ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42123; FRL 3770-6]

Multi-substance Rule for the Testing of Developmental and Reproductive Toxicity; Proposed Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Rule.

SUMMARY: EPA is proposing a test rule under section 4 of the Toxic Substances Control Act (TSCA) that would require manufacturers and processors of the 12 substances listed in this notice to conduct testing for developmental and/or reproductive toxicity.

DATES: Submit written comments on or before May 3, 1991. If persons request an opportunity to submit oral comments by April 18, 1991, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting, see Unit VIII. of this preamble.

ADDRESSES: Submit written comments identified by the document control number [OPTS-42123] in triplicate to: TSCA Public Docket Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. G004, NE Mall, 401 M St., SW., Washington, DC 20460. A public version of the administrative record supporting this action, with any confidential business information deleted, is available for inspection at the above address from 8:00 a.m. to noon, and 1:00 p.m. to 4:00 p.m. Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Michael M. Stahl, Director, Environmental Assistance Division (TS-799), Office of Toxic Substances, Rm. E-543B, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: EPA is proposing a test rule under TSCA section 4 to obtain developmental and/or reproductive toxicity data for the 12 substances designated in this rule.

I. Introduction

A. Background

Section 4 of TSCA authorizes EPA to require testing of chemical substances and mixtures whose manufacture, processing, distribution in commerce, use, or disposal may present an unreasonable risk of injury to human health or the environment, but for which existing data are inadequate to reasonably determine or predict such effects. In this rule, 12 substances which are suspected developmental and/or reproductive toxicants are being proposed for developmental and/or reproductive toxicity testing. Refer to Table 1 for a list of the substances, their testing requirements, and their available percent purities. These substances were selected for consideration under this endpoint rule because EPA believes the available data indicate that they may present an unreasonable risk of injury to human health.

The substances selected as candidates for this rule met one or more of the following criteria:

(1) EPA received a TSCA section 8(e) notice of substantial risk.

(2) Available screening level data or other data on the substances provide suggestive evidence that the substance may be toxic and more definitive data are needed to adequately assess risk.

(3) Available data on structurally related substances provide suggestive evidence that the substance may be toxic.

(4) Adequate developmental toxicity data on one mammalian species are available, but testing in an additional mammalian species is needed to adequately assess risk.

TABLE 1.—PROPOSED TESTING AND TEST STANDARDS FOR DESIGNATED SUBSTANCES

Chemical/CAS No.	Testing requirement(s)	Guideline requirement(s)	Minimum percent purity	Docket No. (OPTS)
acrylonitrile (107-13-1)	Developmental: oral	[1]798.4900	99.0	42123/42124
p-aminophenol (123-30-8)	Developmental: oral	798.4900	98.0	42123/42125
bromochloromethane (74-97-5)	Reproductive: oral	798.4700	99.0	42123/42120
carbon disulfide (75-15-0)	Developmental: inhalation	798.4350	99.9	42123/42126
	Reproductive: inhalation	798.4700	99.9	
dodecylphenol (27193-86-8)	Developmental: oral	[1]798.4900	99.5	42123/42127
2-ethylhexanol (104-76-7)	Developmental: oral	[1]798.4900	99.0	42123/42087C
hexadecanoic acid (57-10-3)	Developmental: oral	798.4900	99.0	42123/42128
o-hydroxyphenol (120-80-9)	Developmental: oral	798.4900	99.0	42123/42129
2-methylpropanoic acid (79-31-2)	Developmental: oral	798.4900	99.0	42123/42130
methyl ester octanoic acid (111-11-5)	Developmental: oral	798.4900	99.0	42123/42131
terephthalic acid (100-21-0)	Reproductive: oral	798.4700	98.0	42123/42132
2,4-toluenediamine (95-80-7)	Developmental: oral	798.4900	98.0	42123/42133
	Reproductive: oral	798.4700	98.0	

[1]Testing will be required in a mammalian species other than the rat.

B. Test Development Under TSCA

Under section 4(a) of TSCA, EPA shall, by rule, require testing of a substance to develop appropriate test data if the Administrator makes certain findings as described in TSCA under section 4(a)(1)(A) or (B). Discussions of the statutory section 4 findings are provided in EPA's first and second proposed test rules which were published in the **Federal Register** of July 18, 1980 (45 FR 48510) and June 5, 1981 (46 FR 30300).

In evaluating the testing needs for these substances, EPA considered the available published and unpublished information on the toxicity, exposure, and production of these substances. From its evaluation of these data, EPA is proposing specific health effects testing for these substances under TSCA section 4(a)(1)(A) and for one substance under both section 4(a)(1)(A) and (B).

EPA will continue to evaluate the need for this type of testing of additional substances and will amend this rule as necessary to require such testing. EPA intends to identify future candidates for this rule from its chemical screening program, TSCA section 8(e) data, Premanufacture Notices, Structure Activity Relationship data, nominations

HeinOnline -- 56 Fed. Reg. 9092 1991

from other EPA programs, and Interagency Testing Committee recommendations, among others.

In addition, elsewhere in this issue of the Federal Register, EPA is proposing another TSCA section 4 multi-substance test rule. That rule requires neurotoxicity testing of 10 substances (none of which are the same as those included in this notice). The codified portion of the proposed rule for neurotoxicity is written as an amendment to the codified portion of this rule. For future multi-substance rules, EPA plans to prepare amendments to the combined proposed section of the CFR (i.e., § 799.5050). By so doing, all multi-substance rules will be listed in a single table, and all test requirements (health, environmental, chemical fate, etc.) for a substance would be in a single location. EPA believes this will be advantageous for those subject to test rules under TSCA section 4 and will simplify and aid in their monitoring and compliance.

II. Review of Available Data

A. Production/Use/Exposure

1. *Acrylonitrile.* An estimated 2.5 billion pounds of acrylonitrile are produced annually in the United States (Ref. 1). Acrylonitrile is used in the manufacture of acrylic and monoacrylic fibers. It is also used in the manufacture of resins (Ref. 1).

EPA believes that exposure to acrylonitrile may result due to the conditions under which the large volume of this substance is manufactured, processed, and disposed. For example, according to the National Occupational Exposure Survey (NOES) (1981 through 1983), an estimated 61,500 workers at more than 1,400 plant sites may be exposed to acrylonitrile during sampling, maintenance activities, clean-up of spills, drumming, and bulk loading of the final product (Ref. 1).

In addition, worker and general population exposure may occur as a result of release and/or disposal of over 11 million pounds/year (Refs. 1 and 2). Additional information on potential exposures are discussed in References 1 and 2.

2. *p-Aminophenol.* An estimated 2000 pounds of *p*-aminophenol are produced annually in the United States, while more than 1 million pounds are imported (Ref. 3). *p*-Aminophenol is used as a dye intermediate and as an oxidative dye, particularly for dyeing feathers and fur (Ref. 3).

According to the NOES survey of 1984, an estimated 375 workers may be exposed to *p*-aminophenol (Ref. 49). In addition, *p*-aminophenol is used as a developing agent for photographic processes (Ref. 3). As such, there may be consumer exposure. An estimated 800,000 to 2.2 million consumer photohobbyists who develop their own film and prints may be exposed to *p*-aminophenol in developers (Ref. 4). EPA believes that many users will immerse both hands in developing solutions without the benefit of gloves (Ref. 13). For a more detailed explanation of typical exposure during developing, refer to Hydroquinone; Final Test Rule (50 FR 53145; December 30, 1985) (Ref. 4).

3. *Bromochloromethane.* The amount of bromochloromethane produced annually in the United States and imported is claimed as confidential business information (Ref. 5). Bromochloromethane is used as a fire extinguishing agent and explosion suppressing agent in area protection systems, and as a solvent or sink/float separation medium (Ref. 6).

More than 100 workers are potentially exposed dermally and via inhalation during the manufacture and use of bromochloromethane as an explosion suppressant in area systems (Ref. 6). General population exposure may also occur as a result of air emissions. More than 200,000 pounds of bromochloromethane are potentially released from one site through air emissions from receivers, storage, and vent scrubbers (Ref. 6). This release is estimated to result in human exposures of 75 to 4,320 mg/year (Ref. 35).

4. *Carbon disulfide.* An estimated 360 million pounds of carbon disulfide are produced annually in the United States (Ref. 5). Carbon disulfide is used in the manufacture of carbon tetrachloride, rayon, cellophane, and rubber chemicals, and is also produced as a by-product from the manufacture of carbon black (Ref. 7 and 47).

EPA believes that there may be worker exposure to this substance based on data from the NOES survey. More than 44,000 workers are potentially exposed to carbon disulfide via inhalation in a variety of occupations including janitors, chemical, health, engineering, and electronic technicians, and machine operators, among others (Ref. 47). EPA believes that exposure to the substance will result due to the conditions under which the large volume of carbon disulfide is manufactured, processed, used, and disposed.

In addition, general population exposure also exists through manufacture and disposal. According to the 1988 Toxic Release Inventory (TRI), 88 manufacturing and processing facilities reported estimated total air releases of more than 82 million pounds of carbon disulfide (Ref. 47). Over 150,000 pounds of carbon disulfide was transferred to waste water treatment (WWT) plants from industrial facilities for treatment, while more than 37,000 pounds was released directly into streams. For more information on the exposure potential of carbon disulfide, see Reference 47.

5. *Dodecylphenol.* An estimated 60.7 million pounds of dodecylphenol are produced per year (Ref. 8). Dodecylphenol is used as an intermediate in the manufacture of calcium phenate salts and alkyl phenol ethoxylates (Ref. 8).

During manufacture of dodecylphenol, calcium phenate salts, and dodecylphenol ethoxylates, more than 100 workers may be exposed to dodecylphenol during bulk transfer from tank cars to storage tanks, sampling, quality control analysis, and maintenance, among other activities (Ref. 8). Dermal exposures may range from 1,300 to 3,900 mg/day if gloves are not worn (Ref. 8).

Based on modeling data of two stream flows, releases of dodecylphenol from manufacturing through on-site WWT are estimated to result in human drinking water exposures of 0.46 to 7.5 mg/year (Ref. 9). Releases of dodecylphenol from industrial use through on-site WWT at two streamflows are estimated to result in drinking water exposures of 0.69 to 11 mg/year (Ref. 9).

