ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42094; FRL 3202-7]

Cyclohexane; Proposed Test Standards and Requirements

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: In response to the Interagency Testing Committee's (ITC) designation of cyclohexane (CAS No. 110-82-7) for health effects testing consideration, EPA is proposing under section 4(a)(1)(B) of the Toxic Substances Control Act (TSCA) that manufacturers and processors of cyclohexane be required to perform testing of this substance for subchronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, neurotoxicity, dermal absorption, and dermal sensitization.

DATES: Submit written comments on or before July 20, 1987. If persons request an opportunity to submit oral comments by July 6, 1987, 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-42094) in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. NE-G004, 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, 202-554-1404.

SUPPLEMENTARY INFORMATION: EPA is issuing a proposed test rule for cyclohexane under section 4(a) of TSCA in response to the ITC's designation of cyclohexane for health effects testing consideration. Testing is being proposed for cyclohexane under section 4(a)(1)(B) of TSCA because there is substantial production and there is or may be substantial human exposure. The Agency has concluded that existing data are inadequate to assess the risks to health posed by exposure to cyclohexane and that testing of cyclohexane 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 recommended cyclohexane with intent to designate for health effects testing in its 17th Report, published in the **Federal Register** of November 19, 1985 (50 FR 47603). The ITC designated cyclohexane for priority consideration in its 18th Report, published in the **Federal Register** of May 19, 1986 (51 FR 18369). The ITC recommended that cyclohexane be tested for chronic toxicity including oncogenicity and neurotoxicity, teratogenicity and reproductive toxicity. The rationale for recommending these tests was as follows: (1) The large production volume and many of the uses of cyclohexane indicating the potential for widespread human exposure; (2) the high number of workers occupationally exposed, and the possibility for general population exposure from cyclohexane's use as a solvent; (3) detection of cyclohexane in body fluids and in ambient air and water; (4) lack of data on chronic effects, including oncogenicity and neurotoxicity; and (5) lack of data on potential teratogenic and reproductive effects.

Ecological effects and chemical fate tests were not recommended because although several static acute toxicity tests with aquatic organisms have indicated moderate toxicity (LC_{50} values greater than 10 and less than 100 mg/L), measured environmental concentrations (low μg/L or less) and expected rapid degradation in air and water suggest that cyclohexane will not cause adverse ecological effects at concentrations likely to be found in the environment.

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:

(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 section 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 Agency 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 discussed at 46 FR 30300.

In evaluating the ITC's testing recommendations for cyclohexane, 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 cyclohexane under the TSCA section

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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) for cyclohexane; information submitted by the Cyclohexane Program Panel of the Chemical Manufacturers Association and published; and unpublished data on cyclohexane available to the Agency. From its evaluation, as described in this proposed rule, EPA is proposing health effects testing requirements for cyclohexane under section 4(a)(1)(B).

II. Review of Available Data

A. Chemical Profile

Cyclohexane is a colorless, flammable, mobile liquid with a pungent sweet odor (Refs. 1 and 2). At 25 °C, cyclohexane has a moderate water solubility of 55 mg/L (Ref. 3). Its vapor pressure is 100 mm Hg at 25.5 °C (Ref. 4) and its specific gravity is 0.779 at 20/4 °C (Ref. 2). The log octanol/water partition coefficient (K_{ow}) was experimentally determined to be 3.44 (Ref. 5). A log soil/sediment-absorption coefficient (K_{oc}) is estimated as 3.25 (Ref. 6). Cyclohexane has an estimated Henry's Law constant of 0.196 atm-m^3/mole (Ref. 6). Because of its high volatility and moderate water solubility, cyclohexane is expected to partition into the atmosphere. An estimated atmospheric half-life of 2.83 days (Ref. 6) suggests that cyclohexane will not persist in the atmosphere. A steady state atmospheric concentration of cyclohexane may arise, however, because of the continued release of cyclohexane (Ref. 6).

