ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42084; FRL-3008-8]

Methylcyclopentane and Commercial Hexane; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: In response to the Interagency Testing Committee's (ITC) designation of methylcyclopentane (MCP; CAS No. 96-37-7) for health effects testing, EPA is proposing that manufacturers and processors of MCP as well as manufacturers and processors of commercial hexane other than as impurities be required under section 4(a)(1)(A) of the Toxic Substances Control Act (TSCA) to perform testing of MCP for neurotoxicity (schedule-controlled operant behavior, neuropathology, functional observation battery, motor activity, and developmental neurotoxicity screen), subchronic toxicity, and inhalation and dermal pharmacokinetics (absorption, distribution, metabolism, and excretion). The Agency also believes that it could find under section 4(a)(1)(B) that there is the potential for substantial human exposure to MCP from its manufacture, processing, and use as a substantial component of commercial hexane and other mixed hexane products. EPA is proposing the testing of MCP because it is the second largest constituent of commercial hexane. The largest constituent, *n*-hexane, is a known neurotoxicant undergoing testing by the National Toxicology Program (NTP) for other toxicological endpoints. The Agency has inadequate information to characterize the toxicity of MCP. If industry should consider reformulating commercial hexane to reduce its *n*-hexane content, the content of MCP in the mixture would increase. Therefore, the Agency believes that testing MCP is necessary to determine its potential impact on human health.

Because there is substantial production and widespread exposure to commercial hexane and because current exposure to MCP occurs primarily following exposure to commercial hexane, EPA is also proposing under section 4(a)(1)(B) of TSCA that manufacturers and processors of commercial hexane other than as an impurity be required to perform testing of this substance for acute and subchronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, mutagenicity, neurotoxicity (schedule-controlled operant behavior, neuropathology, functional observation battery, and motor activity), and inhalation and dermal pharmacokinetics (absorption, distribution, metabolism and excretion).

DATES: Submit written comments on or before July 14, 1986. If persons request an opportunity to submit oral comments by June 30, 1986, 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.

ADDRESS: Submit written comments identified by the document control number (OPTS-42084) in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-108, 401 M St. SW., Washington, DC 20460.

A public version of the administrative record supporting this action is available for inspection at the above address from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St. SW., Washington DC 20460, Toll Free: (800-424-9065), In Washington, DC.: (554-1404), Outside the USA: (Operator--202-554-1404).

SUPPLEMENTARY INFORMATION: EPA is issuing a proposed test rule for MCP and commercial hexane under section 4(a) of TSCA in response to the ITC's designation of MCP for health effects testing consideration. Testing is being proposed for commercial hexane because there is widespread exposure to commercial hexane and because current exposure to MCP occurs primarily following exposure to commercial hexane. The Agency has concluded that existing data are inadequate to assess the risks to health posed by exposure to MCP and commercial hexane and that testing of both substances is necessary to develop such data.

I. Introduction

A. ITC Recommendation

TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.)* established the ITC under section 4(e) to recommend to EPA a list of chemicals to be considered for testing under section 4(a) of the Act. The ITC designated methylcyclopentane (MCP; CAS No. 96-37-7) for priority consideration for health effects testing in its 16th Report, published in the **Federal Register** of May 21, 1985 (50 FR 20930). The ITC recommended that MCP be tested for health effects including neurotoxicity, cardiotoxicity, oncogenicity, genotoxicity, teratogenicity, and reproductive effects. The rationale for conducting these tests was based on: (1) The potentially high exposure of the general population to MCP through its presence in commercial hexane solvents and gasoline; (2) the large number of workers (over one million) thought to have been potentially exposed to MCP; and (3) the irrelevance of existing toxicity studies in which animals were dosed orally rather than by inhalation, the route by which the general population is more likely to be exposed to MCP. No separate justification for cardiotoxicity or oncogencity testing was provided in the Report.

Because of its high volatility and moderate water solubility, the ITC expected MCP to partition into the atmosphere where it would be rapidly degraded. Therefore, the ITC did not recommend testing for environmental effects.

B. Test Rule Development Under TSCA

Under section 4(a) of TSCA, the EPA shall by rule require testing of a chemical substance or mixture to develop appropriate test data if the Administrator finds that:

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(A) (i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment,

(ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B) (i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture,

(ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight-of-evidence approach in making a section 4(a)(1)(A)(i) finding; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the finding under section 4(a)(1)(B)(i), EPA considers only production, exposure, and release information to determine if there is or may be substantial production and significant or substantial human exposure or substantial release to the environment. For the findings under sections 4(a)(1) (A)(ii) and (B)(ii), EPA examines toxicity and fate studies to determine if existing information is adequate to reasonably determine or predict the effects of human exposure to, or environmental release of, the chemical. In making the finding under section 4(a)(1) (A)(iii) or (B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agnecy might require would be capable of developing the necessary information.

EPA's process for determining when these findings apply is described in detail in EPA's first and second proposed test rules, published in the **Federal Register** of July 18, 1980 (45 FR 48524) and June 5, 1981 (46 FR 30300). The section 4(a)(1)(A) findings are discussed at 46 FR 48524 and 46 FR 30300, and the section 4(a)(1)(B) findings are discused at 46 FR 30300.

In evaluating the ITC's testing recommendations concerning MCP, EPA considered all available relevant information including the following: information presented in the ITC's report recommending testing consideration; production volume, use, exposure, and release information reported by manufacturers of MCP under the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 716) concerning MCP; and published and unpublished data on MCP and commercial hexane available to the Agency. From its evaluation, as described in this proposed rule, EPA is proposing health effects testing requirements for MCP under section 4(a)(1)(A). Because there is substantial production and widespread exposure to commercial hexane and because current exposure to MCP occurs primarily following exposure to commercial hexane, EPA is also proposing that manufacturers and processors of commercial hexane be required to perform testing of this substance for health effects under section 4(a)(1)(B).

II. Review of Available Data

A. Chemical Profile

1. *MCP.* MCP is a colorless, flammable liquid with a sweet odor (Ref. 1). At 25 ° C, MCP has a moderate water solubility of 42 mg/l (Ref. 2). Its vapor pressure is 100 mm Hg at 17.9° C (Ref. 3) and 233 mm Hg at 37.8° C (Ref. 4), and its specific gravity is 0.750 g/ml at 20/4 ° C (Ref. 5). The log octanol/water partition coefficient (K_{ow}) is estimated as 3.31 (Ref. 6). A log soil/sediment-absorption coefficient (K_{oc}) is estimated as 3.18 (Ref. 6). MCP has an estimated atmospheric half-life of 1.97 days and an estimated Henry's law constant of 0.322 atm-m^3/mole (Ref. 6). Because of its high volatility and moderate water solubility, MCP is expected to partition into the atmosphere, where it would be rapidly degraded by reaction in the vapor phase with hydroxyl radicals (Ref. 6).

2. *Commercial hexane.* MCP is one of several C_6 hydrocarbons found in commercial hexane (Ref. 9). Normal hexane (*n*-hexane; CAS No. 110-54-3), sometimes known as "hexane," is the saturated straight-chain hydrocarbon with the molecular formula C_6H_{14} (Ref. 9). It is a clear, volatile liquid with a molecular weight of 86.17 daltons and a specific gravity of 0.660 g/ml at 20° C (Ref. 13). *n*-Hexane solidifies between −95 and −100° C, boils at 68.95° C, and has a vapor pressure of 150 mm Hg at 24.8° C (Ref. 13). At room temperature, *n*-hexane has a faint, peculiar odor (Ref. 41). Insoluble in water, *n*-hexane is fairly soluble in organic solvents, e.g., alcohol, ether, and chloroform (Ref. 41).

While in the singular sense "hexane" refers to *n*-hexane, in the plural sense "hexanes" refer to the straight chain compound *n*-hexane, as well as the branched hydrocarbons with the same C_6H_{14} molecular formula known as isohexanes, which include 2-methylpentane (2-MP; CAS No. 107-83-5), 3-methylpentane (3-MP; CAS No. 96-14-0), 2,2-dimethylbutane (2,2-DMB; CAS No. 75-83-2), and 2,3-dimethylbutane (2,3-DMB; CAS No. 79-29-8) (Ref. 9). Commercial hexane is a narrow-boiling mixture of *n*-hexane, the isohexanes 2-MP, 3-MP, 2,2-DMB, 2,3-DMB, with MCP, cyclohexane (CAS No. 110-82-7), and benzene (CAS No. 17-43-2) (Ref. (0. Minor amounts of C_5 and C_7 hydrocarbons may be present (Refs. 9) and 13). Refer to Figure 1 below.

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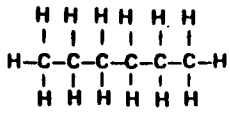
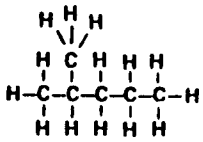
FIGURE 1 -- C_6 HYDROCARBONS PRESENT IN COMMERCIAL HEXANE

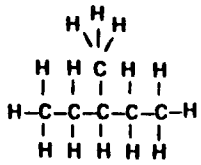
1. n-Hexane
CAS No. 110-54-3



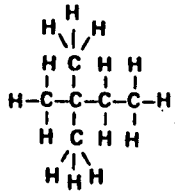
2. 2-Methylpentane (2-MP)
CAS No. 107-83-5



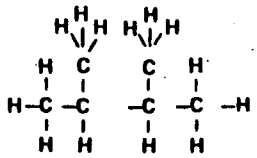
3. 3-Methylpentane (3-MP)
CAS No. 96-14-0



4. 2,2-Dimethylbutane (2,2-DMB)
CAS No. 75-83-2

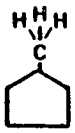


5. 2,3-Dimethylbutane (2,3-DMB)
CAS No. 79-29-8



6. Cyclohexane
CAS No. 110-82-7

7. Methylcyclopentane (MCP)
CAS No. 96-37-7



8. Benzene
CAS No. 71-43-2

B. Production

1. *MCP.* MCP occurs naturally in crude oil and natural gas liquids and therefore is a constituent of some refinery hydrocarbon processing streams, e.g., straight-run gasoline, and finished petroleum products, e.g., jet fuel and hexane solvent (Ref. 7). MCP also is present as a nonisolated, in-stream component of a feed stream used in the production of hexane isomers, e.g., *n*-hexane, and cyclohexane, from C_6 hydrocarbon petroleum fractions in a closed-loop system (Refs. 8, 21, and 22). Phillips Petroleum Co. (Phillips), the sole manufacturer of isolated MCP, once separated MCP from the naphtha stream that was used to produce 98-percent cyclohexane. This naphtha stream consisted of benzene and C_6 naphthenes, 60 to 80 percent of which is MCP. While Phillips no longer isolates MCP for sale, production of MCP by this process was incidental to the production of cyclohexane (Ref. 20) and continues to occur.

According to the public portion of the TSCA Inventory, production of MCP in 1977 was 50 to 100 million pounds (Ref. 15). Phillips' Philtex Plant in Borger, Texas, is cited in the 1985 SRI Directory of Chemical Producers as the sole manufacturer of MCP (Ref. 16). However, Phillips pointed out that there has been no production of pure MCP in over 3 years, and that during each of the last years it was manufactured, 1980 through 1982, an average of 435 pounds of pure MCP was sold to laboratories for research (Ref. 8). This amount reflects the 0 to 1,000 pounds of MCP listed in the TSCA Inventory.

In addition, Phillips stated that the 50–100 million pounds of MCP reported in the TSCA Inventory as having been produced at its Sweeney, Texas, plant does not reflect production of pure MCP for sale, but reflects the amount of MCP used as an in-stream component which is converted into cyclohexane (Ref. 8).

The second manufacturer listed on the TSCA Inventory, Ashland Chemical Co., produced a maximum of 17,000 pounds of MCP per year as a byproduct of the manufacture of a high-energy fuel, RJ4, in previous years (Ref. 17). Ashland has recently lost the RJ4 contract to Koch Chemical Company and so will not produce any MCP for at least the next 4 years (Ref. 18). Koch chemical claims that its RJ4 fuel does not contain MCP (Ref. 50). Ashland used the byproduct MCP as a boiler fuel (Ref. 17).

Since the 1977 TSCA Inventory was conducted, PGP Gas Products, the third manufacturer listed on the TSCA Inventory, has split into two companies,

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Valero Energy Corp. and Perry Gas Processors, both of Houston, Texas. Neither company currently produces MCP (Ref. 19).