Because of expected strong sorption of dodecylphenol on WWT sludges, 90 percent of the total water release is estimated to be sorbed to sludge and subsequently landfilled (Ref. 9). If this sludge went to unrestricted landfills, there could be a maximum exposure to individuals of 27 mg/year from groundwater (Ref. 9), assuming the dodecylphenol migrates from the sludge to the groundwater in one year. The extent to which this may occur is uncertain due to the strong sorption of the dodecylphenol on the sludge.

6. *2-Ethylhexanol.* An estimated 570 million pounds of 2-ethylhexanol are produced annually for intermediate uses and for merchant sale (Ref. 5). It is estimated that 11,550 to 45,000 workers are potentially exposed to 2-ethylhexanol or products containing 2-ethylhexanol (Ref. 10). EPA believes that exposure to the substance will result due to the conditions under which the large volume of 2-ethylhexanol is manufactured, processed, distributed in commerce, and used.

In addition, consumer and general population exposure also exists through disposal. 2-Ethylhexanol has been

HeinOnline -- 56 Fed. Reg. 9093 1991

detected in a concentration range of 3 to 5 ppb in the Delaware River, a major source of drinking water for many surrounding cities (Ref. 10). The use of 2-ethylhexanol in defoaming agents for the manufacture of paper products, and its use as a lubricant, may also contribute to environmental and general population exposure (Ref. 10). For more information on the exposure potential for 2-ethylhexanol, refer to the 2-Ethylhexanol; Proposed Test Rule (51 FR 45487; December 19, 1986).

7. *Hexadecanoic acid.* An estimated 9.4 million pounds of hexadecanoic acid are produced annually in the United States (Ref. 11). Hexadecanoic acid is produced and used in the manufacture of soaps/detergents, lube oils, waterproofing, and metallic palmitates (Ref. 11).

According to the NOES survey of 1988, National Institute for Occupational Safety and Health (NIOSH) estimates that more than 50,000 workers may be potentially exposed to hexadecanoic acid in the workplace (Ref. 28). Potential worker exposure may occur during chemical manufacture and use as an intermediate during sampling, drumming, and transferring to reactors. Workers may also be exposed during soap and lube oil processing and use. There is potential for inhalation exposure to particulates if the substance is manufactured and handled as a powder. Potential inhalation exposure could be up to 150 mg/day, while dermal exposure could be up to 3,900 mg/day (Ref. 28).

In addition, millions of consumers and tens of thousands of janitors are expected to be exposed dermally to hexadecanoic acid from its use in a wide variety of commercial and consumer products which involve skin contact (Refs. 11 and 12). Exposure estimates range from 50 mg/year for diluted floor polish to 3,700 mg/year for liquid dishwashing detergent (Ref. 11). Refer to Diethylene Glycol Butyl Ether and Diethylene Glycol Butyl Ether Acetate, Proposed Test Rule (51 FR 27880), for further information on typical exposure from cleaning products (Ref. 12).

Monitoring data revealed maximum concentrations of hexadecanoic acid in industrial effluents from 1.5 to 33,563 ppm (Ref. 11). Human drinking water exposures range from 0.02 mg/year for estimated release from manufacture of soaps and detergents to 12,033 mg/year estimated from monitoring data from the paint and ink manufacturers (Ref. 11). For further information on exposure to hexadecanoic acid, see Reference 11.

8. *o-Hydroxyphenol.* The annual production and importation volume of *o*-hydroxyphenol is approximately 10 million pounds (Ref. 5). *o*-Hydroxyphenol is used as an intermediate in the production of *t*-butyl catechol (an antioxidant), adhesives, and oxidation bases for dyeing furs. It is also formulated as a developer for black and white films (Ref. 13).

Dermal exposure to *o*-hydroxyphenol is estimated to range from 600 to 4,000 mg/day during manufacturing processes (Ref. 13). During manufacture of *t*-butyl catechol and developer, worker exposure to particulates may occur via the dermal route in transferring solid *o*-hydroxyphenol. More than 100 workers may be exposed to concentrations of 1,000 to 4,000 mg/day, while an estimated 600 workers may be exposed in packaging the liquid developer at concentrations of 100 to 800 mg/day (Ref. 13).

Because *o*-hydroxyphenol is used as a component in developers, consumer exposure may also occur. Photohobbyist exposure to *o*-hydroxyphenol is expected to be comparable to that for *p*-aminophenol as discussed in Unit II.A.2 of this preamble.

9. *2-Methylpropanoic acid.* The amount of 2-methylpropanoic acid produced annually in the United States and imported is claimed as confidential business information (Ref. 5). 2-Methylpropanoic acid is manufactured and used as an intermediate in the manufacture of varnish and ethers for solvents (Ref. 14) and in the leather industry as a tanning and deliming agent (Ref. 28). According to the NOES survey of 1988, more than 5,000 workers may be exposed in the workplace to 2-methylpropanoic acid (Ref. 34). Workers may be potentially exposed during chemical manufacture and use as an intermediate during sampling, drumming, and transfer to reactors (Ref. 28). During use in leather tanneries, worker exposure may occur during transfer of components to mixing drums, mixing, transfer to dyeing wheels, operation of dyeing wheels, and clean-up (Ref. 28). Inhalation exposure is estimated to be up to 56 mg/day, while dermal exposure is estimated to be up to 3,900 mg/day (Ref. 28).

Monitoring data revealed maximum concentrations of the substance in the effluents at 9 industrial sites ranging from 8.6 to 14,827 ppm (Ref. 14). General population exposure through drinking water may occur at a range of 0.01 to 14,348 mg/year for estimated release from manufacture of ethers and monitoring data from the organic chemical manufacturers (Ref. 14).

10. *Methyl ester octanoic acid.* The amount of methyl ester octanoic acid produced annually in the United States and imported is claimed as confidential business information (Ref. 5). Methyl ester octanoic acid is produced and used in the synthesis of dyes and ore separators (Ref. 46).

More than 350 workers are estimated to be exposed to methyl ester octanoic acid (Ref. 28). Potential worker exposure may occur during manufacturing and use as a chemical intermediate during sampling, drumming, and transfer to reactors. Exposure to vapor has been estimated to be 15 mg/day, while dermal exposure is estimated to be 3,900 mg/day (Ref. 28).

11. *Terephthalic acid.* An estimated 2.9 billion pounds of terephthalic acid are produced annually in the United States (Ref. 15). Terephthalic acid is used as an intermediate in the manufacture of polyethylene terephthalate (PET) resins. Polymer-grade terephthalic acid is used to make cookware, amorphous nylon used to make plastic autobody parts, solvent-free coating powders, hot-melt adhesives, wire enamels, motor oils and hydraulic fluids, and high performance, low temperature plasticizers; it is also used in electronic applications.

General population exposure to terephthalic acid may occur as a result of air emissions from storage vents, unloading, and transfers during manufacture and use (Ref. 15). Average releases for seven manufacturing facilities are estimated at 41,000 kg/year/site, while user facilities involved in the manufacture of plastics range from 430 to 14,000 kg/site/year based on 1987 TRI data (Ref. 15).

General population exposure may also occur as a result of water releases from disposal of filtrate and decanted liquids and during manufacturing and purification processes (Ref. 15). The average water releases from users of terephthalic acid are estimated based on the 1987 TRI data to range from 0 to 3,000 kg/year/site (Ref. 15). The largest release to a Publicly-Owned Treatment Works (POTW) is 167,000 kg/year/site from a facility which recycles PET bottles to produce fibers (Ref. 15).

In the **Federal Register** of December 10, 1990 (55 FR 50687) EPA deleted terephthalic acid from the list of toxic substances under section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA), also known as Title III of the Superfund Amendments and Reauthorization Act of 1986. By delisting this substance, EPA is relieving facilities of their obligation to report releases of terephthalic acid that occurred during the 1990 calendar year, and thereafter. This relief applies only to reporting requirements under

HeinOnline -- 56 Fed. Reg. 9094 1991

section 313 of EPCRA. If the proposed testing of this substance under TSCA section 4 provides EPA with evidence that terephthalic does meet the section 313 listing criteria, EPA would immediately initiate rulemaking to add terephthalic acid back to the EPCRA section 313 list.

12. *2,4-Toluenediamine.* An estimated 450 million pounds of 2,4-toluenediamine are produced annually in the United States (Ref. 16). 2,4-Toluenediamine is used as an intermediate in the production of toluene diisocyanate and in dyes used for textiles, leather, and fur (Ref. 16).

EPA believes that exposure to 2,4-toluenediamine will result due to the conditions under which the large volume of this substance is manufactured and disposed. An estimated 750 workers are potentially exposed to 2,4-toluenediamine via inhalation during routine process attention, sampling, maintenance, non-routine spills or leaks, and loading of containers to be shipped off-site, and as a result of fugitive emissions from pumps and clean up operations (Ref. 16). According to NIOSH figures, 2,4-toluenediamine levels in the workplace air may range from 0.001 to 0.415 ppm (Ref. 16).

The general population may also be exposed to 2,4-toluenediamine through plant emissions. According to data on toluene diisocyanate manufacture compiled under the Resource Conservation and Recovery Act, more than 365,000 pounds/year of 2,4-toluenediamine are released from manufacturing facilities (Refs. 16 and 17). However, this release figure is based on 1977 production volume data of 407 million pounds and would be expected to be slightly greater given the current production volume of 450 million pounds. For further information on the exposure potential of 2,4-toluenediamine, refer to References 16 and 17.

B. Health Effects

1. *Acrylonitrile.* Murray et al. (Ref. 18) examined the developmental toxicity of ingested and inhaled acrylonitrile in rats. Rats were exposed from day 6 through 15 of gestation to 10, 25, or 65 mg/kg/day by gavage or to 40 or 80 ppm for 6 hours/day via inhalation. Exposure by gavage to doses as low as 25 mg/kg resulted in a dose-related decrease in fetal body weight and increase in the incidence of delayed ossification, as well as a variety of malformations. Similar malformations were seen after inhalation of 40 ppm, which was the lowest dose tested. The lowest observed adverse effect level (LOAEL) for developmental toxicity was 25 mg/kg, and the no observed adverse effect level (NOAEL) was 10 mg/kg.

