reproductive toxicity or respiratory sensory irritation. Given the low vapor pressure of phthalic anhydride (2×10^{-4} mm Hg at 20°), it may not be possible to reach a maximally tolerated dose; thus, EPA is proposing that phthalic anhydride be tested by aerosol exposure.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of phthalic anhydride is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, carcinogenicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of phthalic anhydride does or does not present an unreasonable risk of injury to human health from inhalation exposure.

S. 1,2,4-Trichlorobenzene (120-82-1)

EPA is proposing testing of 1,2,4-trichlorobenzene (TCB) under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of TCB may present an unreasonable risk of injury to health. A screening study on TCB for developmental toxicity in rats was judged negative for teratogenicity but showed retarded embryonic development at 360

mg/kg (EPA, 1982). Industry recently submitted an carcinogenicity study on TCB conducted pursuant to the chlorinated benzenes test rule (EPA, 1986). TCB was administered daily in the diet to mice at concentrations of 150, 700, and 3200 ppm. Hepatocellular carcinomas, hepatocellular adenomas, and centrilobular hepatocytomegaly were reported at the two highest treatment levels (Moore, 1994). Based on the exposure discussed below and these concerns, EPA finds that TCB may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that TCB is produced in substantial quantities. Production data on TCB is claimed to be CBI, but exceeds 1 million pounds.

(i) EPA believes that there is or may be substantial human exposure to TCB. TCB is used in some pesticides, as a dye carrier, in dielectric fluids, in lubricants as a heat-transfer medium, and as an organic intermediate and solvent used in chemical manufacturing; the market for these uses, however, is small and declining (Bryant, 1993). NIOSH estimates that 4,032 workers are exposed to TCB (NIOSH, 1989). Occupational exposure may occur from inhalation or dermal contact in industries that produce TCB or use it as a dye carrier or solvent. Dye carriers are used in the textile industry to achieve complete dye penetration of polyester fibers (Wannamacher and DeMaria, 1979).

There is general population exposure to TCB. TCB has been found in breast milk and milk fat at concentrations of 0.6 and 64 ppb, respectively, in a Canadian study (Davies and Mes, 1987). In a 1980 study, Great Lakes trout were found to contain between

0.5 and 5 ppb of TCB (Oliver and Nicol, 1982). Fish have been shown to bioconcentrate TCB with a bioconcentration factor of 1,300 for rainbow trout and an average bioconcentration factor in fish of 863 (Geyer et al., 1985). According to the 1993 TRI, 262,843 pounds of TCB were released to the atmosphere (EPA, 1995). Atmospheric concentrations of TCB ranged from 8.7 to 339.4 ppt, with means ranging between 29.5 and 69.3 ppt (Singh et al., 1980). TCB has also been found in industrial and municipal wastewater discharge, with highest concentrations of 1,854 and 1,350 ppb, respectively (Shackelford et al., 1983).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of TCB. EPA conducted a screening level developmental toxicity study of TCB in rats. No teratogenicity was seen, but retarded development was noted (EPA, 1982). The study is inadequate because the exposure period did not cover the period of organogenesis and the sample size was limited in some exposure groups to as few as six animals. Black et al. conducted an oral developmental toxicity study in the rat at 75, 150, and 300 mg/kg/day and reported maternal toxicity but not developmental toxicity (Black et al., 1988). This study is inadequate because there were only 11 to 14 animals per exposure group.

The acute study of TCB conducted by DuPont used only 6 animals per exposure group, included only males, and did not include histopathology.

Two studies were found that had neurotoxicology components. The study by Robinson et al. was a multigeneration oral reproductive effects study in rats (at 25, 100, and 400 ppm TCB in drinking water) with limited behavioral measurements (Robinson et al., 1981). Coate et al. exposed rats, rabbits, and monkeys by inhalation (25 and 100 ppm) to TCB for 26 weeks (Coate et al., 1977). This study included some evaluation of neurotoxicity. Data on monkeys were selectively collected on the best performance days during the first and last 4 weeks of the study and no positive control group was used. There are no functional data from the rats or rabbits (e.g., functional observational battery or motor activity). Histopathology was done using immersion rather than perfusion techniques. No data were located for immunotoxicity or respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of 1,2,4-trichlorobenzene is necessary to develop data for acute toxicity, developmental toxicity, neurotoxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of TCB does or does not present an unreasonable risk of injury to human health from inhalation exposure.