2. *Commercial hexane.* There are three major types of commercial hexane, each produced in a different manner (Ref. 9). The composition of a commercial hexane depends upon the choice of feedstock and the process used to separate components (Ref. 9). The three most commonly used feedstocks are staight-run gasolines distilled from crude oil, the higher boiling portion of the liquid product stripped from natural gas, and a refinery stream known as "BTX raffinate," which is the paraffinic portion that remains after the removal of benzene, toluene, and xylene from a naphtha which has been refined to convert naphthalenes to aromatics (Ref. 41). While there is no current production of pure MCP, it is a major component of commercial hexane (8–19 percent), a high-volume solvent (Ref. 9). According to the International Trade Commission, approximately 500 million pounds of hexane were produced in 1984 (Ref. 10). This translates into 40–95 million pounds of MCP. Most of the exposures occur to the commercial hexane mixture rather than to pure MCP.

Commercial hexane A, or solvent grade, derived from the fractionation of straight-run gasoline (Ref. 41), has high benzene and sulfur contents and contains approximately 64 liquid volume percent *n*-hexane and 19 liquid volume percent MCP (Ref. 9). Commercial hexane B, or food grade, recovered in a refinery operation, is purer than A and is low in benzene, sulfur, and olefins (Ref. 9). It contains approximately 81 liquid volume percent *n*-hexane and 12 liquid volume percent MCP. Commercial hexane C, or reaction grade, is the result of extremely close fractionation of a natural gas liquid stock (Ref. 41). This relatively pure commercial hexane is low in impurities and contains approximately 88 liquid volume percent *n*-hexane and 8 liquid volume percent MCP (Ref. 9). EPA notes that as the percent of *n*-hexane increases, the percent of MCP decreases in commercial hexane.

According to EPA's economic analysis for this proposed rule (Ref. 23), commercial hexane is produced by several companies. Individual plant capacities are not available, but producers include Phillips Petroleum Co. (Borger, Texas, and Sweeney, Texas), Pennzoil Co. (Shreveport, Louisiana), Ashland Oil, Charter International Oil, Chemical Exchange Industries, Exxon Chemical Americas, Shell Oil, and Union Oil Co. of California. As industry conditions change from time to time, it is possible some of these producers do not currently manufacture hexane but they have been listed in trade sources as producers in recent years.

C. Uses

1. *MCP.* MCP can be used as a synthesis intermediate, as an extractive solvent, and as an azeotropic distillation agent (Ref. 5). Most of the in-stream MCP in the production of hexane isomers is converted into cyclohexane by Phillips (Ref. 8). Phillips at one time sold 99.9+ percent research grade, 99.5+ percent pure grade, 95+ percent technical grade, and 60 percent commercial grade MCP preparations to laboratories or research facilities (Ref. 20).

2. *Commercial hexane.* Commercial hexane A is used in motor fuels, commercial hexane B as a solvent to extract seed oils, and commercial hexane C as a reaction medium for various polymerization reactions and to formulate various products (Ref. 9). According to Kirk-Othmer (Ref. 9), the greatest volume of commercial hexane B is used during the extraction of oils from soybeans, cottonseed, flaxseed, safflower seed, corn germ, peanuts, and other minor crops. High solvency for the oil that is to be extracted, low boiling point to facilitate separation of the oil from the meal, low benzene content, and low cost are properties of commercial hexane B which have made it the predominant solvent for oil seed extraction (Ref. 9). These same properties apparently make commercial hexane B a desirable reaction medium and solvent in the manufacture of polyolefins, synthetic rubbers, and pharmaceuticals. When it is necessary to use a solvent which has been treated to reduce impurities to low levels, commercial hexane C may be used in polymerization reactions. It is also used as a component of quick-drying rubber cements and certain 2-solvent-system adhesives where it controls viscosity and reduces drying time. In addition, commercial hexane C is used in the preparation of lacquers and printing inks requiring a quick-drying diluent (Ref. 9).

D. Human Exposure

1. *Occupational exposure.* a. *MCP.* Although isolated MCP is currently not manufactured for sale, its presence in various hexane-containing refinery streams and products leads to widespread exposure of workers to MCP along with other C_6 hydrocarbons. The ITC's concern for occupational exposure to MCP was based upon the National Occupational Hazard Survey (NOHS) of 1972–74 in which 1,058,700 workers in 130 occupations were estimated to have been potentially exposed to MCP (Ref. 11). Phillips correctly noted that this estimate was high (Ref. 8). Only 3 percent of the observations had trade name products containing MCP. MCP was not seen in the workplace in its pure form.

Subsequently, the National Institute for Occupational Safety and Health (NIOSH) estimated that there are approximately 38,000 workers with potential exposure to either MCP itself or in a trade name product (Ref. 11). The data from the survey indicate that occupations involving contact with petroleum-based products, i.e., fuels, paints, and solvents, contain the largest number of exposed workers. A study by Brugnone *et al.* has established a correlation between environmental, alveolar, and blood MCP levels after exposure of shoe workers to solvents used in that industry (Ref. 40). EPA believes that this correlation, together with the NOHS survey and NIOSH exposure estimates, supports the concern for widespread worker exposure to MCP.

When Phillips examined 1,580 area samples at 104 locations and 5,589 personal samples at 72 locations for MCP, the average 8-hour time-weighted average (TWA) for all the samples was 0.25 ppm (Ref. 8). Personal sampling measurements for MCP ranged from <1ppm to 48 ppm (Ref. 12). These monitoring data were obtained from service stations, exploration/production facilities, chemical plants, and refineries (Ref. 12).

While EPA is not basing its findings upon MCP's presence in gasoline, gas station employees are expected to be exposed to MCP. Although no exposure data exist for these workers, the American Petroleum Institute (API) has predicted exposures ranging from 0.04 to 0.95 ppm (TWA) using an API theoretical model (Ref. 7). API stated that the high end of the range represented a worst-case exposure estimate (Ref. 7).

There is neither an Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) (29 CFR 1910.1000, Table Z–1) nor an American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) (Ref. 13) for MCP.

b. *Commercial hexane.* According to the National Occupational Exposure Survey (NOES) of April 3, 1985, 83,000 workers were estimated to have actual exposure to hexane solvents. Of these,

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12,576 were women (Ref. 42). Since there is no CAS Number for commercial hexane, EPA presumes that the bulk of the NOES estimate represents exposure to commercial hexanes. There are neither OSHA PELs (29 CFR 1910.1000, Table Z-1) nor ACGIH TLVs (Ref. 13) for the major components of commercial hexane (MCP, 2-MP, and 3-MP) other than *n*-hexane. There is a 500 ppm PEL and a 50 ppm TLV for *n*-hexane. There is a 500 ppm TLV and a 1,000 ppm STEL for hexane isomers other than *n*-hexane. Phillips has a corporate standard of 100 ppm for hexanes (Ref. 14).

2. *General population exposure.* a. *MCP.* Although isolated MCP is currently not manufactured for sale, its presence in various hexane-containing refinery streams and products leads to widespread exposure of the general population to MCP along with other C_6 hydrocarbons. There are numerous human-generated sources of MCP. It is estimated that approximately 179 million pounds of MCP are released by oil spills, evaporation of gasoline from gasoline stations and hydrocarbon emissions from land transportation vehicles (Ref. 24). Other potential sources of MCP release that cannot be quantified are combustion of JP-4 jet fuel, deliberate venting of waste hydrocarbon gases, and dumping of formation waters (water produced with oil and gas) associated with offshore crude oil production operations.

MCP has been detected 9 times at $<10\mu g/1$ and once at 10 to 100 $\mu g/1$ in 63 samples of industrial waste water effluents (Ref. 38). MCP also has been detected and quantified in underwater hydrocarbon vents and formation water from offshore oil production facilities (Ref. 25). Having examined MCP's environmental fate, EPA believes that virtually all MCP released into the environment will partition into the atmosphere (Ref. 6).

Furthermore, a number of studies have been conducted in which MCP has been quantified or simply detected in air (Refer to Ref. 6). MCP has been detected both outdoors in air surrounding automotive painting plants when *n*-hexane is used as a paint diluent (Ref. 32) as well as in four indoor telephone control offices and one telephone business office in five States (ppb range) (Ref. 39). In addition, MCP is widespread in urban air, probably due to its presence in automobile exhaust, as discussed above. Although a measured atmospheric half-life of MCP is unavailable, the estimated half-life of 1.97 days suggests that released MCP will not persist in the atmosphere, although constant replenishment near urban areas and petroleum refining and processing facilities may establish steady-state concentrations (Ref. 6).

MCP has been detected as a constitutent ($\leqslant$1.0 liquid volume percent) of commercial hexane solvents used in chemical analyses (Ref. 31). *n*-Hexane of unspecified grade is used as a paint diluent (Ref. 5) and several studies indicate the release of MCP from automotive painting plants along with *n*-hexane, 2-MP, and 3-MP (Refs. 32, 33, and 34).

The potential for general population exposure to MCP is high, since the results of monitoring surveys indicate that MCP has been detected in air, water, and human body fluids. Results from an EPA monitoring survey of human breast milk indicated that three of the seven components of commercial hexane were qualitatively identified in breast milk samples: *n*-hexane—8/8 samples; MCP—6/8 samples; and cyclohexane—5/8 samples (Refs. 36 and 37). In this survey, samples of mother's milk were analyzed from five cities for volatile (purgeable) and semivolatile (extractable) organics using gas chromatography/mass spectrometry. Environmental pollutants were measured in the milk to evaluate the utility of using this body fluid in specific pollutant studies for populations living near chemical manufacturing plants. MCP was present in breast milk samples collected from women in 3 States.

The investigators pointed out that the small sample size (no attempt was made to develop a statistically valid sample), the lack of control over participants (subjects were volunteers), and the selection of sites as having a high probability of detecting pollutants (urban areas with hydrocarbon pollutants) preclude extrapolating these data to the general population.

Despite these noted limitations, EPA believes that the results from this survey are valuable because they indicate that: (1) *n*-hexane, cyclohexane, and MCP are present in a body fluid, indicating their absorption and transport to breast milk; and (2) *n*-hexane, cyclohexane, and MCP were detected in samples collected from three States, indicating potentially widespread exposure.

b. *Commercial hexane.* Between 1979 and 1984, annual production of commercial hexane increased from 390 to 470 million pounds (Ref. 10). Approximately 32 percent of this production was used in vegetable oil extraction, 25 percent in polyolefin manufacturing, 22 percent in elastomer manufacturing, and 21 percent in adhesives and other uses (Ref. 9). Fifty percent of that used for vegetable oil extraction alone is lost through evaporation from seals and equipment (Ref. 23). In addition, motor fuels contain commercial hexane A. Such uses and losses likely contribute to general population exposure to commercial hexane and various C_6 isomers. Although the volume of commercial hexane in motor fuels is not known, the Agency expects this to be the major source of exposure to the general population.

The Agency is basing its estimation of general population exposure to commercial hexane not only on the production and use figures cited above but also on the assumption that the general population exposure as discussed above (Unit II.D.2.a.) is indicative of widespread general population exposure to commercial hexane and other hexane containing refininery streams and products.

3. *Consumer exposure.* a. *MCP.* EPA believes that consumer exposure to MCP may occur during the use of commercial hexane-based petroleum solvents, paints, and thinners. In addition, MCP has been detected in an unspecified adhesive (Ref. 35), wherein it probably occurs due to the commercial hexane contained in the adhesive. Liquid adhesives may, therefore, constitute another source of consumer exposure to MCP.

b. *Commercial hexane.* EPA believes that widespread consumer exposure to commercial hexane may occur during the use of petroleum solvents, paints, thinners, and other consumer products containing commercial hexane. Although EPA lacks specific data on the amount of such solvents in consumer products, their widespread use in industrial products as indicated by NOES data (Ref. 42) suggests that such solvents probably are used in a variety of similar products available to consumers.

E. Health Effects

1. *Pharmacokinetics.* The Agency has reviewed several absorption, distribution, and metabolism studies and has found them insufficient to predict the inhalation and dermal pharmacokinetics behavior of either MCP or commercial hexane.

a. *Absorption and distribution.* In order to compare alveolar and blood monitoring to environmental monitoring for solvents, Brugnone *et al.* (Ref. 40) studied the simultaneous exposure of Italian shoe factory workers to five solvents, i.e., acetone, *n*-hexane, MCP, 2-MP, and 3-MP, over a 4.5 hour period of the work shift. The authors reported that alveolar and blood concentrations

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as well as lung uptake were significantly correlated with environmental air samples taken at selected times during the workshift for all five solvents.