Willhite et al. (Refs. 19 and 20) gave hamsters an intraperitoneal injection of acrylonitrile on day 8 of gestation. Developmental toxicity was evident after exposure to 1.51 mmol/kg (80 mg/kg) as manifested by increased resorptions and malformations, including encephalocoele and fused or bifurcated ribs.

2. *p-Aminophenol.* Kavlock (Ref. 21) tested 27 substituted phenols using a modified Chernoff/Kavlock screening assay for developmental toxicity. Rats were administered 100, 333, 667, or 1,000 mg/kg of *p*-aminophenol by oral intubation on day 11 of gestation. Exposure to *p*-aminophenol resulted in decreased viability potencies and malformations involving the limbs, tail, and urogenital system.

3. *Bromochloromethane.* Torkelson et al. (Ref. 22), exposed groups of 10 male and 10 female guinea pigs and 2 male and 2 female rabbits to concentrations of 0, 490, or 1,010 ppm bromochloromethane 7 hours/day, 5 days/week for 79 to 82 exposures in 114 days. In the male guinea pig at 1,010 ppm, histological examination of the testes showed decreased spermatogenesis in the tubules, with fibrosis in numerous tubules and only the germinal epithelium remaining in other tubules. In the male rabbit at 1,010 ppm, histological examination showed testicular tubule changes, characterized by decreased spermatogenesis with replacement fibrosis occurring in the tubules.

4. *Carbon disulfide.* In a range finding study, pregnant rabbits were exposed via inhalation to concentrations of 100, 300, 1,000, or 3,000 ppm carbon disulfide for 6 hours/day on days 6 through 19 of gestation (Ref. 36). All animals exposed to 3,000 ppm died. Maternal and developmental toxicity were evident at 1,000 ppm; developmental toxicity was manifested as an increase in resorptions and a reduction in mean litter size.

Tabacova et al. (Ref. 23) exposed maternal (F0) rats to carbon disulfide vapor throughout gestation. Exposure to 100 and 200 mg/m^3 resulted in a dose-related reduction in fetal weight and a high incidence of malformations in the first generation (F1) progeny. After reaching maturity, the F1 females were mated; these dams received no carbon disulfide exposure during pregnancy. Malformations of the same type as those found in the F1 at 100 and 200 mg/m^3 were observed in second generation (F2) progeny. In a subsequent study, Tabacova et al. (Ref. 24) exposed F0 and F1 dams to carbon disulfide vapor throughout the gestation period only. Exposure of the F0 dams to concentrations of 100 and 200 mg/m^3 resulted in a reduction in fetal body weight and a high incidence of malformations in the F1 progeny; malformations were not observed after exposure to 0.03 or 10 mg/m^3. However, the exposure of the F1 dams to 0.03 or 10 mg/m^3 during pregnancy resulted in a high incidence of malformations in the F2 pups; the malformations were of the same type as observed after exposure to higher concentrations of carbon disulfide. In addition, at the higher exposure levels, the incidence of the malformations in the F2 fetuses exceeded that in F1 fetuses by 150 percent.

In addition to the prenatal effects noted above, the studies of Tabacova et al. (Refs. 23 and 24) provided evidence of postnatal developmental toxicity. In the first study, exposure of F0 dams to 100 and 200 mg/m^3 during gestation resulted in a reduction in postnatal viability and body weight in the F1 pups and behavioral changes in both the F1 and F2 (F2 pups received no supposed exposure) pups (Ref. 23). In the second study, behavioral abnormalities were observed in the F1 pups after exposure to 10 mg/m^3, and in the F2 pups after exposure to 0.03 or 10 mg/m^3.

A report by Cai and Bao (1981) reported increased incidences of menstrual disturbances and of pregnancy toxemia in rayon workers (Ref. 48). In the report, evidence was also presented that carbon disulfide can be secreted in mothers' milk.

Lancranjan et al. (Ref. 45) studied testicular changes in workers in a factory who had been exposed to carbon disulfide at average concentrations of 13 to 26 ppm. Disturbances of sexual dynamics were observed in 78 percent of the patients, decreased libido and erection difficulty being the most common problems. Semen analysis revealed that the workers had significantly higher frequencies of asthenospermia, hypospermia, and teratospermia.

5. *Dodecylphenol.* A developmental toxicity study was conducted in rats via gavage and established both a LOAEL of 100 mg/kg and a NOAEL of 20 mg/kg (Ref. 25). At both 100 and 300 mg/kg there was a significant increase in the incidence of delayed ossification. At 300 mg/kg, there was a significant increase in resorptions, a concomitant significant reduction in litter size and mean fetal body weight, and a significant increase in a variety of malformations.

6. *2-Ethylhexanol.* Pregnant rats were administered 2-ethylhexanol by gavage for 10 days in daily doses of 130, 650, or

HeinOnline -- 56 Fed. Reg. 9095 1991

1,300 mg/kg body weight/day (Ref. 26). At the highest dose level, maternal toxicity, including death, was observed. Fetotoxicity was also observed, substantiated by an increase in resorptions and a reduction in mean fetal body weight. There was also a higher frequency of fetuses exhibiting soft tissue variations, skeletal malformations, and retardations. Maternal toxicity and fetotoxicity was also observed in the 650 mg/kg body weight/day group, substantiated by a reduction in mean fetal body weight and an increase in the number of skeletal variations and retardations observed.

7. *Hexadecanoic acid.* There are no developmental toxicity studies conducted with hexadecanoic acid; however, concern for the potential developmental toxicity of hexadecanoic acid is based upon its structural analogy to octanoic acid, which has been found to be developmentally toxic in a rat embryo culture system (Ref. 27). Twelve short chain carboxylic acids were tested in an in vitro screen using a whole rat embryo culture system; 11 of the carboxylic acids, including octanoic acid, exhibited a spectrum of malformations similar to valproic acid, a known human teratogen (Ref. 27).

8. *o-Hydroxyphenol.* Kavlock (Ref. 21) tested 27 substituted phenols using a modified Chernoff/Kavlock screening assay for developmental toxicity. Rats were administered 100, 333, 667, or 1,000 mg/kg of *p*-aminophenol by oral intubation on day 11 of gestation. Exposure to *p*-aminophenol resulted in decreased viability potencies and malformations involving the limbs, tail, and urogenital system.

9. *2-Methylpropanoic acid.* There are no developmental toxicity studies conducted with 2-methylpropanoic acid; however, concern for the potential developmental toxicity of 2-methylpropanoic acid is based upon its structural analogy to 2-ethylhexanoic acid which has been found to be developmentally toxic to rats (Ref. 42) and valproic acid, a known human teratogen (Refs. 27 and 33).

10. *Methyl ester octanoic acid.* There are no developmental toxicity studies conducted with methyl ester octanoic acid; however, concern for the potential developmental toxicity of methyl ester octanoic acid is based upon its structural analogy to octanoic acid, which has been found to be developmentally toxic in a rat embryo culture system (Ref. 27). Twelve short chain carboxylic acids were tested in an in vitro screen using a whole rat embryo culture system; 11 of the carboxylic acids, including octanoic acid, exhibited a spectrum of malformations similar to valproic acid, a known human teratogen (Ref. 27).

11. *Terephthalic acid.* Groups of male and female Wistar and CD rats were exposed to dietary levels of 0, 0.03, 0.125, 0.5, 2.0, or 5.0 percent terephthalic acid for 90 days prior to mating (Ref. 29). Although there was no evidence of reproductive toxicity, there was evidence of postnatal developmental toxicity in both strains. At 2.0 and 5.0 percent terephthalic acid, there was decreased postnatal survival and postnatal body weight. Postnatal body weight data at lower doses was inconclusive.

12. *2,4-Toluenediamine.* There are no developmental toxicity studies conducted with 2,4-toluenediamine; however, data are available on *p*-toluenediamine sulfate. A summary of a study conducted by Hazleton Laboratories (Ref. 30) reports developmental toxicity to the rat at 80 mg/kg and the rabbit at 25 or 50 mg/kg *p*-toluenediamine sulfate. In the rat, evidence of developmental toxicity was demonstrated by increased resorptions and a significant increase in the incidence of skeletal variations. In the rabbit, an increased incidence of intrauterine deaths was demonstrated in both the mid- and high-dose groups. It is possible that maternal and/or developmental toxicity occurred at lower doses since no maternal data and only cursory summary tables of fetal data were included in the study summary.

Male Sprague-Dawley rats were fed 2,4-toluenediamine at dietary concentrations of 0, 0.01, or 0.03 percent for 10 weeks (Ref. 31). After 10 weeks, males were mated with virgin untreated females. Fifty-percent of the high-dose rats were unable to achieve fertilization. In addition, reproductive performance was impaired in the high-dose rats and possibly in the low-dose rats. The mating frequency was reduced in both groups. Microscopic abnormalities were noted in the testes of the high-dose rats, but not in the low-dose rats. Affected testes revealed focal or diffuse hypospermatogenesis.

A similar study was conducted by Thysen et al., (Ref. 32). At the end of the 10-week treatment period, rats in the high-dose group exhibited decreased weight gain. Absolute epididymal and seminal vesicle weights for the high-dose group were significantly lower than control values, but relative organ weights were not different. Total mean sperm counts were decreased in both high and low dose rats. Additionally, at the end of an 11-week recovery period, rats exposed to the high-dose exhibited significantly lower sperm counts and absolute testis and epididymal weights than the control group. Luteinizing hormone levels were higher for the high-dose group males than for the controls at both time-points. Conversely, testosterone levels were lower for this group than for the controls.

III. Findings

A. TSCA section 4(a)(1)(A)(i) and (B)(i) findings

1. *Acrylonitrile.* Under 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, and disposal of acrylonitrile may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that acrylonitrile may pose developmental toxicity is based on an oral developmental toxicity study in rats by Murray et al. (Ref. 18) which establishes both a LOAEL and NOAEL. Refer to Unit II.B.1. of this preamble and Reference 18 for additional details supporting this finding.

More than 61,500 workers are potentially exposed to acrylonitrile in the workplace during sampling, maintenance activities, clean-up of spills, drumming, and bulk loading of the final product, among other activities (Ref. 1). General population exposure can be expected as a result of an estimated 11 million pounds/year of acrylonitrile released to air, land, and water (Ref. 2). Refer to Unit II.A.1. of this preamble and References 1 and 2 for additional details on exposure.