T. 1,1,2-Trichloroethane (79-00-5)

EPA is proposing testing of 1,1,2 trichloroethane (TCE) under the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of

TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of TCE may present an unreasonable risk of injury to health. An acute inhalation study in rats reported that exposure to TCE at 250 ppm for 4 hours produced kidney and liver necrosis (Torkelson and Rowe, 1981). The carcinogenicity of TCE has been demonstrated in mice. Hepatocellular carcinomas developed in B6C3F1 mice administered 195 and 390 mg/kg/day of TCE by oral gavage for 78 weeks (NCI, 1978b). Neurotoxicity (motor impairment) was found in a gavage study in mice (Borzelleca, 1983). Pharmacokinetic data indicate that TCE is readily and rapidly absorbed by the inhalation route (IARC, 1991). Based on the exposure discussed below and these concerns, EPA finds that TCE may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that TCE is produced in substantial quantities. CBI production data confirm that TCE is produced in quantities that exceed one million pounds. A non-CBI estimate of demand for TCE was 210 million pounds in 1987 (Reed, 1993).

(ii) EPA believes that there is or may be substantial human exposure to TCE. TCE is used as a feedstock intermediate in the production of vinylidene chloride and some tetrachloroethanes. It is used as a solvent where its high solvency for chlorinated rubbers and other substances is needed, and for pharmaceuticals and electronic components; its relatively high toxicity does not permit its use, however, in consumer products (Dreher, 1986;

Snedecor, 1993). NIOSH estimated that 1,036 workers are exposed to TCE (NIOSH, 1989).

According to the 1993 TRI, 315,397 pounds of TCE were released to the atmosphere (EPA, 1995). There are large variations in ambient levels of TCE with no TCE detected in rural areas. The median and maximum concentrations of TCE in urban/suburban areas of the United States were 0.009 and 11 ppb, respectively. The median concentration in Lake Charles, Louisiana, a major producing area, was 4.8 ppb (Brodzinsky and Singh, 1982).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of TCE. Although carcinogenicity was demonstrated in mice, but not in rats (NCI, 1978b), these studies were conducted by gavage. Thus, EPA is recommending that a modified cancer bioassay be conducted by inhalation to establish a concentration-effect relationship for inhalation risk estimation.

Although acute studies indicate neurological effects, these studies are inadequate because they did not evaluate the appropriate battery of neurological endpoints (Borzelleca, 1983; DeCeaurriz et al., 1981). No data were located for subchronic neurotoxicity. A screening assay for developmental toxicity of TCE was conducted in mice, but it is inadequate for risk assessment and did not cover the period of organogenesis (Seidenberg et al., 1986; Seidenberg and Becker, 1987).

Sanders et al. and White et al. reported effects on humoral or cell-mediated immune response to sheep red blood cells in mice administered TCE by gavage at doses up to 38 mg/kg for 14 days. These authors report some inconsistent effects on antibody response in a 90-day drinking water study in mice at dose levels of 3.9 to 384 mg/kg/day (Sanders et al., 1985; White et al., 1985). Given the conflicting results reported in these studies, a repeat test is needed using more up-to-date methods for evaluating immune function.

No studies were located on the respiratory tract and other organ effects of TCE after acute and subchronic exposures, as characterized by histopathology. No data were located for reproductive toxicity, in vivo cytogenetics, or respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of TCE is necessary to develop data for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, carcinogenicity, genetic toxicity, immunotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of TCE does or does not present an unreasonable risk of injury to human health from inhalation exposure.

U. Vinylidene Chloride (75-35-4)

EPA is proposing testing of vinylidene chloride (VDC) under

the authority of sections 4(a)(1)(A) and 4(a)(1)(B) of TSCA.