Perbellini *et al.* (Ref. 44) determined the partition coefficients of several industrial aliphatic hydrocarbon compounds in various human tissues. The partition coefficient between blood and air is a determinant of inhalation absorption efficiency. The tissue/air partition coefficients for MCP were as follows (mean±standard deviation): fat (176±10.0); liver (7.8±1.0); brain (7.3±0.8); muscle (5.0±0.8); kidney (4.7±1.1); heart (1.9±0.8); lung (1.7±0.04); and blood (0.86±0.08). The high fat/air partition coefficient (176) and the estimated log octanol/water partition coefficient of 3.31 (Ref. 6) suggest that MCP is lipophilic.

These data concur with the results of a survey in which MCP was detected in breast milk (Refs. 36 and 37) (See Unit II.D.3. above). EPA believes that these results are valuable in terms of absorption because they indicate that inhaled MCP and other components of commercial hexane are present in a body fluid, and suggest transport of these components to breast milk.

Naruse (Ref. 35) studied the effects on mice of exposure to four unspecified adhesives containing various quantities and types of organic solvents. "Adhesive D" contained the following organic solvents as percents of the total adhesive: cyclohexane (36.3), acetone (15.3), isopropyl acetate (7.1), *n*-hexane (6.8), MCP (1.5), 3-MP (1.0), 2,3-DMB+2-MP (0.8), and toluene (0.5).

An unspecified number of male "ddY" mice were exposed for 1 hour to 1 of 3 doses of vapors of the adhesive coated on aluminum foil strips. The air inside the chamber was sampled at intervals throughout the exposure period and analyzed for concentration of organic solvents and for oxygen. Blood samples were taken from the mice before exposure, at the middle and at the end of the 1-hour exposure period, and at 0.5, 1, 2, 3, 6, 12, 18, and 24 hours after cessation of exposure. Air sampling measurements indicated that acetone concentration rapidly increased immediately after the onset of exposure, reaching a maximum level in approximately 15 minutes. The other organic solvents reached maximum concentrations in air proportional to the concentration of adhesive vapor after approximately 30 minutes. Blood sampling measurements immediately after cessation of exposure to vapors of "Adhesive D" indicated that acetone, isopropyl alcohol, and cyclohexane were the major compounds found in blood. MCP and toluene were not detectable in the blood of mice exposed to 30 mil of adhesive vapor (detection level of 1 g/ml), but were detectable within 30 minutes in animals exposed to 50 and 70 ml of vapor. 2,3-DMB, 2-MP, and 3-MP were below detectable levels at all 3 exposure levels. Within 30 minutes after cessation of exposure, *n*-hexane, isopropyl acetate, toluene, and MCP concentrations in blood dropped below detectable levels. Cyclohexane was detected at 2 to 8 hours after cessation of exposure; acetone and isopropyl alcohol were detected at 6 to 12 hours after cessation of exposure. All solvents, however, dropped below detectable levels at 24 hours after cessation of exposure. No other tissues were studied. The Agency believes that this study indicates that these components of commercial hexane were absorbed in the blood following inhalation exposures.

b. *Metabolism and elimination.* Perbellini *et al.* (Refs. 47, 48, and 49) performed a series of studies in which urine samples from Italian shoe factory workers exposed to commercial hexane and to other solvents were analyzed by gas chromatography. However, the authors only looked for substances they thought would be present. No actual pharmacokinetic data obtained from labeled compounds were presented. No urinary metabolites of MCP or 2,3-DMB were specifically identified in these studies.

2. *Acute toxicity.* The Agency has reviewed the acute inhalation toxicity studies available and has found them inadequate to predict the acute toxicity of either MCP or commercial hexane. Based on the chemical profiles, production, and uses of commercial hexane, the most likely route of exposure is by inhalation.

3. *Subchronic toxicity.* The Agency has reviewed available subchronic studies and has found them either inadequate to predict or suggestive of the subchronic toxicity of MCP and commercial hexane.

Phillips (Ref. 8, Att. IV) provided a copy of a pathology report of an API-sponsored 4-week oral nephrotoxicity screening study of numerous test materials, including MCP, 2,3-DMB, and 2-MP. Twenty male F-344 rats were randomly distributed into 2 treatment groups of 10 animals. The two groups received either 0.5 g/kg or 2g/kg of test material by gavage 5 days per week for 4 weeks. Physiological saline (2.0 g/kg) was administered at the same time to 10 control rats. Histopathologic evaluations were performed on kidneys removed the day immediately following final administration of the test material. Lesions associated with experimental hydrocarbon nephropathy, such as hyaline droplet change, regenerative epithelium, and tubular dilation with granular material, were used to grade the extent of nephropathic changes. Rats treated with 2,3-DMB exhibited moderate hydrocarbon nephropathy scores (7.6 at a dose of 0.5 g/kg and 6.1 at a dose of 2.0 g/kg). Rats treated with 2-MP exhibited nephropathy scores slightly above those of controls (4.6 at 0.5 g/kg and 5.9 at 2.0 g/kg). The MCP nephropathy scores (2.9 at 0.5 g/kg and 3.4 at 2.0 g/kg), however, were comparable to those of the saline control group (3.0). EPA believes that this study is inadequate to predict the nephrotoxicity of either MCP or commercial hexane because of the small number of animals, short duration (28 vs. 90 days), and oral rather than inhalation administration.

In addition, the API study (Ref. 8, Att. III), discussed below under neurotoxicity, provides suggestive evidence of the subchronic toxicity potential of MCP and commercial hexane.

4. *Chronic toxicity.* No data on the chronic toxicity of either MCP or commercial hexane have been found in the literature.

5. *Oncogenicity.* No data on the oncogenic effects of either MCP or commercial hexane have been found in the literature.

6. *Developmental and reproductive toxicity.* No data on the developmental and reproductive effects of either MCP or commercial hexane have been found in the literature.

7. *Mutagenicity.* No data on the mutagenic effects of either MCP or commercial hexane have been found in the literature.

8. *Neurotoxicity.* In Italy and in Japan, commercial hexane is used as a solvent for leather adhesives and constitutes a ubiquitous pollutant in shoe-manufacturing industries (Ref. 49). Although *n*-hexane was once believed to have been of low toxicity, outbreaks of peripheral neuropathies in industrial workers exposed to commercial hexane focused attention on occupational exposure to *n*-hexane and its metabolites (Refs. 47 and 49).

It has been well documented that workers exposed to repeatedly high levels of commercial hexane solvents have developed peripheral neuropathies. The first documented cases were Japanese workers who developed polyneuropathy after 3 to 10 months of exposure to industrial atmospheres with high amounts (1,000 to 2,500 ppm) of hexane isomers (Ref. 46). Subsequently, similar cases appeared in U.S. and

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European workers. These cases were supplemented by case reports of polyneuropathies following the intentional inhalation of glue vapors containing commercial hexanes and other solvents (Ref. 46). Clinically observed effects included fatigue, poor appetite, and weight loss, followed by impaired sense of touch and loss of strength in the extremities. Physiological effects included reduced nerve conduction velocities and denervation. Histopathological examinations revealed evidence of axonal degeneration, thereby confirming clinical observations.

Chronic exposure of rats to *n*-hexane has resulted in polyneuropathy (Ref. 43 and 46). When hexacarbon metabolites of *n*-hexane, methyl *n*-butyl ketone and 2,5-hexane-dione, were shown to induce the same type of neuropathy seen in rats exposed to *n*-hexane, other hexacarbon compounds found in commercial hexane were suspected of being neurotoxic (Ref. 43). Consequently, the following studies were performed to determine the neuropathic potential of the other hydrocarbon components of commercial hexane.

Ono *et al.* (Ref. 43) conducted a study to determine the comparative neurotoxicities of *n*-hexane (a known neurotoxicant) and certain of its isomers (2-MP, 3-MP, and MCP) commonly present in commercial hexane mixtures. The chemicals (>99 percent pure) were diluted in olive oil and orally administered to male Wistar rats (5 to 7 per group) daily for 8 weeks. Doses were increased at 4 weeks and at 6 weeks to accommodate the normal weight gain (measured at biweekly intervals) of the animals. For the first 4 weeks of the experiment, animals received 0.4 ml (approximately 700 mg/kg/day) of the appropriate chemical and 0.6 ml of olive oil per day. For weeks 5 and 6, they received 0.6 ml (approximately 1,000 mg/kg/day) of a chemical and 0.4 ml of olive oil per day and for weeks 7 and 8 they received 1.2 ml (approximately 2,000 mg/kg/day) of a chemical and 0.8 ml of olive oil per day. Controls received olive oil alone.

The conduction velocity of the peripheral nerve was measured in the animals' tails at biweekly intervals. Rats were immobilized without anesthesia and three electrodes were inserted in the nerve: the first was placed 3 cm down from the anus (A); the second was 7 to 10 cm down from the first (B); and the third was 5 cm down from the second and 3 to 4 cm up from the tail end (C). After insertion of the electrodes, the tail was immersed in a paraffin bath maintained at 37-38 °C. Motor nerve conduction velocity (MCV) and distal latency (DL) were measured by stimulating point A and point B in turn and observing the electromyogram (EMG) at point C. Mixed nerve conduction velocities (MNCV) were measured by stimulating the nerve at C and observing and summing the nerve impulses at A and B.

No significant differences were observed in body weight between groups over the course of the experiment. MCV in the *n*-hexane group was significantly less than control at 4 weeks ($p<0.05$) and at 8 weeks ($p<0.01$) after the beginning of the study but not at 6 weeks. MCV in the MCP group was significantly less than controls at 8 weeks ($p<0.05$). No significant differences were noted for the other test compounds. No significant differences in DL were noted for any test group when compared with controls. In the *n*-hexane group, MHCV (distal) was significantly less than controls at 4, 6, and 8 weeks ($p<0.05$). No significant differences were noted for the other test compounds. In the *n*-hexane group, MNCV (proximal) was significantly less than controls at 6 ($p<0.01$) and at 8 ($p<0.05$) weeks. In the MCP and 2-MP groups MNCV (proximal) was significantly less than controls at 8 weeks ($p<0.05$). No significant difference was noted for the 3-MP group. No behavioral changes were noted in any group throughout the course of the study.

EPA believes that this study provides suggestive evidence of MCP's and possibly 2-MP's neurotoxic potential. While *n*-hexane distinctly impaired the motor nerve conduction velocities of the peripheral tail nerve of male Wistar rats, MCP slightly, but significantly ($p<0.05$), impaired them.

Egan *et al.* (Ref. 46) conducted a 6-month subchronic continuous inhalation toxicity study to determine whether a mixture of C_6 isomers virtually free of n-hexane could induce in rats a neuropathy similar to that seen in experimental studies in animals chronically exposed to pure *n*-hexane. The mixture of C_6 isomers consisted of: 24.6 percent MCP (431.0 mg/m^3 nominal concentration); 35.3 percent 2-MP (618.0 mg/m^3); 30.0 percent 3-MP (525.0 mg/m^3); 6.2 percent cyclohexane (109.0 mg/m); 3.4 percent 2,3-DMB (60.0 mg/m^3); and 0.3 percent *n*-hexane (5.3 mg/m^3).

Male Sprague-Dawley rats were divided into four groups (6 per group): a sham-exposed group which received hydrocarbon-free air; a positive control which received methyl *n*-butyl ketone (96.66 percent pure) at 400 mg/m^3 (100 ppm); a negative control which received methyl ethyl ketone (99.98 percent pure) at 1,475 mg/m^3 (500 ppm); and an experimental group which received the mixture of C_6 isomers at 1,750 mg/m^3 (500 ppm). Animals were exposed 22 hours/day, 7 days/week for 6 months. Two rats per group were used as the subjects of detailed neuropathological examinations following 2, 4, or 6 months of exposure.

No clinically observable disorders, including neurological impairment, were observed in either exposed or control animals throughout the 6-month course of exposure. After 4 months of exposure, animals exposed to methyl *n*-butyl ketone, the positive control, showed histopathological signs of hexacarbon-induced neuropathy in both the central and peripheral nervous systems. After 6 months of exposure, more advanced neuropathy was observed. Exposure to methyl ethyl ketone, the negative control, for up to 6 months did not produce any histopathological changes in the central or peripheral nervous systems.