2. *p-Aminophenol.* Under section 4(a)(1)(A)(i), EPA finds that the manufacture, processing, and use of *p*-aminophenol may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that *p*-aminophenol may pose developmental toxicity is based upon a Chernoff/Kavlock screening assay. Data from this study suggest that *p*-aminophenol may cause developmental effects (Ref. 21). Refer to Unit II.B.2. of this preamble and Reference 21 for additional details supporting this finding.

According to the NOES survey of 1984, an estimated 375 workers may be potentially exposed to *p*-aminophenol (Ref. 49). In addition, an estimated 800,000 to 2.2 million consumers may be exposed to *p*-aminophenol when photohobbyists who develop their own film and prints use developers containing these substances (Ref. 3 and 12). Refer to References 3, 12, and 49 for

HeinOnline -- 56 Fed. Reg. 9096 1991

further information on the exposure potential of *p*-aminophenol.

3. *Bromochloromethane.* Under section 4(a)(1)(A)(i), EPA finds that the manufacturing and disposal of bromochloromethane may present an unreasonable risk of injury to human health due to its potential to cause reproductive toxicity and the extent of exposure summarized below. The finding that bromochloromethane may pose reproductive toxicity is based on a subchronic study via the inhalation route in guinea pigs and rabbits by Torkelson et al. (Ref. 22). Male guinea pigs and rabbits experienced decreased spermatogenesis, and fibrosis in numerous tubules, among other effects. Refer to Unit II.B.3. of this preamble and Reference 22 for additional details supporting this finding.

Workers are potentially exposed dermally and via inhalation during the manufacture of bromochloromethane as an explosion suppressant in area systems (Ref. 6). General population exposure may also occur when more than 200,000 pounds/year of bromochloromethane is potentially released to air from a single manufacturing site which may result in exposures ranging from 75 to 4,320 mg/year (Refs. 6 and 35). For more details on exposure, refer to Unit II.A.3. of this preamble and References 6 and 35.

4. *Carbon disulfide.* Under section 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, use, and disposal of carbon disulfide may present an unreasonable risk of injury to human health due to its potential to cause developmental and reproductive toxicity and the extent of exposure summarized below. The finding that carbon disulfide may pose developmental effects is based on studies via inhalation by Tabacova (Refs. 23 and 24). Developmental effects observed include a dose-related reduction in fetal weight and a high incidence of malformations in the F1 progeny. For more information on this study, see Unit II.B.4. of this preamble and References 23 and 24 for additional details supporting this finding.

The finding that carbon disulfide may pose reproductive toxicity is also based on the studies by Tabacova (Refs. 23 and 24) which provide evidence of postnatal developmental toxicity. A report by Cai and Bao reported increased incidences of menstrual disturbances and of pregnancy toxemia in rayon workers (Ref. 48). In addition, Lancranjan et al. observed testicular effects in workers who had been exposed to carbon disulfide (Ref. 45). For more information on these studies, see Unit II.B.4. of this preamble and Reference 23, 24, 45, and 48 for additional details supporting this finding.

More than 44,000 workers in a variety of occupations including chemical, health, and engineering technicians and janitors may be exposed via inhalation to carbon disulfide (Ref. 47). General population exposure via inhalation can be expected as a result of an estimated 82 million pounds released to the air from manufacturing facilities (Ref. 47). In addition, over 187,000 pounds of carbon disulfide were released/transferred from industrial facilities to WWT facilities and directly to water (Ref. 47). Refer to Unit II.A.4. of this preamble and Reference 47 for additional details on exposure.

5. *Dodecylphenol.* Under 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, and disposal of dodecylphenol may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that dodecylphenol may pose developmental toxicity is based upon a TSCA section 8(e) notice (Ref. 25). This submission included a developmental toxicity study via gavage in rats. Data in this notice suggest that dodecylphenol may cause developmental toxicity. Refer to Unit II.B.5. of this preamble and Reference 25 for additional details supporting this finding.

More than 100 workers are potentially exposed to dodecylphenol at concentrations of 1,300 to 3,900 mg/day during manufacture of the substance, calcium phenate salts, and dodecylphenol ethoxylates (Ref. 8). General population exposure through drinking water may also occur as a result of releases to water from manufacturing facilities (Ref. 9). Refer to Unit II.A.5. of this preamble and References 8 and 9 for additional details on exposure.

6. *2-Ethylhexanol.* EPA is basing its developmental toxicity testing requirements for 2-ethylhexanol on the authority of both sections 4(a)(1)(A) and (B) of TSCA.

Under section 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, use, distribution in commerce, and disposal of 2-ethylhexanol may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that 2-ethylhexanol may pose developmental toxicity is based upon a TSCA section 8(e) notice (Ref. 26). Data in this notice suggest that 2-ethylhexanol may cause developmental toxicity (Ref. 26). Refer to Unit II.B.6 of this preamble and Reference 26 for additional details supporting this finding.

An estimated 11,550 to 45,000 workers are potentially exposed to 2-ethylhexanol; in addition, consumer and general population exposure may result through use, distribution in commerce, and disposal (Ref. 10). Refer to Unit II.A.6. of this preamble and Reference 10 for more details on the exposure potential of 2-ethylhexanol.

Under section 4(a)(1)(B)(i), EPA has already found in a final test rule (52 FR 28698) that was not challenged that 2-ethylhexanol is produced in substantial quantities and that there is or may be substantial human exposure from its manufacture, processing, use, distribution in commerce, and disposal. Refer to the 2-Ethylhexanol Proposed Test Rule (51 FR 45487) for additional discussion of the basis for EPA's exposure finding for 2-ethylhexanol (Ref. 10).

7. *Hexadecanoic acid.* Under section 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, use, and disposal of hexadecanoic acid may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that hexadecanoic acid may pose developmental toxicity is based upon its structural analogy to octanoic acid, which has been found to be developmentally toxic in a rat embryo culture system (Ref. 27). Refer to Unit II.B.7. of this preamble and Reference 27 for details supporting this finding for developmental toxicity.

Approximately 50,000 workers are potentially exposed to hexadecanoic acid according to the 1988 NOES survey, while millions of consumers and tens of thousands of janitors are expected to be exposed dermally to a variety of commercial and consumer products which involve skin contact (Refs. 11, 28, and 34). In addition, human drinking water exposure may range from 0.02 to 12,033 mg/year as a result of release from industrial effluents (Ref. 11). Refer to Unit II.A.7. of this preamble and References 11, 12, 28, and 34 for further information on the exposure potential of hexadecanoic acid.

8. *o-Hydroxyphenol.* Under section 4(a)(1)(A)(i), EPA finds that the manufacture, processing, and use of *o*-hydroxyphenol may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that *o*-hydroxyphenol may pose developmental toxicity is based upon a

HeinOnline -- 56 Fed. Reg. 9097 1991

Chernoff/Kavlock screening assay. Data in this report suggests that this substance may cause developmental effects (Ref. 21). Refer to Unit II.B.8. of this preamble and Reference 21 for additional details supporting this finding.

Dermal exposure to *o*-hydroxyphenol during its manufacture is estimated to range from 600 to 4,000 mg/day (Ref. 13). During manufacture of *t*-butyl catechol and packaging of liquid developer, worker exposure may occur at concentrations of 1,000 to 4,000 mg/day in manufacturing and 100 to 800 mg/day in packaging (Ref. 13). In addition, an estimated 800,000 to 2.2 million consumers may be exposed to *o*-hydroxyphenol when photohobbyists who develop their own film and prints use developers containing these substances (Ref. 4 and 13). For more information on the exposure potential of *o*-hydroxyphenol, see Unit II.A.8. of this preamble and References 4 and 13.

9. *2-Methylpropanoic acid.* Under section 4(a)(1)(A)(i), EPA finds that the manufacturing, processing, and disposal of 2-methylpropanoic acid may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that 2-methylpropanoic acid may pose developmental toxicity is based upon its structural analogy to 2-ethylhexanoic acid (Ref. 42) and valproic acid, a known human teratogen (Refs. 27 and 33). Refer to Unit II.B.9. of this preamble and References 27, 33 and 42 for details supporting this finding for developmental toxicity.

More than 5,000 workers may be exposed to 2-methylpropanoic acid in the workplace, while general population exposure through drinking water (from manufacturing and monitoring data) may occur at a range of 0.01 to 14,348 mg/year for several sites (Refs. 14, 28, and 34). Refer to Unit II.A.9. of this preamble and References 14, 28, and 34 for further information on exposure.

10. *Methyl ester octanoic acid.* Under section 4(a)(1)(A)(i), EPA finds that the manufacturing and processing of methyl ester octanoic acid may present an unreasonable risk of injury to human health due to its potential to cause developmental toxicity and the extent of exposure summarized below. The finding that methyl ester octanoic acid may pose developmental toxicity is based upon its structural analogy to octanoic acid, which has been found to be developmentally toxic in a rat embryo culture system (Ref. 27). Refer to Unit II.B.10. of this preamble and Reference 27 for details supporting this finding for developmental toxicity.

More than 350 workers may be potentially exposed to methyl ester octanoic acid in the workplace (Ref. 28). Estimated exposures range from 15 mg/day for inhalation to 3,900 mg/day for dermal contact (Ref. 28). Refer to Unit II.A.10. of this preamble and Reference 28 for further information on exposure.

11. *Terephthalic acid.* Under section 4(a)(1)(A)(i) of TSCA, EPA finds that the manufacturing, processing, and disposal of terephthalic acid may present an unreasonable risk of injury to human health due to its potential to cause reproductive toxicity and the extent of exposure summarized below. The finding that terephthalic acid may pose reproductive effects is based on a study that exposed two strains of rats to dietary concentrations of terephthalic acid for 90 days prior to mating (Ref. 29). Effects including decreased postnatal survival and body weight were observed in both rat strains. Refer to Unit II.B.11. of this preamble and Reference 29 for additional details supporting this finding.