1. Section 4(a)(1)(A)(i) findings. EPA believes that the manufacture, processing, and use of VDC may present an unreasonable risk of injury to health. There is a concern for the carcinogenic potential of VDC by inhalation. The concern is based on the following. In an inhalation study (Maltoni et al., 1985), mice were exposed to 10 and 25 ppm VDC for 12 months. A statistically significant increase in kidney adenocarcinomas was noted in male mice and a statistically significant increase in mammary carcinomas was noted in female mice. Liver toxicity was found after long-term inhalation exposure of mice (Lee et al., 1977). Adverse effects have been observed in the kidneys of animals following acute, intermediate, and chronic inhalation exposure to VDC (Lee et al., 1977; Oesch et al., 1983; Reitz et al., 1980).

Murray et al. conducted inhalation developmental toxicity studies in rats and rabbits and found both maternal and developmental toxicity at 80 and 160 ppm in the rat, and maternal toxicity at 80 and 160 ppm and developmental effects at 160 ppm in the rabbit (Murray et al., 1979). Murray et al. found an increase in the incidence of skeletal effects following inhalation exposure of VDC in rats and increased resorptions and skeletal effects in rabbits (Murray et al., 1977).

Based on the exposure discussed below and these concerns, EPA finds that VDC may present an unreasonable risk of injury to human health.

2. Section 4(a)(1)(B)(i) findings. (i) EPA believes that

VDC is produced in substantial quantities. Estimated United States production of VDC in 1989 was 230 million pounds (ATSDR, 1994). The exact production figures are CBI.

(ii) EPA believes that there is or may be substantial human exposure to VDC. VDC is used to manufacture polyvinylidene chloride (PVDC) and its copolymers with vinyl chloride, acrylonitrile, and acrylates (Dreher, 1986; Heiling, 1991). These polymers are used for food packaging films, in paints and coatings, and coatings in controlled-release fertilizers (Dreher, 1986; Goertz, 1993; Heiling, 1991; Wicks, 1993). NIOSH estimated that 2,675 workers are exposed to VDC in the United States (NIOSH, 1989). Levels as high as 1,900 ppm were found in a VDC ethyl acrylate copolymer monofilament fiber production plant (Ott et al., 1976). VDC levels of 0.6 to 63 ppm have been reported in telephone offices across the United States (IARC, 1986).

Consumers may be exposed to VDC as the residual monomer in food wrap. Residual VDC was found ranging up to 10.4 ppm in food wrap; the levels in food were reported to range up to 0.01 ppm (Birkel et al., 1977; Gilbert et al., 1980).

The general population may be exposed from emissions from facilities involving the manufacturing, use, and processing of VDC. 1993 TRI emissions from these facilities were reported to be 195,324 pounds in 1993 (EPA, 1995). VDC may also be formed from the anaerobic degradation of trichloroethylene in landfills and groundwater, and from the thermal decomposition of 1,1,1-trichloroethane, a commonly used solvent (Baek et al., 1990; Hallen et al., 1986; Vogel and McCarty, 1987). VDC may,

therefore, be emitted from an incinerator burning waste plastics and solvents (Glisson, 1986). The median and maximum concentrations of VDC in areas where VDC is manufactured and processed were 3.6 and 6.7 ppb, respectively. In two cities where VDC is manufactured, the mean concentrations were 0.13 ppb (Freeport, Texas) and 6.7 ppb (Lake Charles, Louisiana) (Brodzinsky and Singh, 1982).

3. Section 4(a)(1)(A)(ii) and 4(a)(1)(B)(ii) findings. EPA believes that there are inadequate data and experience to determine or predict the effects on human health from the manufacturing, processing, and use of VDC. No neurotoxicity studies were located.

Acute studies were incomplete in that the respiratory tract and extra-respiratory effects were not evaluated. No data were located for respiratory sensory irritation.

4. Section 4(a)(1)(A)(iii) and 4(a)(1)(B)(iii) findings. Therefore, EPA believes that the testing of VDC is necessary to develop data for acute toxicity, neurotoxicity, and respiratory sensory irritation. EPA believes that this testing is needed to determine if the manufacture, processing, and use of VDC does or does not present an unreasonable risk of injury to human health from inhalation exposure.

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