Animals exposed to the mixure of C_6 isomers for up to 6 months showed no significant histopathological differences from controls. As above, nervous tissue sections examined after 2 months of exposure appeared normal. At 4 months, age-associated changes in the medulla oblongata and chronic traumatic damage to plantar nerves were observed, but these changes were not attributed to compound administration. Single teased nerve fiber preparations appeared normal (in contrast to the giant axonal swellings seen in preparations from positive controls).

EPA believes that this study is well-conducted. Egan *et al.* used appropriate control animals and carefully monitored actual exposure concentrations and other variables, such as diet. However, EPA believes that the doses used were too low to adequately demonstrate lack of neurotoxic potential of the C_6 isomer mixture. For any repeated exposure study to provide adequate evidence of a substance or mixture's lack of potential to cause a specific effect, EPA feels that exposure to a maximum tolerated dose is necessary. Therefore, the study was inadequate to reasonably predict the neurotoxic potential of either MCP or commercial hexane.

In 1982, API sponsored a two-part study of the neuropathic potential of *n*-hexane in the presence of other hexane isomers (Ref. 8, Att. II). The mixture of C_6 isomers consisted of 30 percent MCP, 30 percent 2-MP, 30 percent 3-MP, 5 percent cyclohexane, 5 percent 2,3-DMB, and less than 1 percent *n*-hexane. Phase I of the study was designed to determine

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whether rats treated with non-neurotoxic doses of *n*-hexane would develop neuropathy when treated concurrently with a mixture of *n*-hexane-free C_6 isomers. Phase II of the study was designed to determine whether a mixture of *n*-hexane-free C_6 isomers would potentiate the neurotoxic effects of *n*-hexane given to rats in neurotoxic doses.

In Phase I, young adult male Charles River CD rats were exposed by inhalation to combinations of *n*-hexane and C_6 isomers for 22 hours/day, 7 days/week for up to 6 months at International Research and Development Corp. Animals were killed by perfusion with paraformaldehyde followed by glutaraldehyde, and dissected to remove the brain, spinal cord, and sciatic/tibial nerve complex. Tissues were examined by light microscopy.

A total of 54 animals in six groups were examined. The first group (controls) consisted of 14 animals; the second group (four animals) was exposed to 125 ppm *n*-hexane for 6 months; the third group (four animals) was exposed to 125 ppm *n*-hexane and 125 ppm C_6 isomers for 6 months; the fourth group (four animals) was exposed to 125 ppm *n*-hexane and 375 on ppm C_6 isomers (approximately 112.5 ppm MCP, 2-MP, and 3-MP, respectively) for 6 months; the fifth group (four animals) was exposed to 125 ppm *n*-hexane and 1,375 ppm C_6 isomers (approximately 412.5 ppm MCP, 2-MP, and 3-MP, respectively) for 6 months; and the sixth group (24 animals) was exposed to 500 ppm *n*-hexane. Selected animals from the first and sixth groups were killed at monthly intervals throughout the study.

Weight loss and/or functional signs of abnormality expressed as hindlimb weakness were observed in all animals treated with 500 ppm *n*-hexane beginning with the fourth month of exposure. All other animals were reported to appear normal. Microscopic examination of animals treated with 500 ppm *n*-hexane revealed early pathological changes in the tissues studied beginning with the 2-month exposure group. Characteristic *n*-hexane-induced pathological changes were observed at the third month, and advanced pathological changes were seen by the fourth month.

Of the animals in the other groups (subjected to different exposure levels and examined at 6 months), age-related dystrophic axons were observed in all groups, including the controls. In the groups exposed to 125 ppm *n*-hexane in combination with either 375 or 1,375 ppm C_6 isomers, scattered axonal swellings were also observed, but these were not considered by the investigators to have been pathological changes consistent with *n*-hexane-induced neuropathy.

In Phase II, young adult male Charles River CD rats were exposed to combinations of *n*-hexane and C_6 isomers by a protocol detailed in the companion study (Ref. 8, Att. III). This report details the findings of the light microscopy examination of the brain, spinal cord, and sciatic/tibial nerve complex of animals after 2 months and 6 months of exposure. Five animals were examined from each exposure group at each time point, making a total of 40 animals. The exposure groups included controls, animals exposed to 500 ppm C_6 isomers, animals exposed to 500 ppm *n*-hexane concurrently with 500 ppm C_6 isomers, and animals exposed to 500 ppm *n*-hexane alone. Animals were exposed for 22 hours/day, 7 days/week for 2- or 6-month periods. Sacrifice was by perfusion with 4-percent paraformaldehyde followed by 5-percent glutaraldehyde.

All of the animals receiving *n*-hexane either alone or in combination with C_6 isomers exhibited signs of abnormality. After 2 months of exposure, weight loss, flat-footedness, and poor fur texture were noted. After 6 months, weight loss and hindlimb weakness were observed. All other animals were reported to appear normal.

Upon microscopic examination, animals not exposed to *n*-hexane exhibited only age-related changes. Animals exposed to *n*-hexane alone displayed pathological changes consistent with *n*-hexane-induced neuropathy at 2 and 6 months of exposure. Animals exposed to *n*-hexane concurrently with other C_6 isomers did not display compound-related pathological changes at 2 months exposure. Compound-related changes typical of *n*-hexane-induced neuropathy were seen at 6 months and were reported to be similar in degree to changes induced by *n*-hexane alone.

In 1983, API sponsored a study designed to evaluate the inhalation toxicity, particularly neurotoxicity, of *n*-hexane alone and mixed with other C_6 isomers commonly found in commercial hexanes (Ref. 8, Att. III). The chemicals and mixtures under study were administered to male Charles River CD rats (20 per group) for approximately 22 hours/day, 7 days/week for 6 consecutive months. No rationale was given for the selection of exposure levels.

Four groups of rats were employed. Group VII was exposed to filtered air only (methods control); Group VIII was exposed to 500 ppm mixed hexanes; Group IX was exposed concurrently to 500 ppm *n*-hexane and 500 ppm mixed hexanes, making a total of 1,000 ppm; and Group X was exposed to 500 ppm *n*-hexane (positive control). Two lots of *n*-hexane were employed during the course of the study. The purity of *n*-hexane was 99.3 to 99.4 weight percent. The major contaminant was MCP at 0.4 to 0.5 weight percent. Two lots of mixed hexanes were also used, consisting of approximately 30 percent MCP, 30 percent 2-MP, 30 percent 3-MP, 5 percent cyclohexane, 5 percent 2,3-DMB, and less than 1 percent *n*-hexane. Minor amounts of 2,2-DMB and an unknown component were reported in one lot.

After 2 months and 6 months of exposure, five animals/group were removed from this study for independent examination of the brain, spinal cord and sciatic/tibial nerve complex. These results are reported separately in the 1982 API study (Ref. 8, Att. II).

After 6 months of exposure, all surviving animals were killed by intraperitoneal administration of sodium pentobarbital followed by exsanguination. All animals (including those that died during the course of the study or were killed *in extremis*) were subjected to complete necropsy.

The only treatment-related pharmacotoxic sign observed was abnormal gait, which first appeared at week 16 in one animal from Group X and at week 17 in one animal from Group IX. The incidence and severity increased over time in both animals. Group IX (15 percent MCP and 50 percent *n*-hexane) and X (*n*-hexane only) had significantly ($p<0.01$) lower body weights than either Group VII (controls) or VIII (30 percent MCP). The difference first became significant at week 5 in Group IX and by week 26 was about 25 percent less than controls. In Group X, significance was first noted at week 7, and at week 26 was about 30 percent less than controls.

In all three experimental groups, kidney weights were significantly increased when compared with controls. Upon microscopic examination, a slightly increased incidence of chronic nephritis was observed which was considered to be consistent with the increase in weight. The severity of the condition was also increased in treated animals when compared with controls, but it was unclear whether this was due to amplification of the process seen in control animals or to additional tubular injury caused by the administered hexanes and typically seen in hydrocarbon-induced renal disease.

Groups IX and X, but not Group VIII, exhibited other organ weight variations,

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but no significant alterations were noted upon histological examination. These variations were considered to be reflections of decreased body weight gain.

Abnormal gait was observed in 8/15 rats in Group IX and 9/15 rats in Group X by week 25 of the study. Microscopic examination revealed peripheral nerve lesions including atrophy, axonal degeneration, and mono-nuclear cell infiltration, in some cases accompanied by secondary skeletal muscle atrophy. These microscopic lesions and the clinical sign of abnormal gait were found only in the groups receiving *n*-hexane, either alone or in combination with mixed hexanes. Administration of mixed hexanes without *n*-hexane (Group VIII) did not result in detectable signs of neurotoxicity.

EPA believes that while the experimental protocol and exposure information in the 1982 API Study (Ref. 8, Att. II) were minimally presented, the 1983 API Study (Ref. 8, Att. III) appears to be well-conducted, with careful monitoring of actual exposure concentrations. Both these studies allow a comparison of effects in male rats after inhalation exposure for up to 6 months to C_6 isomers less *n*-hexane versus *n*-hexane alone. EPA further believes that these studies indicate that *n*-hexane produces clear clinical signs, e.g. abnormal gait, and neuropathy at 500 ppm, the OSHA, PEL, but not at 125 ppm. Exposure to up to 1,375 ppm C_6 isomers produced neither clinical signs nor neuropathy. For any repeated exposure study to provide adequate evidence of a substance or mixture's lack of potential to cause a specific effect, however, EPA believes that a maximum tolerated dose is necessary, and was not used in these studies. Therefore, these studies were inadquate to predict the neurotoxic potential of either MCP or commercial hexane.

F. Ongoing Testing

n-Hexane and its metabolites, methyl *n*-butyl ketone and 2, 5-hexanedione, have been shown to induce polyneuropathy in rats (Refs. 43 and 46). The National Toxicology Program (NTP) is conducting a subchronic inhalation toxicity test of *n*-hexane in $B6C3F_1$ mice (Ref. 26). There is continuous exposure at the low dose of 1,000 ppm. Exposure to 4,000 and 10,000 ppm occurs for 6 hours/day, 5 days/week for 13 weeks (90 days). Because Cavender *et al.* (Ref. 27), sponsored by the Chemical Industry Institute of Toxicology (CIIT), have published the results of a subchronic (13-week) inhalation toxicity study in Fischer rats exposed to 0, 3,000, 6,500, and 10,000 ppm of *n*-hexane for 6 hours/day, 5 days/week, NTP will evaluate the need for chronic toxicity testing (oncogenicity) after reviewing CIIT's data in rats and their own data in mice (Ref. 26). In addition, NTP has arranged for reproductive and developmental toxicity testing of *n*-hexane by inhalation (Ref. 26). Finally, NIOSH is testing potential motor and sensorimotor effects of acute inhalation exposures of rats to *n*-hexane, methyl ethyl ketone, and methyl amyl ketone (Ref. 29).

III. Findings

EPA is basing proposed testing requirements upon TSCA section 4(a)(1)(A) for MCP and upon section 4(a)(1)(B) for commerical hexane.

1. Under section 4(a)(1)(A)(i), EPA finds that the manufacture, processing, and use of MCP, whether as an isolated product or as a substantial component of mixed hexane products, may present an unreasonable risk of neurotoxicity and subchronic toxicity. Ono *et al.* (Ref. 43) reported impaired motor nerve conduction velocities in rats exposed to MCP, providing suggestive evidence of the neurotoxic potential of MCP. API (Ref. 8, Att. III) reported that a mixture of C_6 isomers virtually free of *n*-hexane caused significantly increased kidney weights and increased incidence in severity of chronic nephritis, providing suggestive evidence of the subchronic toxicity potential of MCP which was a major constituent of this mixture. Although isolated MCP has not been sold in the U.S. since 1982 (Ref. 8), MCP is a substantial component of various hexane-containing refinery streams and products whose manufacture, processing, and use result in extensive exposure of workers, consumers, and the general population to MCP as described in Unit II. D.

Under section 4(a)(1)(A)(ii), EPA finds that existing data and experience are inadequate to reasonably determine or predict the potential for exposure to MCP resulting from its manufacture, processing, and use, either as an isolated product or as a substantial component of mixed hexane products, to produce neurotoxicity, subchronic toxicity, and pharmacokinetic effects. EPA believes that the studies conducted by Egan *et al.* (Ref. 6) and API (Ref. 8, Att. II and Att. III) are inadequate because animals were not exposed to maximum tolerated doses of the test substance. EPA believes that exposure to maximum tolerated doses is necessary in order for such studies to provide adequate evidence of a substance or mixture's lack of potential to cause a specific effect. Thus, these studies cannot refute the positive findings of neurotoxicity provided by Ono *et al.* (Ref. 43) or the kidney effects provided by API (Ref. 8, Att. III). Furthermore, EPA believes that the nephrotoxicity oral screening study (Ref. 8, Att. IV) is inadequate to predict the nephrotoxicity of MCP because of the small number of animals, short duration (28 vs. 90 days), and oral rather than inhalation administration. In addition, while the absorption, distribution, and metabolism studies of MCP and other C_6 isomers indicate the absorption of MCP in blood, they are inadequate to predict to pharmacokinetic behavior of MCP.