General population exposure near plant sites can be expected through air emissions of terephthalic acid during manufacture and use, and through water releases from disposal of filtrate and decanted liquids during manufacturing and purification processes (Ref. 15). Average air releases for seven manufacturing sites are estimated at 41,000 kg/year/site, while emissions from user facilities range from 430 to 14,000 kg/site/year (Ref. 15). Water releases to a POTW from a recycling facility for PET bottles was estimated at 167,000 kg/year. Refer to Unit II.A.11. of this preamble and Reference 15 for additional details on exposure.

12. *2,4-Toluenediamine.* Under 4(a)(1)(A)(i), EPA finds that the manufacture and disposal of 2,4-toluenediamine may present an unreasonable risk of injury to human health due to its potential to cause developmental and reproductive effects and the extent of exposure summarized below. The finding that 2,4-toluenediamine may pose developmental toxicity is based upon positive data for the salt, *p*-toluenediamine sulfate (Ref. 30). Rats and rabbits administered *p*-toluenediamine sulfate by gavage exhibited an increase in resorptions and skeletal anomalies. Refer to Unit II.B.12. of this preamble and Reference 30 for additional details supporting this finding for developmental toxicity.

The finding that 2,4-toluenediamine may pose reproductive toxicity is based upon a dietary study in which rats were fed 0, 0.01, or 0.03 percent 2,4-toluenediamine (Refs. 31 and 32). In the high-dose group, several effects were observed including reduced weight gain and inability to achieve fertilization. Reproductive performance was also impaired in the high-dose group and possibly in the low-dose group. Refer to Unit II.B.12. of this preamble and References 31 and 32 for additional details supporting this finding for reproductive toxicity.

An estimated 750 workers are potentially exposed to 2,4-toluenediamine in the workplace during routine process attention, sampling, maintenance, non-routine spills or leaks, and loading of containers to be shipped, and as a result of fugitive emissions from pumps and clean up operations (Ref. 16). General population exposure can also be expected as a result of releases to water from manufacturing facilities (Ref. 16). Refer to Unit II.A.12. of this preamble and References 16 and 17 for additional details on exposure.

B. TSCA Section 4(a)(1)(A)(ii) and (B)(ii) Findings

Under section 4(a)(1)(A)(ii) and for one substance under both sections 4(a)(1)(A)(ii) and (B)(ii), EPA finds that there are insufficient data and experience from which the potential health risks from: (1) Manufacturing, processing, use, distribution in commerce, and disposal of 2-ethylhexanol; (2) manufacturing, processing, use, and disposal of carbon disulfide and hexadecanoic acid; (3) manufacturing, processing, and disposal of acrylonitrile, dodecylphenol, 2-methylpropanoic acid, and terephthalic acid; (4) manufacturing, processing, and use of *p*-aminophenol and *o*-hydroxyphenol; (5) manufacturing and disposal of bromochloromethane and 2,4-toluenediamine; and (6) manufacturing and processing of methyl ester octanoic acid can reasonably be determined or predicted.

EPA believes that the guidelines, found at 40 CFR parts 795 through 798, represent state-of-the-art methodology and form the basis for a valid and scientifically acceptable test standard for evaluating the developmental and/or reproductive toxicity of these substances. The available studies are not acceptable to EPA because they do not conform with the guidelines, as detailed in the following Table 2.

HeinOnline -- 56 Fed. Reg. 9098 1991

TABLE 2.—FINDINGS UNDER TSCA SECTION 4(a)(1)(A)(ii)

Chemical	Data insufficiency under TSCA Section 4(a)(1)(A)(ii)	References
Developmental toxicity testing:		
acrylonitrile (107-13-1)	c	37
	e,k,o	38
p-aminophenol (123-30-8)	e, f	33
carbon disulfide (75-15-0)	h, j	39
dodecylphenol (27193-86-8)	c	40
2-ethylhexanol (104-76-7)	c,k	38
	c	41
hexadecanoic acid (57-10-3)	g	33
o-hydroxyphenol (120-80-9)	e, f	33
2-methylpropanoic acid (79-31-2)	g	33, 42
methyl ester octanoic acid (111-11-5)	g	33
2,4-toluenediamine (95-80-7)	a	43, 44
Reproductive toxicity testing:		
Bromochloromethane (74-97-5)	d, f	33
carbon disulfide (75-15-0)	h, j, l	39
terephthalic acid (100-21-0)	d, m, k	15
2,4-toluenediamine (95-80-7)	b, d, n	43, 44

a. Inadequate dosing of animals — the maximum tolerated dose tested was not maternally toxic.
b. Inadequate analysis of effects on one or both sexes and/or only one sex tested.
c. Adequate testing of one species only.
d. Inadequate duration of test — the test was a one-generation test.
e. Inadequate exposure of animals over the critical period of organogenesis.
f. Inadequate test — the test was a screening level test.
g. Positive data exist on an analogue.
h. Inadequate data reported on a number of endpoints including fetal malformations and maternal toxicity.
i. Inadequate controls.
j. Inadequate verification of test dose.
k. Inadequate animal sample size.
l. Inadequate data reported on postnatal behavioral effects.
m. Inadequate data reported on a number of endpoints including male fertility and maternal and pup weights.
n. Inadequate data reported on continuous exposure as modeled by the F generations in a multi-generational study.
o. Inadequate data reported on a number of endpoints including maternal and fetal body weights, fetal sex, and internal or skeletal examination data.

C. TSCA Section (4)(a)(1)(A)(iii) and (B)(iii) Findings

Under section 4(a)(1)(A)(iii) and for one substance under both sections 4(a)(1)(A)(iii) and (B)(iii), EPA finds that testing each of these substances is necessary to develop such data for developmental and/or reproductive toxicity. EPA believes the data resulting from the proposed testing will be relevant to a determination as to the following: (1) Whether manufacturing, processing, use, distribution in commerce, and disposal of 2-ethylhexanol; (2) manufacturing, processing, use, and disposal of carbon disulfide and hexadecanoic acid; (3) manufacturing, processing, and disposal of acrylonitrile, dodecylphenol, 2-methylpropanoic acid, and terephthalic acid; (4) manufacturing, processing, and use of *p*-aminophenol and *o*-hydroxyphenol; (5) manufacturing and disposal of bromochloromethane and 2,4-toluenediamine; and (6) manufacturing and processing of methyl ester octanoic acid does or does not present an unreasonable risk of injury to human health.

D. Section 4(a)(1)(B) findings

With the exception of 2-ethylhexanol for which the finding was made in a previous rulemaking, EPA has chosen not to make section 4(a)(1)(B) findings where it could have for these substances. This was done to conserve resources. EPA may choose at a later date to make such findings for any or all of these substances and does not want to imply that not doing so at this time in any way suggests that such findings could not be made or are inappropriate.

IV. Proposed Rule

A. Proposed Testing and Test Standards

On the basis of the findings provided in Unit III. of this preamble, EPA is proposing developmental and/or reproductive toxicity testing for the 12 substances included in this proposed rule (see Unit I. of this preamble). The tests would be conducted according to specific test guidelines set forth in 40 CFR part 798 and identified in Table 1. The studies are to be conducted in accordance with TSCA Good Laboratory Practice (GLP) Standards in 40 CFR part 792.

To adequately assess health risk to the developing fetus, this rule proposes requiring developmental toxicity testing in at least two mammalian species. For those substances that have an adequate test in one mammalian species, testing is limited to proposing a second mammalian species. Similarly, to adequately assess health risk to reproduction, this rule proposes a standard two-generation reproductive toxicity test.

The oral route is being proposed as the route of administration except as noted. In the instance where EPA has identified positive inhalation data that

HeinOnline -- 56 Fed. Reg. 9099 1991

are inadequate for risk assessment and/or where exposure is primarily via inhalation, testing is being proposed via the inhalation route. Inhalation exposure shall be for 6 hours per day and 5 days per week prior to mating. Throughout the periods of mating, gestation, and lactation, animals shall be exposed for 7 days a week. Pregnant and lactating animals should not be exposed from day 20 to 21 of gestation to day 4 to 5 postnatally.

At this time, EPA is only proposing developmental and/or reproductive toxicity testing for the 12 substances included in this proposed rule. EPA may, in the future, find other data deficiencies for these substances and propose other tests.

B. Test Substances

EPA is proposing that each of the test substances be of the highest percent purity commercially available. EPA has specified relatively pure substances for testing because EPA is interested in evaluating the effects attributable to each of the substances themselves. This requirement lessens the likelihood that any effects seen are due to impurities or additives. EPA believes that the percent purities listed in Table 1 of this preamble are readily available.

C. Persons Required to Test

Because of the findings in Unit III. of this preamble, EPA is proposing that persons who manufacture (including import) and/or process, or who intend to manufacture and/or process one or more of the named test substances, other than as an impurity, at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements in this proposed rule. This period is defined in 40 CFR 791.3(h). By-product manufacturers and importers of one or more of these substances would be considered manufacturers under this rule. As explained in 40 CFR part 790, initially manufacturers but not processors of one or more of these substances would be required to submit letters of intent or exemption applications. Pursuant to a recent amendment to part 790, small quantity research and development manufacturers are not required to submit letters of intent or exemption applications initially. Such manufacturers should consult the **Federal Register** of May 7, 1990 (55 FR 18881) for further details.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for these substances. EPA is interested in evaluating the effects attributable to the substances themselves and has specified relatively pure substances for testing.

D. Reporting Requirements

As required in 40 CFR 799.10, all data developed under the final rule would be conducted and reported in accordance with its TSCA GLP Standards which appear in 40 CFR part 792.

As required by TSCA section 4(b)(1)(C), EPA is proposing specific reporting requirements for each of the proposed test standards as follows:

Final reports for substances which are subject to 40 CFR part 798.4900 or 798.4350 would be due 12 and 15 months, respectively, from the effective date of the final rule; interim progress reports would be due at 6-month intervals beginning 6 months from the effective date of the final rule.

Final reports for substances which are subject to 40 CFR part 798.4700 would be due 29 months from the effective date of the final rule; interim progress reports would be due at 6-month intervals beginning 6 months from the effective date of the final rule.

The effective date of the final rule will be 44 days after the date of its publication in the **Federal Register**.

According to a recent EPA report entitled "EPA Census of the Toxicological Testing Industry", laboratory availability for developmental and reproductive toxicity testing should be adequate to accommodate the testing proposed in this rule (Ref. 50). If potential test sponsors can document that the developmental and/or reproductive toxicity testing proposed in this rule needs to be staggered due to insufficient laboratory availability, thereby necessitating extending the reporting deadlines, EPA proposes the following. Each substance would be ranked according to production and importation volume as reported in the TSCA inventory. Those substances with the largest production/importation volumes would be required to be tested first, followed by those substances with the next largest volumes. If staggered testing is necessary, EPA proposes testing in this order since all of the substances are being proposed for testing due to concern for their hazard potential.

EPA would extend the reporting requirements of the lower production volume substances subject to this rule by an additional 6 months to initially accommodate any shortfall in laboratory capacity. EPA anticipates that laboratory capacity would increase, if necessary, to accommodate the demand created by future amendments to this rule.

V. Issues for Comment

1. EPA solicits additional information on the developmental or reproductive toxicity of the substances in this rule. Such information may cause EPA to alter its decision on the need for testing of one or more of these substances.

2. This proposed rule specifies TSCA test guidelines with minor modifications as the test standards. EPA is soliciting comment as to whether these test guidelines are appropriate and adequate to characterize the developmental and/or reproductive effects of substances listed in Table 1.

3. This rule would require that 10 developmental and 4 reproductive toxicity tests be run concurrently. EPA believes that adequate laboratory capacity exists for conducting this testing within the reporting deadlines. Further, EPA believes that if it were to periodically amend the rule by requiring testing of an additional 15 to 20 substances per year, laboratory facilities would still be able to meet this testing demand. EPA requests comment on laboratory availability and the reporting requirements.

4. Developmental toxicity test guidelines in 40 CFR 798.4900 specify that testing shall be performed on at least two mammalian species. EPA has regularly required two species testing in past test rules to adequately evaluate the potential risk of substances for developmental effects. EPA solicits comments on this procedure.

5. Three of the substances, 2-methylpropanoic acid, hexadecanoic acid, and methyl ester octanoic acid, are being proposed for testing on the basis of structure activity relationships and exposure potential. 2-Methylpropanoic acid is analogous to valproic acid (2-propylpentanoic acid), a known human and experimental animal developmental toxicant and 2-ethylhexanoic acid, an experimental animal developmental toxicant. These substances are all branched, short chain carboxylic acids.

Hexadecanoic acid and methyl ester octanoic acid, straight chain carboxylic acids, are analogous to octanoic acid. Octanoic acid was tested in an *in vitro* screen using a whole rat embryo culture system and exhibited a spectrum of malformations similar to valproic acid, which increases EPA's concern for this class of substances.

In addition to these structure activity relationships, these three substances are high production and/or exposure substances. Testing of these acids will help identify the characteristics of carboxylic acids such as the length of the backbone and position, length, and

HeinOnline -- 56 Fed. Reg. 9100 1991

composition of the branching which may affect biological activity. EPA requests comment on the proposed testing for these members of the class of carboxylic acids and solicits information on alternative substances that the public may feel are more appropriate for testing.

6. Several of the substances proposed in this rule for testing via the oral route are included on the Clean Air Toxics List. For those substances, dosing via the inhalation route may be a more appropriate route of exposure. EPA solicits comment on this issue.

7. The following issues concern the criteria used to select chemicals for testing for this particular rule:

(a) Some have questioned whether, as a matter of policy, the criteria are appropriate for selecting chemicals for developmental and reproductive toxicity. EPA solicits comments on this issue.

(b) Some have questioned whether, as a matter of policy, it is appropriate to use SAR alone without additional criteria being met as the basis for testing. They have questioned whether evidence from SAR is compelling enough to justify testing given other available information. They have also questioned whether the burden/cost of tests for these substances is reasonable given the criteria of SAR and exposure potential. EPA solicits comments on this issue.

(c) Some have questioned whether, as a matter of policy, the receipt of an 8(e) notice is a sufficient basis for testing. EPA solicits comments on this issue.

VI. Economic Analysis of the Proposed Rule

EPA has prepared an economic analysis that evaluates the potential for significant economic impacts on test sponsors as a result of the proposed testing. The economic analysis estimates the costs of conducting the proposed testing for each of the 12 substances, including both laboratory and administrative costs, and evaluates the potential for adverse economic impacts as a result of these test costs, using a comparison between a substance's annualized test costs and its annual revenues.

The estimated total costs of testing for all 12 substances are $2.0 to $2.9 million, including $1.6 to $2.3 million in laboratory costs and $400,000 to $600,000 in administrative costs. The total costs of testing for each substance are as follows: acrylonitrile, dodecylphenol and 2-ethylhexanol— $48,000 to $67,000; *p*-aminophenol, hexadecanoic acid, *o*-hydroxyphenol, and 2-methylpropanoic acid—$92,000 to $129,000; bromochloromethane and terephthalic acid—$240,000 to $357,000; 2,4-toluenediamine—$332,000 to $486,000; carbon disulfide—$573,000 to $875,000.

To evaluate the potential economic impacts of the proposed testing, test costs are annualized and compared with annual revenues. The annualized test costs, using a 7 percent cost of capital over a period of 15 years, are as follows: acrylonitrile, dodecylphenol and 2-ethylhexanol—$5,000 to $7,000; *p*-aminophenol, hexadecanoic acid, *o*-hydroxyphenol, and 2-methylpropanoic acid—$10,000 to $14,000; bromochloromethane and terephthalic acid—$26,000 to $39,000; 2,4-toluenediamine—$36,000 to $53,000; carbon disulfide—$63,000 to $96,000.

Based on the comparison between annual costs and revenues, it appears that for 11 out of the 12 substances the test costs will have no significant adverse economic impacts. The test costs for bromochloromethane may pose some potential for adverse impact. If comments are received which indicate that the impact is greater, a more comprehensive and detailed analysis will be conducted which more precisely predicts the magnitude and distribution of the expected impacts. Refer to the economic analysis contained in the public record for this rulemaking for more detail on test cost estimation and the evaluation of economic impacts.

VII. Availability of Test Facilities and Personnel

As required by section 4(b)(1) of TSCA, EPA determined that there will be available test facilities and personnel to perform the testing specified in this proposed rule. This rule would require concurrent developmental and reproductive toxicity testing of 12 substances. According to a the report entitled "EPA Census of the Toxicological Testing Industry", EPA believes that space within the laboratories is available to adequately accommodate the 10 substances proposed for developmental and the 4 substances proposed for reproductive toxicity testing (Ref. 50). EPA anticipates that laboratory capacity would increase, if necessary, to accommodate the demand created by future amendments to this rule.

VIII. Public Meeting

If requested, EPA will hold a public meeting in Washington, DC after the close of the public comment period. Persons who wish to attend or to present comments at the meeting should call Mary Lou Hewlett, Chemical Testing Branch (202) 475-8162 by April 18, 1991. The meeting is open to the public, but active participation will be limited to EPA representatives and those who requested to comment. Participants are requested to submit copies of their statements by the meeting date. These statements and a transcript of the meeting will become part of EPA's rulemaking record.

IX. Comments Containing Confidential Business Information

All comments will be placed in the public file unless they are clearly labeled as Confidential Business Information (CBI) when they are submitted. While a part of the record, CBI comments will be treated in accordance with 40 CFR part 2. A sanitized version of all CBI comments should be submitted to EPA for the public record.

It is the responsibility of the commenter to comply with 40 CFR part 2 in order that all materials claimed as confidential may be properly protected. This includes, but is not limited to, clearly indicating on the face of the comment (as well as on any associated correspondence) that CBI is included, and marking "CONFIDENTIAL", "TSCA CBI" or a similar designation on the face of each document or attachment in the comment which contains CBI. Should information be put into the public file because of failure to clearly designate its confidential status on the face of the comment, EPA will presume any such information which has been in the public file for more than 30 days to be in the public domain.

X. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42123). In addition, each substance in the rule has a separate docket number. This record contains the basic information considered by EPA in developing this proposal and appropriate **Federal Register** notices. EPA will supplement this record as necessary.

A public version of the record, from which all CBI has been deleted, is available for inspection in the TSCA Public Docket Office, Rm. G004, NE Mall, 401 M St., SW., Washington, DC 20460, from 8:00 a.m. to noon, and 1:00 p.m. to 4:00 p.m. Monday through Friday, except legal holidays.

The record includes the following information:

A. Supporting Documentation

(1) **Federal Register** notices pertaining to this rule consisting of:

HeinOnline -- 56 Fed. Reg. 9101 1991

(a) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (54 FR 34034; August 17, 1989).

(b) Notice of final rule on data reimbursement policy and procedures (48 FR 31786; July 11, 1983).

(2) TSCA test guidelines cited as test standards for this rule.

(3) Communications before proposal consisting of:

(a) Contact reports of telephone conversations.

(b) Meeting summaries including RM1 Meeting. (July 12, 1990).

(4) Reports—published and unpublished factual materials.

(5) Data received under section 8(e) of TSCA.

B. References

(1) United States Environmental Protection Agency. (USEPA). Production exposure profile of acrylonitrile. Russell E. Farris to Frank D. Kover. Existing Chemicals Assessment Division, Washington, DC. (August 10, 1989).

(2) USEPA. Summary document on acrylonitrile. Prepared by Nancy Chiu. Chemical Screening Branch, Office of Toxic Substances, Washington, DC. (July 1990).

(3) Oak Ridge National Laboratory. Chemical hazard information profile on *p*-aminophenol. Prepared by Michael G. Ryon. (March 29, 1984).

(4) USEPA. Hydroquinone; final test rule. (50 FR 53145; December 30, 1985).

(5) USEPA. Economic Impact Analysis of the Multi-Substance Proposed Test Rule on Developmental and Reproductive Toxicity, Non-Confidential version, Washington, DC (July 1990).

(6) USEPA. Occupational exposure/environmental release analysis of bromochloromethane. Prepared by Vanessa E. Rodriguez. Economics and Technology Division, Washington, DC. (May 7, 1990).

(7) USEPA. Summary of exposure information on carbon disulfide obtained from the Toxic Release Inventory System. Prepared by Andrew Battin, Exposure Assessment Division, Washington, DC. (July 1990).

(8) USEPA. Production-exposure profile of dodecylphenol. Larry E. Longanecker to Frank D. Kover. Chemical Screening Branch, Washington, DC. (May 26, 1989).