Under section 4(a)(1)(A)(iii), EPA finds that testing of MCP for neurotoxicity, subchronic toxicity, and pharmacokinetic behavior is necessary to develop adequate data to assess the effects of human exposure to MCP resulting from its manufacture, processing, and use.

2. EPA also believes that there is substantial production of MCP as a component of mixed hexane products and that it could find that there is substantial human exposure to MCP from the manufacture, processing, and use of such products. Although isolated MCP is currently not manufactured for sale, its presence in various hexane-containing refinery streams and products leads to widespread exposure of workers, consumers, and the general population to MCP along with other C_6 hydrocarbons. Under a section 4(a)(1)(B) finding, EPA could require testing of MCP for additional health effects (e.g., reproductive effects) for which data currently do not exist and for which a section 4(a)(1)(A) finding of potential unreasonable risk cannot be made. However, because EPA simultaneously is proposing testing of commercial hexane for all such effects, and because such testing of commercial hexane will screen for the potential of MCP and other components of commercial hexane to produce any of these effects, the Agency is proposing to limit the testing of MCP at this time to neurotoxicity, subchronic toxicity, and pharmacokinetics under section 4(a)(1)(A). EPA believes that this limited testing will provide enough information to determine MCP's effective dose on various target organs and provide a basis for determining the need for any additional testing if the results of this testing and that on commercial hexane indicate other effects.

3. Under section 4(a)(1)(B), EPA finds that commercial hexane is produced in substantial quantities and that there is substantial human exposure from its manufacture, processing, and use. Approximately 500 million pounds of hexanes were produced in 1984 (Ref. 10).

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In addition, according to the National Occupational Exposure Survey of 1985 (NOES), 83,000 workers are estimated to have actual exposure to hexane solvents. Of these, 12,576 are women (Ref. 42). Commercial hexanes are used as a component of motor fuels, lacquers, printing inks, and adhesives, and as a seed oil extractant (Ref. 9). Such uses may result in potentially widespread exposure to workers and consumers, and the general public may be exposed through fugitive emissions from anthropogenic sources.

While EPA believes that there may be substantial human exposure to C_6 hydrocarbons in gasoline, EPA is not considering exposure to the finished gasoline as part of its basis for finding substantial human exposure to commercial hexane. The Agency believes that exposures associated with the manufacture and processing of commercial hexanes and use of solvents containing significant concentrations of C_6 isomers provide sufficient basis for a finding of substantial human exposure under TSCA section 4(a)(1)(B)(i) for commercial hexane.

EPA finds that there are insufficient data to reasonably determine or predict the acute, subchronic, oncogenic, reproductive, developmental, mutagenic, neurotoxic, and pharmacokinetic effects of human exposure to commercial hexane resulting from its manufacture, processing, and use. EPA further finds that testing is necessary to develop such data.

IV. Proposed Rule

A. Proposed Testing and Test Standards

The Agency is proposing that testing be conducted in accordance with specific test guidelines set forth in sections in Title 40 of the Code of Federal Regulations (CFR) as enumerated below. Test methods under new Parts 796, 797, and 798 were published in the **Federal Register** of September 27, 1985 (50 FR 39252). Proposed revisions to these guidelines were published in the **Federal Register** of January 14, 1986 (51 FR 1522). Elsewhere in this issue of the **Federal Register**, new Part 795—Provisional Test Guidelines is being proposed.

On the basis of the findings presented above for health effects testing, the Agency is proposing that MCP be tested under TSCA section 4(a)(1)(A) for: (1) neurotoxicity by inhalation using the tests specified in §§ 795.250, 798.6050, 798.6200, 798.6400, and 798.6500; (2) subchronic inhalation toxicity using the test specified in § 798.2450; and (3) inhalation and dermal pharmacokinetics using the test specified in § 795.232 of this chapter.

Acute neurological effects are of concern because such effects may increase accident proneness, impair self-rescue, or reduce work efficiency (Ref. 45). This is of particular concern to the 38,000 workers potentially exposed to either actual MCP or MCP in a trade name product (Ref. 11). In order to assess the acute neurologic effects of inhaled MCP at low levels on behavior, the Agency is proposing that the neurotoxicity testing include a schedule-controlled operant behavior study (§ 798.6500). In order to assess the effects of repeated inhalation exposures to MCP, the Agency is proposing a subchronic neurobehavioral toxicity evaluation, consisting of neuropathologic evaluation of tissues perfused *in situ* (§ 798.6400), a functional observation battery (§ 798.6050), and measurement of motor activity (§ 798.6200). Furthermore, EPA believes that MCP's presence in breast milk samples raises concerns for neonates and children, whose developing neurological systems may be more susceptible to damage from exposure to MCP than adults. Therefore, in order to assess potential functional and morphological hazards to the nervous system which may arise in neonates from exposure of the mother to MCP during pregnancy and lactation, the Agency is proposing that MCP be tested for developmental neurotoxicity (§ 795.250), which is being proposed elsewhere in this issue of the **Federal Register**.

In order to assess the degree of toxicological activity of MCP upon various target organs, the Agency is proposing that MCP be tested for subchronic toxicity by inhalation (§ 798.2450).

In order to compare actual uptake levels by inhalation of MCP vapors and by dermal absorption following contact with liquid MCP in solvents, testing to compare inhalation and dermal pharmacokinetics (§ 795.232) is also proposed. Because MCP is moderately water soluble (Ref. 2) while *n*-hexane is insoluble (Ref. 4), EPA is concerned that dermal exposure to commercial hexane in solvents by workers and the general population could cause greater exposure to MCP than to *n*-hexane. The Agency believes that this testing will allow it to determine the pharmacokinetic behavior of MCP through solvent use.

On the basis of the findings presented above for health effects testing, the Agency also is proposing that commercial hexane be tested under TSCA section 4(a)(1)(B) for: (1) acute inhalation toxicity using the test specified in § 798.1150; (2) subchronic inhalation toxicity using the test specified in § 798.2450; (3) oncogenicity by inhalation using the test specified in § 798.3300; (4) reproductive toxicity by inhalation using the test specified in § 798.4700; (5) developmental toxicity by inhalation using the test specified in § 798.4350; (6) neurotoxicity by inhalation using the tests specified in §§ 798.6050, 798.6200, 798.6400, and 798.6500; and (7) inhalation and dermal pharmacokinetics using the test specified in § 795.232 of this chapter.

To assess the potential for commercial hexane to cause gene mutations, the Agency is proposing that a reverse mutation assay in *Salmonella typhimurium* be conducted with and without metabolic activation using the procedures specified in § 798.5265. If the results from the *Salmonella typhimurium* test are negative, a gene mutation test in mammalian cells in culture will be required with and without metabolic activation using the procedures specified in § 798.5300. Unless the results of both the *Salmonella typhimurium* test and the mammalian cells in culture test are negative, a sex-linked recessive lethal test in *Drosophila melanogaster* will be required using the procedures specified in § 798.5275. A positive result in the sex-linked recessive lethal test will trigger a mouse specific locus test using the procedures specified in § 798.5200. If the sex-linked recessive lethal test is negative, then the mouse specific locus test will not be required.

To asess the potential for commercial hexane to cause chromosomal aberrations, the Agency is proposing that *in vitro* cytogenetic assays be conducted on commercial hexane as specified in § 798.5375. Unless the results of the *in vitro* test are negative, a dominant-lethal assay will be required using the procedures specified in § 798.5450. A positive result in the dominant-lethal assay will trigger a heritable translocation assay using the procedures specified in § 798.5460. If the *in vitro* cytogenetics assay is negative, an *in vivo* bone marrow assay using procedures specified in § 798.5385 will be required. Should the *in vivo* bone marrow test results prove negative, no further chromosomal aberration testing would be required. A non-negative result in the *in vivo* bone marrow test would trigger the dominant-lethal assay. Again, if the dominant-lethal test is positive, a heritable translocation assay will be required. If the dominant-lethal test is negative, no further chromosomal

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aberration testing will be required for commercial hexane.

Before testing is initiated in one or both of the endpoint mutagenicity tests, EPA will hold a public program review, if the results of the previous tier tests are positive. Public participation in this program review will be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting will be published in the **Federal Register.** Should EPA determine, based on the available weight of evidence, that proceeding to the mouse specific locus or to the heritable translocation test is no longer warranted, the Agency would propose to repeal these testing requirements and, after public comment, issue a final amendment to rescind these requirements.

For a more detailed discussion concerning mutagenicity-tiered testing and public program review procedures see EPA's final test rule for the C_9 aromatic hydrocarbon fraction published in the **Federal Register** of May 17, 1985 (50 FR 20662).

Because of the large exposures to commercial hexane, the requirement for oncogenicity testing will be independent of the outcome of the mutagenicity testing, and the deadline for its completion will be based on its intiation immediately after completion of the subchoronic study.

The Agency is proposing that the above-referenced TSCA health effects test guidelines be employed as the test standards for the purposes of the proposed tests for MCP and commercial hexane. The TSCA test guidelines for health effects testing specify generally accepted minimal conditions for determining the health effects for substances like MCP and commercial hexane to which humans are expected to be exposed. The Agency's review of the TSCA Test Guidelines, which occurs on a yearly basis according to the process described at 47 FR 41857 (September 22, 1982), has found no reason to conclude that these protocols need to be modified significantly. However, because of the high volatility of commercial hexane and because human exposure occurs primarily by inhalation, EPA is proposing chemical-specific modifications to the proposed mutagenicity tests that take into account these factors. In addition, because of the numerous components of commercial hexane, EPA is proposing chemical-specific modifications to the proposed inhalation and dermal pharmacokinetics testing to facilitate identification of the radiolabeled components of the mixture.

EPA published in the **Federal Register** certain proposed revisions to these TSCA Test Guidelines to provide more explicit guidance on the necessary minimum elements for each study (51 FR 1522; January 14, 1986). In addition, these revisions will avoid repetitive chemical-by-chemical changes to the guidelines in their adoption as test standards for chemical-specific test rules. EPA is proposing that these modifications be adopted in the test standards for MCP and commercial hexane.

B. Test Substance

EPA is proposing under TSCA sections 4(a)(1)(A) that methylcyclopentane (MCP; CAS No. 96-37-7) of at least 99.9 percent purity be used as the test substance. EPA has specified a relatively pure substance for testing because the Agency is interested, in evaluating the effects attributable to MCP itself. Because Phillips stated that it sold 99.9+ percent research grade MCP preparations to laboratories or research facilities (Ref. 20), EPA believes that this research grade MCP is readily available for testing purposes. Radiolabeled MCP will be needed for the inhalation and dermal pharmacokinetics testing.

EPA is proposing under TSCA section 4(a)(1)(B) that commercial hexane A, or solvent grade, derived from the fractionation of straight-run gasoline and consisting of no more than 64 liquid volume percent *n*-hexane and no less than 19 liquid volume percent MCP, be used as the test substance. According to Kirk-Othmer (Ref. 9), commercial hexane A, or solvent grade, consists of the following components: 63.91 liquid volume percent *n*-hexane (CAS No. 110-54-3); 19.43 liquid volume percent methylcyclopentane (MCP; CAS No. 96-37-7); 9.38 liquid volume percent 3-methylpentane (3-MP; CAS No. 96-14-0); 3.48 liquid volume percent 2-methylpentane (2-MP; CAS No. 107-83-5); 2.81 liquid volume percent benzene (CAS No. 71-43-2); 0.78 liquid volume percent cyclohexane (CAS No. 110-82-7); 0.16 liquid volume percent 2,2- and 2,4-dimethylpentane (2,2-DMP; CAS No. 590-35-2; 2,4-DMP; CAS No. 108-08-7), 0.05 liquid volume percent 2,3-dimethylbutane (2,3-DMB; CAS No. 79-29-8); and 25 ppm sulfur (CAS No. 7704-34-9). EPA believes that commercial hexane A is readily available for testing purposes. Radiolabled components of commercial hexane A will be needed for the inhalation and dermal pharmacokinetics testing.