(9) USEPA. Summary of dodecylphenol environmental exposures screening estimates. Prepared by Conrad Flessner, Jr., Exposure Assessment Division, Washington, DC. (May 16, 1990).

(10) USEPA. 2-Ethylhexanol; proposed test rule (51 FR 45487; December 19, 1986).

(11) USEPA. Exposure assessment for hexadecanoic acid. Christina Cinalli to Clare Stine. Office of Toxic Substances, Washington, DC. (July 1990).

(12) USEPA. Diethylene glycol butyl ether and diethylene glycol butyl ether acetate; proposed test rule (51 FR 27880; August 4, 1986).

(13) USEPA. Production-exposure profile for catechol (*o*-hydroxyphenol). Russell E. Farris to Frank D. Kover, Existing Chemicals Assessment Division, Washington, DC. (1989).

(14) USEPA. Exposure assessment for 2-methylpropanoic acid. Christina Cinalli to Clare Stine. Office of Toxic Substances, Washington, DC. (July 1990).

(15) USEPA. Summary fact sheet on the petition to delist terephthalic acid from section 313 list. Briefing document. Washington, DC. (February 6, 1990).

(16) USEPA. Occupational exposure and environmental release of toluenediamine. Vinay Kumar to Andrea Blaschka. Office of Toxic Substances, Washington, DC. (June 5, 1984).

(17) USEPA. Air releases during manufacture of 2,4-toluenediamine. Vinay Kumar to Joan Lefler. Exposure Assessment Branch, Washington, DC. (1984).

(18) Murray, F., B. Schwetz, K. Nitschke, J. John, J. Norris, and P. Gehring. "Teratology of acrylonitrile given to rats by gavage or by inhalation". *Food and Cosmetics Toxicology* 16:547–551. (1978).

(19) Willhite, C., V. Ferm, and R. Smith. "Teratogenic effects of aliphatic nitriles". *Teratology* 23:317–323. (1981).

(20) Willhite, C., M. Marin-Padilla, V. Ferm, and R. Smith. "Morphogenesis of axial skeletal (dyraphic) disorders induced by aliphatic nitriles". *Teratology* 23:324–333. (1981).

(21) Kavlock, Robert J. "Structure-Activity Relationships in the Developmental Toxicity of Substituted Phenols: In Vivo Effects". *Teratology* 41:43–59. (1990).

(22) Torkelson, T. R., F. Oyen, and V. K. Rowe. "The toxicity of bromochloromethane (methylene chlorobromide) as determined on laboratory animals". *American Industrial Hygiene Association Journal*. 21(4): 275–286. (1960).

(23) Tabacova, S., L. A. Hinkova, and L. Balabaeva. "Carbon disulfide teratogenicity and postnatal effects in rats". *Toxicology Letters*. 2:129–133. (1978).

(24) Tabacova, S., B. Nikiforov, and L. Balabaeva. "Carbon disulphide intrauterine sensitization". *Journal of Applied Toxicology*. 3(5):223–229. (1983).

(25) TSCA section 8(e) submission. Submitted by Monsanto Corporation. Submission No. 8EHQ–0687–0682. (June 17, 1987).

(26) TSCA section 8(e) submission. Submitted by CBI company. Submission No. 8EHQ–0390–0910 S. (May 1, 1990).

(27) Brown, N. A. and M. E. Coakley. "Valproic acid teratogenesis. II. Actions of related acids and potential antagonists and the role of coenzyme A". *Teratology*. 29(2): 20A–21A. (1984).

(28) USEPA. Intra-agency memorandum from Greg Macek to Clare Stine. Office of Toxic Substances, Washington, DC. (July 23, 1990).

(29) Chemical Industry Institute of Toxicology. A 90–day study of terephthalic acid-induced urolithiasis and reproductive performance in Wistar and CD rats. CIIT Docket #11622. The Chemical Industry Institute of Toxicology, Six Davis Drive, Post Office Box 12137, Research Triangle Park, NC 27709. (1982).

(30) Spengler, J., I. Osterburg and R. Korte. "Teratogenic evaluation of *p*-toluendiamine sulfate, Resorcinol, and *p*-aminophenol in rats and rabbits". *Teratology* 33: 31A. (1986).

(31) Thysen, B., S. Varma and E. Bloch. "Reproductive toxicity of 2,4-toluenediamine in the rat. 1. Effect on male fertility". *Journal of Toxicology and Environmental Health* 16: 753–761. (1985).

(32) Thysen, B., E. Bloch and S. Varma. "Reproductive toxicity of 2,4-toluenediamine in the rat: Spermatogenic and hormonal effects". *Journal of Toxicology and Environmental Health* 16: 763–769. (1985).

(33) USEPA. Endpoint test rule for developmental and reproductive toxicity. Intra-agency memorandum. Elaine Francis to Virginia Werling. Office of Toxic Substances, Washington, DC. (April/October 1990).

(34) Syracuse Research Corporation. Technical support document on the health and environmental effects of aliphatic monocarboxylic acids. Syracuse, New York. (September 30, 1988).

(35) USEPA. Bromochloromethane screening exposure assessment. G. Thom to Clare Stine. Office of Toxic Substances. Washington, DC. (May 18, 1990).

(36) TSCA section 8(e) submission. Submitted by Akzo Chemicals Inc. Submission No. 8EHQ–0390–0904. (March 19, 1990).

(37) USEPA. Review of acrylonitrile for Endpoint Test Rule. Intra-agency memorandum. Jennifer Seed to Virginia Werling. Office of Toxic Substances, Washington, DC. (March 30, 1990).

(38) USEPA. Comments on the developmental toxicity studies of acrylonitrile and 2-ethylhexanol. Intraagency memorandum from Jennifer Seed to Clare Stine. Office of Toxic Substances, Washington DC. (July 5, 1990).

(39) USEPA. Chemicals to be considered for the Endpoint Specific Test Rule for Developmental Toxicity. Intra-Agency memorandum. Carole A. Kimmel to Claire Stine. Office of Toxic Substances, Washington, DC. (March 5, 1990).

(40) USEPA. Data review of dodecylphenol for Endpoint Test Rule. Intra-agency memorandum. Jennifer Seed to Virginia Werling, Office of Toxic Substances, Washington DC. (April 2, 1990).

(41) USEPA. Review of Developmental Toxicity Study of 2-ethylhexanol. Intra-agency memorandum. Jennifer Seed to Virginia Werling. Office of Toxic Substances. (March 26, 1990).

(42) USEPA. Review of developmental toxicity studies on 2-ethylhexanoic acid. Intra-agency memorandum. Elaine Francis to Robert Jones. Test Rules Development Branch, Washington, DC. (August 1, 1988).

(43) USEPA. An update on data adequacy for 2,4-toluenediamine. Intra-Agency memorandum. Jennifer Seed to Virginia Werling. Office of Toxic Substances, Washington, DC. (March 1, 1990).

(44) USEPA. Review of studies on the reproductive and developmental toxicity of 2,4-toluenediamine. Intra-Agency memorandum. Marlissa Campbell to Andrea Blaschka. Office of Toxic Substances, Washington, DC. (June 21, 1988).

(45) USDHEW. Occupational exposure to carbon disulfide; Criteria for a recommended

HeinOnline -- 56 Fed. Reg. 9102 1991

standard. III. Biological effects of exposure. (May 1977).

(46) USEPA. Exposure assessment for methyl ester octanoic acid. Christina Cinalli to Clare Stine. Office of Toxic Substances, Washington, DC. (July 1990).

(47) USEPA. Engineering report for carbon disulfide. Kathleen Franklin to Clare Stine. Chemical Testing Branch, Washington, DC. (June 4, 1990).

(48) DOL. Occupational Safety and Health Administration. Air Contaminants; Final Test Rule (54 FR 2332; January 19, 1989).

(49) USEPA. Intra-agency memorandum from Joseph B. Fernandes to Clare Stein. Office of Toxic Substances, Washington, DC. (July 11, 1990).

(50) USEPA. EPA Census of the Toxicological Testing Industry. Office of Toxic Substances, Washington, DC. (June 1990). (Draft Report).

XI. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a rule is "major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that this proposed test rule would not be major because it does not meet any of the criteria set forth in section 1(b) of the Order; i.e., it would not have an annual effect on the economy of at least $100 million, would not cause a major increase in prices, and would not have a significant adverse effect on competition or the ability of US enterprises to compete with foreign enterprises.

This proposed rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (5 U.S.C. 601 et seq., Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, would not have a significant impact on a substantial number of small businesses because: (1) They would not be expected to perform testing themselves or to participate in the organization of the testing effort; (2) they would experience only very minor costs, if any, in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this proposed rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 et seq., and has assigned OMB control number 2070-0033.

Public reporting burden for this collection of information is estimated to vary from 100 to 4,500 hours per respondent with an average of 600 hours per respondent. The estimates include time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, US Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (2070-0033), Washington, DC 20503. The final rule will respond to any OMB or public comments on the information collection requirements contained in this proposal.

List of Subjects in 40 CFR Part 799

Chemicals, Chemical export, Environmental protection, Hazardous substances, Testing laboratories, Reporting and recordkeeping requirements, and Testing.

Dated: February 25,1991.

Victor J. Kimm,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that 40 CFR, Chapter I, Subchapter R, part 799 be amended as follows:

PART 799—[AMENDED]

1. The authority citation for Part 799 would continue to read as follows:

Authority: 15 U.S.C. 2603, 2611, and 2625.

2. By adding § 799.5050 to read as follows:

§ 799.5050 Multi-test requirements for specific chemical substances.

(a) *General testing provisions*—(1) *Identification of test substance.* Table 1 in paragraph (a)(5) of this section identifies those chemical substances that shall be tested in accordance with this section. The purity of each test substance shall be 99 percent or greater, unless otherwise specified in the "Additional testing requirements" column of Table 1 under paragraph (a)(5) of this section.

(2) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture (including import) or process or intend to manufacture or process, including persons who manufacture or process or intend to manufacture or process one or more of the substances in paragraph (a)(5) of this section as a by-product, or who import or intend to import products which contain one or more of the substances in paragraph (a)(5) of this section after the date specified in Table 1 under paragraph (a)(5) of this section to the end of the reimbursement period, shall submit letters of intent to conduct testing, submit study plans, conduct tests and submit data, or submit exemption applications, as specified in this section, subpart A of this part, and parts 790 and 792 of this chapter for single-phase rulemaking. Persons who manufacture, import, or process one or more of the substances in paragraph (a)(5) of this section only as an impurity are not subject to these requirements.

(3) *Applicability of test guidelines.* The guidelines and other test methods cited in Table 1 under paragraph (a)(5) of this section are referenced here as they exist on the effective date of the specific final rule for the individual chemical substance being listed.

(4) *Reporting requirements.* All testing requirements in this section are subject to the submission of interim progress reports every 6 months beginning 6 months after the effective date for the individual chemical substance listed under paragraph (a)(5) of this section, and the deadline for the submission of all final reports is specified in the "limitations and restrictions" column of Table 1 under paragraph (a)(5) of this section.

(5) *Designation of specific chemical substances and applicable testing requirements.* The substances identified in this paragraph by name and CAS number shall be tested in accordance with the designated testing requirements and any additional requirements and limitations specified in the following Table 1 :

HeinOnline -- 56 Fed. Reg. 9103 1991

TABLE 1.—CHEMICAL SUBSTANCES SUBJECT TO TESTING UNDER THIS SECTION

CAS No.	Chemical name/types of testing	Basic testing requirements	(b) Additional testing requirements	Limitations and restrictions	Effective dates
57-10-3	hexadecanoic acid				
	Health effects testing:				
	Developmental toxicity	§ 798.4900		Reports: 12 mo.	(--/--/--)
74-97-5	bromochloromethane				
	Health effects testing:				
	Reproductive toxicity	§ 798.4700		Reports: 29 mo.	(--/--/--)
75-15-0	carbon disulfide				
	Health effects testing:				
	Developmental toxicity	§ 798.4350		Reports: 15 mo.	(--/--/--)
	Reproductive toxicity	§ 798.4700, except paragraphs (c)(4) and (5)(i)	(2)(iii), (3)(i)	Reports: 29 mo.	(--/--/--)
79-31-2	2-methylpropanoic acid				
	Health effects testing:				
	Developmental toxicity	§ 798.4900		Reports: 12 mo.	(--/--/--)
95-80-7	2,4-toluenediamine				
	Health effects testing:				
	Developmental toxicity	§ 798.4900	(4)(i)	Reports: 12 mo.	(--/--/--)
	Reproductive toxicity	§ 798.4700	(4)(i)	Reports: 29 mo.	(--/--/--)
100-21-0	terephthalic acid				
	Health effects testing:				
	Reproductive toxicity	§ 798.4700	(4)(i)	Reports: 29 mo.	(--/--/--)
104-76-7	2-Ethylhexanol				
	Health effects testing:				
	Developmental toxicity	§ 798.4900, except paragraph (e)(1)(i)	(1)(i)	Reports: 12 mo.	(--/--/--)
107-13-1	acrylonitrile				
	Health effects testing:				
	Developmental toxicity	§ 798.4900, except paragraph (e)(1)(i)	(1)(i)	Reports: 12 mo.	(--/--/--)
111-11-5	methyl ester octanoic acid				
	Health effects testing:				
	Developmental toxicity	§ 798.4900		Reports: 12 mo.	(--/--/--)
120-80-9	*o*-hydroxyphenol				
	Health effects testing:				
	Developmental toxicity	§ 798.4900		Reports: 12 mo.	(--/--/--)
123-30-8	*p*-aminophenol				
	Health effects testing:				
	Developmental toxicity	§ 798.4900	(4)(i)	Reports: 12 mo.	(--/--/--)
27193-86-8	dodecylphenol				
	Health effects testing:				
	Developmental toxicity	§ 798.4900, except paragraph (e)(1)(i)	(1)(i)	Reports: 12 mo.	(--/--/--)

(b) *Additional requirements.* For the purposes of the specific chemical substances subject to the requirements of this section, the following additional requirements apply when cited for the specific chemical substance in the "(b) Additional testing requirements" column in Table 1 under paragraph (a)(5) of this section:

(1) *Species*—(i) *Mammals.* A mammalian species other than the rat shall be used as the test species. Commonly used species include the mouse, rabbit, and hamster. If other mammalian species are used, the tester shall provide justification/reasoning for their selection. Commonly used laboratory strains shall be employed. The strain shall not have low fecundity and shall preferably be characterized for its sensitivity to developmental toxins.

(ii) The test species shall be the rat.

(2) *Duration and frequency of exposure.* (i) Animals shall be exposed for 6 hours per day for 1 day.

(ii) Animals shall be exposed for 6 hours per day, 5 days per week for a 90-day period.

(iii) The animals shall be exposed to the test substance for 6 hours per day and 5 days per week, prior to mating. Throughout the periods of mating, gestation, and lactation, animals shall be exposed for 7 days a week. Pregnant and lactating animals should not be exposed from day 20 to 21 of gestation to day 4 to 5 postnatally.

(iv) - (xix) [Reserved]

(xx) A multiple schedule shall be employed. Fixed ratio and differential reinforcement of low rate contingencies

HeinOnline -- 56 Fed. Reg. 9104 1991

shall alternate throughout daily test sessions of at least 60 minutes duration.

(3) *Route of exposure.* (i) Animals shall be exposed via the inhalation route.

(ii) [Reserved]

(4) *Percent purity.* The percent purity for the designated substances shall be 99 percent or greater, as specified in paragraph (a)(1) of this section. However, an alternate percent purity shall be used if referenced in the "Additional testing requirements" column of Table 1 under paragraph (a)(5) of this section. The alternate percent purities are:

(i) 98 percent pure or greater.

(ii) 97 percent pure or greater.

(iii) 96 percent pure or greater.

(iv) 95 percent pure or greater.

[FR Doc. 91-5012 Filed 3-1-91; 8:45 am]

BILLING CODE 6560-50-F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42134; FRL 3774-7]

Multi-substance Rule for the Testing of Neurotoxicity

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing a test rule, under section 4 of the Toxic Substances Control Act (TSCA), that would require manufacturers and processors of 10 substances to conduct testing for neurotoxicity. The 10 substances are related in that all are volatile solvents with high production volumes, occupational exposure, consumer exposure, and presence in and/or release to the environment. This rule proposes cognitive function and screening level tests for neurotoxicity where such data are not available for that substance. This proposed rule supports EPA's effort to require the testing of many substances for a single effect or endpoint, in this case neurotoxicity.

DATES: Submit written comments on or before May 3, 1991. If persons request an opportunity to submit oral comments by April 18, 1991, EPA will hold a public meeting on this rule in Washington, DC. For further information on arranging to speak at the meeting, see Unit VIII. of this preamble.

ADDRESSES: Submit written comments, identified by the docket number (OPTS-42134), in triplicate to: TSCA Public Docket Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. G004, NE Mall, 401 M St., SW., Washington, DC 20460. A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 am to noon, and 1 pm to 4 pm, Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Michael M. Stahl, Director, Environmental Assistance Division (TS-799), Office of Toxic Substances, Rm. E-543B, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: EPA is proposing a test rule under section 4(a) of TSCA to obtain neurotoxicity data for 10 volatile substances that have substantial production, for which there is or may be substantial human exposure, and for which data on neurotoxicity are insufficient.

I. Introduction

A. Background

EPA has developed this multi-substance test rule to test a number of substances for a single toxicological endpoint, neurotoxicity. EPA believes that available data on the neurotoxic effects of many chemicals in commerce, to which millions of Americans are exposed, are insufficient to evaluate human health risk and has initiated this program to test them. This approach is supported by a recent study by the Office of Technology Assessment (OTA) on the health threat from neurotoxic chemicals (Ref. 1). The OTA study stated that little is known about the potentially adverse effects of thousands of chemicals on the nervous system because of inadequate research and testing. EPA intends this proposed rule to be the first in a series of rules to obtain data on neurotoxicity.

Organic solvents were targeted for the first neurotoxicity endpoint rule because as a group they are thought to be associated with neurological effects and because they contain some high exposure chemicals (Ref. 4). Each solvent in this rule has a high vapor pressure, and their widespread use in the workplace and by consumers assures that many people will have acute and/or chronic exposure. Although some neurotoxicity data is available on most of these solvents, animal testing using methods equivalent to the TSCA neurotoxicity guidelines is rare. It is anticipated that data derived from testing according to these guidelines will not only screen for certain neurotoxic effects of each solvent, but will also indicate the relative safety of the tested solvents for this endpoint.

During the development of this proposed test rule EPA considered two basic approaches to chemical selection. The first approach was to identify those chemicals that are believed to cause health effects in man or laboratory animals, based on toxicity studies and/or structural-activity relationships (SAR), and to then select those with the highest exposure potential. This is the approach EPA followed in construction of the developmental and reproductive toxicity endpoint rule published elsewhere in this issue of the **Federal Register** The second approach was to select chemicals solely on exposure potential. EPA determined that the second approach was more appropriate for selecting chemicals for the neurotoxicity test rule. For some types of test rules the first approach of basing chemical selection on available toxicity studies or SAR is preferable. In the case of an endpoint like neurotoxicity, however, EPA does not believe that reliance on available toxicity studies and SAR is the best approach for the following reasons. The existing literature and knowledge of SAR are fairly sparse on the neurotoxic effects of organic solvents. In addition, the few studies that have been identified are typically short-term or high-dose studies which, although they might support concern for more testing (as is the case for 6 of the 10 chemicals in this proposed rule), do not necessarily reflect higher potency or hazard potential than non-tested chemicals. Because of this EPA chose the second approach, i.e., selection based on exposure. By selecting those organic solvents with high exposure the limited resources available for testing would be focused on the few chemicals with widespread use and human exposure, instead of requiring EPA to consider the whole universe of organic solvents for testing.

The initial selection of specific organic solvents by EPA as candidates for testing was based on five criteria: production level greater than 10 million pounds, occupational exposure greater than 10,000 workers, consumer exposure, vapor pressure greater than 5 mmHg, and presence in or release to the environment (Ref. 2). Production data from 1986 to 1988 were considered in prioritizing the substances by production volume. Occupational exposure data were obtained from the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and

HeinOnline -- 56 Fed. Reg. 9105 1991