Because of the numerous kinds of exposure to the C_6 hydrocarbon fraction and because of the variability in composition of commercial hexanes, EPA believes that specifying commercial hexane A as the test substance will alleviate the problem of selecting an appropriate C_6 mixture as the test substance under section 4(a)(1)(B). There are several reasons which led to the proposal of commercial hexane A as the test substance. First, the Agency feels that testing is needed to characterize the toxicity of a type of commercial hexane to which people are actually exposed, rather than a synthetic blend of C_6 hydrocarbons. Second, because the neurotoxic and other effects of *n*-hexane are under study by the National Toxicology Program (NTP), the Agency believes that industry may reduce the *n*-hexane content in C_6 hydrocarbon solvents, thereby increasing exposure to the other constituents, but primarily to MCP. Third, the Agency believes that testing commercial hexane A is more appropriate than testing commercial hexanes B or C because commercial hexane A has the greatest MCP content and the highest solvent use.

C. Persons Required To Test

Section 4(b)(3)(B) specifies that the activities for which the Agency makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "imports"). Processors are required to test if the findings are based on processing ("process" is defined in section 3(10) of TSCA as the preparation of a chemical substances or mixture, after its manufacture, for distribution in commerce). Both manufacturers and processors are required to test if the exposures giving rise to the potential risk occur during use, distribution, or disposal.

Because EPA has found that there are insufficient data and experience to reasonably determine or predict the effects on human health of the manufacture, processing, and use of MCP and commercial hexane, EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process, MCP or commercial hexane other than as impurities 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. In addition, manufacturers and processors of MCP or commercial hexane who do so in the course of producing gasoline or other motor or heating fuels are subject to this rule because the Agency's section 4(a)(1)

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(A)(ii) and (B)(ii) findings are based on the manufacture, processing, and use of MCP and commercial hexane. The end of the reimbursement period will be 5 years after the last final report is submitted or an amount of time equal to that which was required to develop data if more than 5 years after the submission of the last final report required under the test rule.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement. The Agency anticipates that the current manufacturers of MCP or commercial hexane will form the reimbursement pool and sponsor the required testing. EPA promulgated procedures for appyling for TSCA section 4(c) exemptions in 40 CFR Part 790.

Manufacturers (including importers) subject to this rule are required to submit either a letter of intent to perform testing or an exemption application within 30 days after the effective date of the final test rule. The required procedures for submitting such letters and applications are described in 40 CFR Part 790.

Processors subject to this rule, unless they are also manufacturers, will not be required to submit letters of intent or exemption applications, or to conduct testing, unless manufacturers fail to submit notices of intent to test or later fail to sponsor the required tests. The Agency expects that the manufacturers will pass an appropriate portion of the costs of testing on to processors through the pricing of their products or reimbursement mechanisms. If manufacturers perform all the required tests, processors will be granted exemptions automatically. If manufacturers fail to submit notices of intent to test or fail to sponsor all the required tests, the Agency will publish a separate notice in the **Federal Register** to notify processors to respond; this procedure is described in 40 CFR Part 790.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for MCP and commercial hexane. As noted in Unit IV.B. above EPA is interested in evaluating the neurotoxic and subchronic effects of MCP itself and has specified a relatively pure substance for testing. In addition, the Agency has proposed a specific type of commercial hexane for testing and believes that testing of commercial hexane A will allow reasonable prediction of the potential of various commercial hexane products to cause the effects to be studied.

Manufacturers and processors who are subject to this test rule must comply with the test rule development and exemption procedures in 40 CFR Part 790 for single-phase rulemaking.

D. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practice (GLP) standards which appear in 40 CFR Part 792.

In accordance with 40 CFR Part 790 under single-phase rulemaking procedures, test sponsors are required to submit individual study plans at least 45 days prior to the initiation of each study.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. The Agency is proposing specific reporting requirements for each of the proposed test standards in Table 1 as follows:

TABLE 1.—REPORTING REQUIREMENTS

Test	Reporting deadline for final report (No. of months after the effective date of the final rule)	No. of interim (6-mo) reports required
1. Testing for MCP:		
A. Neurotoxicity tests: §§ 795.250, 798.6050, 798.6200, 798.6400, and 798.6500	12	1
B. Inhalation and dermal pharmacokinetics: § 795.232	12	1
C. Subchronic inhalation toxicity: § 798.2450	15	2
2. Testing for commercial hexane:		
A. Acute inhalation toxicity: § 798.1150	6	0
B. Subchronic inhalation toxicity: § 798.2450	15	2
C. Oncogenici- ty: § 798.3300	53	8
D. Reproduction and fertility effects: § 798.4700	29	4
E. Inhalation developmental toxicity: § 798.4350	12	1
F. *Salmonella typhimurium*: § 798.5265	4	0
G. Mammalian cells in culture: § 798.5300	12	1
H. *Drosophila* sex-linked recessive lethal: § 798.5275	24	1
I. Mouse specific locus: § 798.5200	48	3
J. *In vitro* cytogenetics: § 798.5375	4	0
K. *In vivo* cytogenetics: § 798.5385	12	1
L. Dominant lethal assay: § 793.5450	24	1
M. Heritable translocation assay: § 798.5460	48	3
N. Neurotoxicity tests: §§ 798.6050, 798.6200, 798.6400, and 798.6500	12	1
O. Inhalation and dermal pharmacokinetics: § 795.232	12	1

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the **Federal Register** as required by section 4(d).

Persons who export a chemical substance or mixture which is subject to a section 4 test rule are subject to the export reporting requirements of section 12(b) of TSCA. Final regulations interpreting the requirements of section 12(b) are in 40 CFR Part 707 (45 FR 82844). In brief, as of the effective date of this test rule, an exporter of MCP or commercial hexane must report to EPA the first export or intended export of MCP or commercial hexane to a particular country in a calendar year. EPA will notify the foreign country concerning the test rule for the chemical.

E. Enforcement Provisions

The Agency considers failure to comply with any aspect of a section 4 rule to be a violation of section 15 of TSCA. Section 15(1) of TSCA makes it unlawful for any person to fail or refuse to comply with any rule or order issued under section 4. Section 15(3) of TSCA makes it unlawful for any person to fail or refuse to: (1) Establish or maintain records, (2) submit reports, notices, or other information, or (3) permit access to or copying of records required by the Act or any regulation or rule issued under TSCA.

Additionally, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce. * * *" The Agency considers a testing facility to be a place where the chemical is held or stored, and therefore, subject to inspection.

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Laboratory inspections and data audits will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11 by duly designated EPA representatives to determine compliance with any final rule for MCP and commercial hexane. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations and evaluations to determine compliance with TSCA GLP standards under 40 CFR Part 792 and the test standards established in the rule.

EPA's authority to inspect a testing facility also derives from section 4(b)(1) of the TSCA, which directs EPA to promulgate standards for the development of test data. These standards are defined in section 3(12)(B) of TSCA to include those requirements necessary to assure that data developed under testing rules are reliable and adequate, and such other requirements as are necessary to provide such assurance. The Agency maintains that laboratory inspections are necessary to provide this assurance.

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to $25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers or processors that fail to submit a letter of intent or an exemption request and that continue manufacturing or processing after the deadlines for such submissions. This provision would also apply to processors who fail to submit a letter of intent or an exemption application and continue processing after the Agency has notified them of their obligation to submit such documents (See 40 CFR 790.28(b)). Intentional violations could lead to the imposition of criminal penalties of up to $25,000 for each day of violation and imprisonment for up to 1 year. In determining the amount of penalty, EPA will take into account the seriousness of the violation and the degree of culpability of the violator as well as all the other factors listed in section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

Individuals as well as corporations could be subject to enforcement actions. Sections 15 and 16 of TSCA apply to "any person" who violates various provisions of TSCA. EPA may, at its discretion, proceed against individuals as well as companies themselves. In particular, this includes individuals who report false information or who cause it to be reported. In addition, the submission of false, fictitious, or fraudulent statements is a violation under 18 U.S.C. 1001.

V. Issues for Comment

1. Are there health effects studies on commercial hexane A which would adequately characterize its potential to cause any of the effects for which EPA has proposed testing?

2. Which substance should be tested to characterize the toxicity of commercial hexane under section 4(a)(1)(B): commercial hexane A or *n*-hexane-free C_6 isomers?

Normally, EPA would require testing of the most representative substance to which people are exposed. In this proposed rule, EPA has specified commercial hexane A, or solvent grade, as the test substance because there is actual exposure to it and because it contains the highest amount of MCP, 1 of its 2 largest constituents. The largest constituent, *n*-hexane, is a known neurotoxicant undergoing testing by NTP and NIOSH for other toxicological endpoints. EPA is concerned that the presence of *n*-hexane (64 liquid volume percent) in commercial hexane A may mask the adverse health effects of the other components. In addition, benzene, a known carcinogen, is present in commercial hexane A at 2.81 liquid volume percent.

EPA seeks comment on whether testing *n*-hexane-free C_6 isomers may be a more appropriate test substance. If industry should consider reformulating commercial hexane to reduce its *n*-hexane content, the content of the other C_6 isomers (MCP, 2-MP, and 3-MP) would increase in the mixture. Testing of *n*-hexane-free C_6 isomers would complement the ongoing testing of *n*-hexane because it would characterize the toxicity of the other components collectively. In fact, this synthetic blend has been tested by API and has no benzene and less than 1 liquid volume percent *n*-hexane. On the other hand, because this is a synthetic mixture, testing would provide toxicological information on a mixture to which there currently is no actual exposure.

3. The authors of the EPA monitoring study raised concerns that infants might be uniquely susceptible to some pollutants because of their small body weights and their metabolic systems which differ from those of adults. Is additional testing of MCP and/or commercial hexane needed to assess potential adverse health effects upon neonates, who may be exposed to hexanes and MCP through mother's milk, and whose developing neurological systems may be more susceptible to damage from exposure to these compounds? What test methods should be used for such testing?

4. Since the API study (Ref. 8, Att. III) showed significantly increased kidney weights in rats dosed for 22 hours per day, 7 days per week for 6 consecutive months, should the subchronic test standard for MCP be modified to follow this dosing regimen?

VI. Economic Analysis of Proposed Rule

To assess the economic impact of this rule, EPA has prepared an economic analysis (Ref. 23) that evaluates the potential for significant economic impacts on the industry as a result of the required testing. The economic analysis estimates the costs of conducting the required testing and evaluates the potential for significant adverse economic impact as a result of these test costs by examining four market characteristics of commercial hexane: (1) price sensitivity of demand, (2) industry cost characteristics, (3) industry structure, and (4) market expectations. If these indications are negative for commercial hexane, no further economic analysis is performed. However, if the first level of analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted which more precisely predicts the magnitude and distribution of the expected impact.

Testing costs for the proposed testing of MCP are estimated to range from $297,000 to $559,000 and for commercial hexane are estimated from $2,016,000 to $3,310,000, for a total estimated testing cost for the proposed rule of $2,313,000 to $3,869,000. The annualized test costs (using a cost of capital of 25 percent over a period of 15 years) range from $0.6 to $1.0 million. Based on 1984 production of 470 million pounds, the unit test costs range from $0.0013 to $0.0021 per pound. Relative to a current list price of $0.20 per pound of commercial hexane, these costs are equivalent to 0.7 to 1.1 percent of price.

Based on these costs and the market characteristics of commercial hexane, the economic analysis indicates that the potential for significant adverse economic impact as a result of this test

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rule is low. This conclusion is based on the following observations:

1. The annual unit cost of the testing required in this rule is low;
2. Demand for commercial hexane is relatively inelastic with respect to price in all of its major uses; and
3. Market expectations for commercial hexane are positive.

Refer to the economic analysis for a complete discussion of the potential for economic impact resulting from these costs.

VII. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "* * * the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules. Copies of the study, Chemical Testing Industry: Profile of Toxicological Testing, can be obtained through the NTIS (PB 82-140773). On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing in this proposed rule.

VIII. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); In Washington, DC: (554-1404); Outside the U.S.A. (Operator—202-554-1404), by June 30, 1986. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, the Agency would transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

IX. Public Record

EPA has established a record for this rulemaking, (docket number OPTS-42084). This record contains the basic information considered by the Agency in developing this proposal, and appropriate **Federal Register** notices.

This record includes the following information:

A. Supporting Documentation

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

(a) Notice containing the ITC designation of MCP to the Priority List (50 FR 20930; May 21, 1985).

(b) Rules requiring TSCA section 8(a) and 8(d) reporting on MCP (50 FR 20909; May 21, 1985).

(c) Notice of final rule on EPA's TSCA Good Laboratory Practice Standards (48 FR 53922; November 29, 1983).

(d) Notice of interim final rule on single-phase test rule development and exemption procedures (50 FR 20652; May 17, 1985).

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

(f) Notice of proposed rule revising TSCA test guidelines (51 FR 1522; January 14, 1986).

(2) Support documents consisting of:

(a) MCP technical support document for proposed rule.

(b) Economic impact analysis of NPRM for MCP and commercial hexane.

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

(4) Communications before proposal consisting of:

(a) Written public comments and letters.

(b) Contact reports of telephone conversations.

(c) Meeting summaries.

(5) Reports—published and unpublished factual materials.

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X. Other Regulatory Requirements

A. Executive Order 12291

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

This proposed regulation 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 (15 U.S.C. 601 *et seq.*, Pub. L. 96–354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses because: (1) They are not likely to perform testing themselves, or to participate in the organization of the testing effort; (2) they will experience only very minor costs in securing exemption from testing requirements; and (3) they are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

The Office of Management and Budget (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. Submit comments on these requirements to the Office of Information and Regulatory Affairs: OMB; 726 Jackson Place, NW., Washington DC 20503, marked "Attention: Desk Officer for EPA." The final rule will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Parts 795 and 799

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

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Dated: May 2, 1986.

Victor J. Kimm,

Deputy Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that 40 CFR Chapter I be amended as follows:

PART 795—[AMENDED]

1. In proposed Part 795:

a. The authority citation continues to read as follows:

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

b. By adding new § 795.232 to read as follows:

§ 795.232 Inhalation and dermal pharmockinetics.

(a) *Purpose.* The purpose of these studies is to:

(1) Determine bioavailability of the test substance after dermal or inhalation administration.

(2) Ascertain whether the metabolism of the test substance is similar after dermal or inhalation administration.

(3) Examine the effects of repeated dosing on the metabolism of the test substance.

(b) *Definitions.* (1) Pharmacokinetics is the study of the kinetics of absorption, distribution, metabolism, and exertion of a test substance in animals.

(2) Bioavailability refers to the rate and relative amount of administered test substance which reaches the systemic circulation.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species.* The rat shall be used for pharmacokinetics testing because it has been used extensively for absorption, metabolism, and toxcicological studies. For dermal penetration studies, the female guinea pig shall also be used to provide additional information on dermal absorption.

(ii) *Animal strains.* Adult male and female Fischer 344 rats and female Hartley guinea pigs shall be used. At 7 to 9 weeks of age, the male rats shall weigh 125 to 175 grams and the female rats 110 to 150 grams. The female guinea pigs, 5 to 7 weeks old, shall weigh between 400 and 500 grams. The animals should be purchased from a reputable dealer and shall be identified with ear tags upon arrival. The animals shall be selected at random for the testing groups, and any animal showing signs of ill health shall not be used.

(iii) *Animal care.* (A) Animal care and housing shall be in accordance with DHEW Publication No. NIH)–78–23, 1978, "Guidelines for the Care and Use of Laboratory Animals."

(B) The animals shall be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms shall be maintained at a temperature of 25± 2°C and humidity of 5±10 percent with a 12-hour light/dark cycle per day. The rats shall be kept in a quarantine facility for at least 7 days prior to use.

(C) During the acclimatization period, the rats and guinea pigs shall be housed in suitable cages on hardwood chip bedding. All animals shall be provided with certified feed and tap water *ad libitum.* The guinea pig diet shall be supplemented with adequate amounts of ascorbic acid in the drinking water.

(2) *Administration*—(i) *Test substance.* The proposed study will require the use of both nonradioactive and radiolabled (preferably^{14}) test substance.

(ii) *Dosage and treatment.* (A) In the inhalation studies, three concentrations shall be used. The higher two concentrations should ideally induce some overt symptoms of toxicity after the exposure period is over, although the intermediate level of exposure may be excluded from this condition. The low concentration should not induce any observable signs of toxicity and, ideally, should approximate the human exposure level.

(B) Inhalation treatment shall be conducted using a "nose-cone" apparatus or other method that minimizes dermal exposure of the rats to the test substance. This procedure is preferable to a "bell jar" type, since rats "groom" themselves and could increase the dosage by licking their coat and swallowing the test substance.

(C) For dermal treatment, the doses shall be administered in a suitable vehicle and applied at a volume adequate to deliver the prescribed doses. The backs of the animals shall be lightly shaved with an electric clipper 24 hours before treatment. The dose shall be applied with a micropipette on a specific area (2 cm_2 for rats, 5 cm_2 for guinea pigs, or at least 10 percent of body surface) of the intact shaven skin. The dosed areas shall be concluded with a suitable patch which is secured in place.

(iii) *Washing efficiency study.* Before initiation of the dermal absorption studies described in paragraphs (c)(2)(iv) (A)(*2*) and (B) of this section, an initial washing efficiency experiment shall be conducted to assess the removal of the applied test compound by washing the exposed skin area with soap and water or organic solvents. Four rats and four guinea pigs shall be lightly anesthetized and then the test compound applied at the low dose level to a specific area. After application (5 to 10 minutes), the areas shall be washed with soap and water (2 rats, 2 guinea pigs) or appropriate solvent (2 rats, 2 guinea pigs), and the animals then housed in individual cages for excreta collection. Urine and feces shall be collected at least once following dosing. The amount of test substance recovered shall be determined to assess efficacy of the test substance removal by washing of the skin.

(iv) *Determination of pharmacokinetics*—(A) *Rat studies.* Each experimental group shall contain at least 4 animals of each sex for a total of at least 8 rats.

(*1*) *Inhalation studies* (6-hour exposure periods).

(*i*) Group A shall be exposed to a mixture of radioactive test substance in air at the low concentration.

(*ii*) Group B shall be exposed to a mixture of radioactive test substance in air at the intermediate concentration.

(*iii*) Group C shall be exposed to a mixture of radioactive test substance in air at the high concentration.

(*iv*) Group D—identical to paragraph (c)(2)(iv)(A)(*1*)(*i*) of this section.

(*v*) Group E—identical to paragraph (c)(2)(iv)(A)(*1*)(*ii*) of this section.

(*vi*) Group F—identical to paragraph (c)(2)(iv)(A)(*1*)(*iii*) of this section.

(*vii*) *Kinetic studies.* Groups A, B, and C shall be used to determine the kinetics of absorption of the test substance through the lungs. The concentration of the test substance in inspired and expired air and blood shall be measured at selected time intervals during and after inhalation exposure. The values for the test substance's retention, body burden, and saturability shall be calculated from these experiments.

(*viii*) *Metabolism studies.* At the end of the exposure periods, rats from Groups D, E, and F shall be placed in individual metabolic cages. Excreta (urine, feces, and expired air) shall be collected at 8, 24, 48, 72, and 96 hours post-treatment.

(*2*) *Dermal studies.* Two doses shall be used in this study. The high dose should, if possible, induce some overt toxicity, while the low dose should not. If feasible, the high and low doses for the dermal studies should be equivalent to the applied high and low doses administered during the inhalation studies.

(*i*) Group G shall be dosed once dermally with the low dose of the test substance (combination of radiolabeled and nonradiolabeled test substance components).

(*ii*) Group H shall be dosed once dermally with the high dose of the test substance (combination of radiolabeled and nonradiolabeled test substance components).

(*iii*) For the dermal studies, the test substance shall be kept on the skin for a

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minimum of 6 hours, or as determined by the absorption properties of the compound. After application, each animal shall be placed in a separate metabolic cage for excreta collection. Urine and feces shall be collected at 8, 24, 48, 72, and 96 hours. At the time of removal of the patch, the occluded area shall be washed with an appropriate solvent to remove any test substance which may remain on the skin surface. At the termination of the experiments, each animal shall be sacrificed and the exposed skin area removed. The skin (or an appropriate section) shall be solubilized and assayed for radioactivity to ascertain if the skin acts as a reservoir for the test substance.

(B) *Guinea pig studies.* The dermal studies conducted on groups G and H as specified in paragraph (c)(2)(iv)(A)(*2*) of this section shall be repeated using female guinea pigs. Groups I and J shall each contain at least 4 female guinea pigs.

(v) *Repeated dosing study.* Group K (4 rats, 2 of each sex) shall receive a series of single daily inhalation doses of nonradioactive test compound over a period of at least 14 days, followed at 24 hours after the last dose by a single inhalation dose of radiolabeled test compound. Each dose shall be at the low dose level.

(3) *Observation of animals*—(i) *Bioavailability.* The levels of radioisotope shall be determined in whole blood and blood plasma or blood serum at 8, 24, 48, 72, and 96 hours or at other time intervals necessary for completion of the study after dosing rats as specified in paragraph (c)(2) (iv)(A) and (v) of this section and guinea pigs as specified in paragraph (c)(2)(iv)(B) of this section. Four animals from each group shall be used for this purpose.

(ii) *Urinary and fecal excretion.* The quantities of radioisotope excreted in the urine and feces by rats dosed as specified in paragraph (c)(2) (iv)(A) and (v) of this section and guinea pigs dosed as specified in paragraph (c)(2)(iv)(B) of this section after dosing, and if necessary, daily thereafter until at least 90 percent of the applied dose has been excreted or until 7 days after dosing (whichever occurs first). Four animals from each group shall be used for these analyses.

(iii) *Biotransformation after inhalation and dermal dosing.* Appropriate qualititaive and quantatitive methods shall be used to assay urine and fecal specimens collected from rats dosed as specified in paragraph (c)(2)(iv)(A) of this section. Efforts shall be made to identify any metabolite which comprises 10 percent or more of the dose excreted.

(iv) *Changes in biotransformation.* Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of radiolabeled compounds in excreta (collected 24 and 48 hours after dosing) from rats dosed as specified in paragraph (c)(2)(iv)(A)(*l*)(*iv*) of this section with those in the excreta (collected at 24 and 48 hours after the radiolabeled dose) from rats in the repeated-dose study as specified in paragraph (c)(2)(v) of this section.

(d) *Data and reporting*—(1) *Treatment of results.* Data shall be summarized in tabular form.

(2) *Evaluation of results.* All observed results, quantitative or incidental, shall be evaluated by an appropriate statistical method.

(3) *Test report.* In addition to the reporting requirements as specified in the TSCA Good Laboratory Practice Standards under Part 792 of this chapter, the following specific information shall be reported:

(i) Species and strains of laboratory animals.

(ii) Information on the degree (i.e., specific activity for a radiolabel) and site(s) of labeling of the test substance.

(iii) A full description of the sensitivity and precision of all procedures used to produce the data.

(iv) Percentage absorption of radiolabeled test substance after inhalation and dermal exposures to rats and dermal exposure to guinea pigs.

(v) Quantity of isotope, together with percent recovery of administered dose of feces, urine, blood and skin and skin washings (dermal study only for last two portions of rats and guinea pigs).

(vi) Quantity and distribution of radiolabeled test substance in various tissues of rats, including bone, brain, fat, gonads, heart, kidney, liver, lung, muscle, spleen, and in residual carcass.

(vii) Biotransformation pathways and quantities of test substance and metabolites in excreta collected after administering single high, intermediate, and low inhalation and high and low dermal doses to rats.

(viii) Biotransformation pathways and quantities of test substance and metabolites in excreta collected after administering repeated low inhalation doses of test substance to rats.

PART 799—[AMENDED]

2. In Part 799:

a. The authority citation continues to read as follows:

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

b. By adding new § 799.2535 to read as follows:

§ 1799.2535 Methylcyclopentane.

(a) *Identification of test substance.* (1) Methylcyclopentane (MCP; CAS No. 96-37-7) shall be tested in accordance with this section.

(2) MCP of at least 99.9-percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests, and submit data.* All persons who manufacture or process, or intend to manufacture or process, MCP, other than as an impurity, and all persons who manufacture or process commercial hexane, other than as an impurity, from the effective date of this rule (44 days after the publication date of the final rule in the **Federal Register**) to the end of the reimbursement period shall submit letters of intent to conduct testing, submit study plans, conduct tests in accordance with Part 792 of this chapter, and submit data or submit exemption applications as specified in this section, Subpart A of this Part, and Part 790 of this chapter for single-phase rulemaking.

(c) *Health effects testing*—(1) *Neurotoxicity*—(i) *Required testing.* Neurotoxicity tests shall be conducted with MCP in accordance with §§ 795.250, 798.6050, 798.6200, 798.6400; and 798.6500 of this chapter.

(ii) *Reporting requirements.* (A) The study plans for the neurotoxicity tests must be submitted at least 45 days before the initiation of testing.

(B) The neurotoxicity tests shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

(C) Progess reports shall be submitted 6 months from the effective date of the final rule.

(2) *Inhalation and dermal pharmacokinetics*—(i) *Required testing.* An inhalation and dermal pharmacokinetics test shall be conducted with MCP in accordance with § 795.232 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the inhalation and dermal pharmacokinetics test must be submitted at least 45 days before initiation of testing.

(B) The inhalation and dermal pharmacokinetics testing shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

(C) Progress reports shall be submitted 6 months from the effective date of the final rule.

(3) *Subchronic inhalation toxicity*—(i) *Required testing.* A subchronic inhalation toxicity test shall be

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conducted with MCP in accordance with § 798.2450 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the subchronic inhalation toxicity test must be submitted at least 45 days before initiation of testing.

(B) The subchronic inhalation toxicity test shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final rule.

(C) Progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

PART 799—[AMENDED]

2. In Part 799: By adding § 799.2155 to read as follows:

§ 799.2155 Commercial hexane.

(a) *Identification of test substance.* (1) "Commercial hexane," for purposes of this rule, is a product obtained from crude oil, natural gas liquids, or petroleum refinery processing which consists primarily of six-carbon alkanes or cycloalkanes and contains at least 50 liquid volume percent n-hexane (CAS No. 110-54-3) and at least 5 liquid volume percent methylcyclopentane (MCP; CAS No. 96-37-7).

(2) The test substance shall be commercial hexane A, or solvent grade, derived from the fractionation of straight-run gasoline, and shall consist of no more than 64 liquid volume percent *n*-hexane and no less than 19 liquid volume percent MCP.

(b) *Persons required to submit study plant, conduct tests, and submit data.* All persons who manufacture or process, or intend to manufacture or process, commercial hexane, other than as an impurity, from the effective date of this rule (44 days after the publication date of the final rule in the **Federal Register**) to the end of the reimbursement period shall submit letters of intent to conduct testing, submit study plans, conduct tests in accordance with Part 792 of this chapter, and submit data, or submit exemption applications, as specified in this section, Subpart A of this Part, and Part 790 of this chapter for single-phase rulemaking.

(c) *Health effects testing*—(1) *Acute inhalation toxicity*—(i) *Required testing.* An acute inhalation toxicity test shall be conducted with commercial hexane in accordance with § 798.1150 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the acute inhalation toxicity test must be submitted at least 45 days before the initiation of testing.

(B) The acute inhalation toxicity test shall be completed and the final results submitted to the Agency within 6 months of the effective date of the final rule.

(2) *Subchronic inhalation toxicity*—(i) *Required testing.* A subchronic inhalation toxicity test shall be conducted with commercial hexane in accordance with § 798.2450 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the subchronic inhalation toxicity test must be submitted at least 45 days before initiation of testing.

(B) The subchronic inhalation toxicity test shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final rule.

(C) Progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

(3) *Oncogenicity*—(i) *Required testing.* An oncogenicity test shall be conducted by inhalation with commercial hexane in accordance with § 798.3300 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the oncogenicity test must be submitted at least 45 days before the initiation of testing.

(B) The oncogenicity test shall be completed and the final results submitted to the Agency within 53 months of the effective date of the final rule.

(C) Progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

(4) *Reproduction and fertility effects*—(i) *Required testing.* A reproduction and fertility effects test shall be conducted by inhalation with commercial hexane in accordance with § 798.4700 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the reproduction and fertility effects test must be submitted at least 45 days before the initiation of testing.

(B) The reproduction and fertility effects test shall be completed and the final results submitted to the Agency within 29 months of the effective date of the final rule.

(C) Progress reports shall be submitted at 6-month intevals beginning 6 months after the effective date of the final rule.

(5) *Inhalation developmental toxicity*—(i) *Required testing.* An inhalation developmental toxicity test shall be conducted with commercial hexane in accordance with § 798.4350 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the inhalation developmental toxicity test must be submitted at least 45 days before the initiation of testing.

(B) The inhalation developmental toxicity test shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

(C) Progress reports shall be submitted 6 months from the effective date of the final rule.

(6) *Mutagenic effects—gene mutations*—(i) *Required testing.* (A)(*1*) A *Salmonella typhimurium* reverse mutation assay shall be conducted with commercial hexane both with and without metabolic activation in accordance with § 798.5265 of this chapter and as modified in paragraph (c)(6)(i)(A)(*2*) of this section.

(*2*) Test standard modifications. The requirement under § 798.5265 of this chapter is modified so that the assay shall be performed using the desiccator method described as follows: The agar overlay plates shall be placed uncovered in a 9-liter desiccator. A volume of the liquid test substance shall be added to the glass Petri dish suspended beneath the porcelain shelf of the desiccator. A magnetic stirring bar to serve as a fan to assure rapid distribution and even distribution of the vapor shall be placed on the bottom of the inside of the desiccator. The desiccator shall be placed on a magnetic stirrer within a 37° C room or chamber for 7 to 10 hours. The plates shall then be removed, their lids replaced, followed by incubation for an additional 40 hours at 37° C before counting.

(B)(*1*) A gene mutation test in mammalian cells shall be conducted with commercial hexane both with and without metabolic activation as specified in § 798.5300 of this chapter and as modified in paragraph (c)(6)(i)(B)(*2*) of this section if the results from the *Salmonella typhimurium* test conducted pursuant to paragraph (c)(6)(i)(A) of this section are negative.

(*2*) Test standard modifications. The requirement under § 798.5300 of this chapter is modified to read as follows: Cells should be exposed to the test substance both with and without metabolic activation. Treatment flasks shall be incubated on a rocker panel to insure maximum contact between the cells and the test agent. Incubation shall be at 37° C for 18 hours for experiments without metabolic activation and for 5 hours for experiments with activation. Each flask shall be closed with a cap with a rubber septum. Headspace samples shall be taken at the beginning and the end of exposure period and analyzed to determine the amount of test substance in each flask.

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(C)(*1*) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with commercial hexane in accordance with § 798.5275 of this chapter and as modified in paragraph (c)(6)(i)(C)(*2*) of this section unless the results of both the *Salmonella typhimurium* test conducted pursuant to paragraph (c)(6)(i)(A) of this section and the mammalian cells in the culture gene mutation test conducted pursuant to paragraph (c)(6)(i)(B) of this section, if required, are negative.

(*2*) Test standard modifications. The requirement under § 798.5275 of this chapter is modified so that the route of administration shall be inhalation.

(D)(*1*) A mouse specific locus test shall be conducted with commercial hexane by inhalation in accordance with § 798.5200 of this chapter and as modified in paragraph (c)(6)(i)(D)(*2*) of this section if the results of the sex-linked recessive lethal test conducted pursuant to paragraph (c)(6)(i)(C) of this section are positive.

(*2*) Test standard modifications. The requirement under § 798.5200 of this chapter is modified so that the duration of exposure shall be for 6 hours per day.

(ii) *Reporting requirements.* (A) The study plans for each gene mutation test must be submitted at least 45 days before the initiation of testing.

(B) Gene mutation tests shall be completed and final results submitted as follows: *Salmonella typhimurium*, 4 months; mammalian cells in culture, 12 months; *Drosophila* sex-linked recessive lethal, 24 months; and mouse specific locus, 48 months.

(C) Except for the *Salmonella typhimurium* test, progress reports shall be submitted at 6-month intervals beginning 6 months after the effective date of the final rule.

(7) *Mutagenic effects—chromosomal aberrations*—(i) *Required testing.* (A)(*1*) An *in vitro* cytogenetics test shall be conducted with commercial hexane in accordance with § 798.5375 of this chapter and as modified in paragraph (c)(7)(i)(A)(*2*) of this section.

(*2*) Test standard modifications. The requirement under § 798.5375 of this chapter is modified so that the assay shall be performed using flasks flushed with commercial hexane vapors, then closed with a cap with a rubber septum.

(B)(*1*) An *in vivo* cytogenetics test shall be conducted with commercial hexane by inhalation in accordance with § 798.5385 of this chapter and as modified in paragraph (c)(7)(i)(B)(*2*) of this section if the *in vitro* test conducted pursuant to paragraph (c)(7)(i)(A) of this section is negative.

(*2*) Test standard modifications. The requirement under § 798.5385 of this chapter is modified so that the duration of exposure shall be for 6 hours per day for 5 consecutive days.

(C)(*1*) A dominant lethal assay shall be conducted with commercial hexane by inhalation in accordance with § 798.5450 of this chapter and as modified in paragraph (c)(7)(i)(C)(*2*) of this section unless both the *in vitro*. and *in vivo* cytogenetics tests conducted pursuant to paragraphs (C)(7)(i) (A) and (B) of this section are negative.

(*2*) Test standard modifications. The requirement under § 798.5450 of this chapter is modified so that the duration of exposure shall be for 6 hours per day for 5 consecutive days.

(D) A heritable translocation test shall be conducted with commercial hexane by inhalation in accordance with § 798.5460 of this chapter if the results of the dominant lethal assay conducted pursuant to paragraph (c)(7)(i)(C) of this section are positive.

(ii) *Reporting requirements.* (A) The study plans for each chromosomal aberration test must be submitted at least 45 days before the initiation of testing.

(B) Chromosomal aberration tests shall be completed and final results submitted as follows: *in vitro* cytogenetics, 4 months; *in vivo* cytogenetics, 12 months; dominant lethal assay, 24 months; and heritable translocation assay, 48 months.

(C) Except for the *in vitro* cytogenetics test, progress reports shall be submitted beginning 6 months after the effective date of the final rule.

(8) *Neurotoxicity*—(i) *Required testing.* Neurotoxicity tests shall be conducted with commercial hexane in accordance with §§ 798.6050, 798.6200, 798.6400, and 798.6500 of this chapter.

(ii) *Reporting requirements.* (A) The study plan for the neurotoxicity tests must be submitted at least 45 days before the initiation of testing.

(B) The neurotoxicity tests shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

(C) Progress reports shall be submitted 6 months from the effective date of the final rule.

(9) *Inhalation and dermal pharmacokinetics*—(i) *Required testing.* (A) An inhalation and dermal pharmacokinetics test shall be conducted with commercial hexane in accordance with § 795.232 of this chapter.

(B) Test standard modifications. The requirement under § 795.232 (c)(2)(i) of this chapter is modified to read as follows:

(2) *Administration of test substance*—(i) *(test substance.* Since the test substance is a mixture of *n*-hexane; MCP; 3-MP; 2-MP; benzene; cycolohexane; 2,2- and 2,4-DMp; 2,3-DMB; and sulfur, the experiments shall be conducted in groups using ^{14}C and ^{3}H labeled components. This type of labeling can be conducted in groups of 2 components. For example, in the first groups, *n*-hexane may be labeled with ^{14}Cv and MCP with tritium with the remaining components unlabeled. The kinetic and metabolic studies would then be run on the test substance and analyzed for *n*-hexane and MCP as described below. In the second group, 3-MP may be labeled with tritium and 2-MP labeled with ^{14}C. The third group would have benzene labeled with ^{14}C and cyclohexane labeled with tritium, etc. If it is feasible from an analytical standpoint, one of the higher liquid volume percent components (*n*-hexane, MCP, or 3-MP) could be labeled with deuterium and a gas chromatograph/mass spectrometer (GC/MS) used to follow the disposition of the deuterium-labeled component of the test substance. This procedure would permit the investigators to use fewer experimental groups to obtain the same amount of information.

(ii) *Reporting requirements.* (A) The study plan for the inhalation and dermal pharmacokinetics test must be submitted at least 45 days before the initiation of testing.

(B) The inhalation and dermal pharmacokinetics test shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

(C) Progress reports shall be submitted 6 months from the effective date of the final rule.

(Information collection requirements have been approved by the Office of Management and Budget under control number 2070-0033)

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40 CFR Parts 795 and 799

[OPTS-42083; FRL-2998-5]

Tetrabromobisphenol A; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing that manufacturers and processors of tetrabromobisphenol A (TBBPA, CAS No. 79-94-7) be required, under section

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