B. Production

1. *Production methods.* High purity cyclohexane is produced by the hydrogenation of benzene over nickel, palladium, or platinum catalysts in the liquid or vapor phase (Ref. 7). Formation of cyclohexane is greater at lower temperatures (Ref. 8). Hydrogenation is usually carried out at 20 to 30 atm and 300 to 350 °C, yielding cyclohexane containing <500 ppm benzene. Higher temperatures promote higher benzene concentrations and isomerization of cyclohexane to methylcyclopentane. Cyclohexane of 98 percent purity can be produced by the catalytic conversion of petroleum-derived cyclohexane to a mixture of benzene and methylcyclopentane followed by hydrogenation and isomerization, respectively (Ref. 8).

Cyclohexane occurs naturally in all crude oils at concentrations of 0.5 to 1.0 weight percent (Ref. 9). According to Kirk-Othmer (Ref. 7), the concentration range is 0.1 to 1.0 percent. A small amount of low purity cyclohexane is produced by fractional distillation of crude oil and from catalytic reformer effluent (Ref. 7). The cyclohexane recovered from petroleum is about 85 percent pure. Low purity cyclohexane is also derived from natural gas naphthas by fractionation and high-efficiency distillation to give an 85 percent pure product (Ref. 8).

2. *Domestic production.* Total U.S. production volume of cyclohexane from 1977 to 1982 ranged from 1.27 to 2.24 billion pounds per year (Ref. 9). The seven U.S. producers of cyclohexane reported 1.788 billion pounds of production in 1985 (Ref. 10). According to the chemical profile for cyclohexane in the Chemical Marketing Reporter of 1983, the projected production of cyclohexane in 1987 is 230 million gallons or 1.5 billion pounds (Ref. 11). It is expected that cyclohexane will be produced at 60 to 65 percent of plant capacity through 1990 (Ref. 11). According to the Chemical Manufacturers Association (CMA), in 1986, there were seven manufacturers of cyclohexane (Ref. 10).

3. *Imports.* Import volume of cyclohexane for the years 1980 to 1982 was 13.5 to 30.6 million pounds per year (Refs. 12 through 14). Imports of cyclohexane for the period January–July, 1985, were only 9,000 pounds compared to 21.1 million pounds for that period in 1984 (Ref. 15). The decline was attributed to increased imports of finished textile products, which lowered the demand for cyclohexane as a synthetic fiber intermediate (see Unit II.C).

4. *Anthropogenic sources—a. Sources from hydrocarbon processing.* Cyclohexane occurs in crude oils at concentrations of 0.5 to 1.0 weight percent (Ref. 9). Approximately 179 billion gallons of crude oil was used as feedstock in domestic refineries in 1983 (Ref. 20). The average specific gravity of Arabian crude oil is 0.86 (Ref. 7). From this value, a weight/gallon ratio of crude oil of 7.16 pounds/gallon was calculated. Assuming the latter value to be representative of crude oil in general, the amount of cyclohexane in the 179 billion gallons of crude oil feedstock was calculated to range from 6.41 to 12.82 billion pounds. Oil spills in the United States during 1981 released 10,697,000 gallons of crude oil to the environment (Ref. 16). Using the range of cyclohexane in crude oil and the average weight/gallon for crude oil given above, this translates into 382,000 to 766,000 pounds of cyclohexane released to the environment in 1981 by oil spills. About 0.2 percent of the annual production, or as much as 1 million pounds/year of cyclohexane may have been lost in the years 1979 to 1980 as fugitive emissions and evaporative losses from refineries, but an unspecified percentage of this cyclohexane is flared (Ref. 17). The amount of cyclohexane entering the atmosphere as a result of these losses, therefore, cannot be estimated. Volatile liquid hydrocarbon (VLH) cycloalkanes, including cyclohexane, are present in underwater vent plumes and formation water from offshore oil production operations (Ref. 18). The amount of cyclohexane released in this way cannot be estimated from the available information.

b. *Sources from the distribution and use of finished fuel products.* According to SRI International (Ref. 9), the concentration of cyclohexane in gasoline ranges from 5 to 15 percent. The concentration of cyclohexane in an unleaded gasoline composite used for comparing gasolines is 1.58 volume percent, and cyclohexane at 1.05 volume percent was detected in one unleaded gasoline (Ref. 19). The value of 1.58 volume percent was used for the following calculations since it probably reflects the cyclohexane concentration in a variety of gasolines. The 1983 production volume of gasoline was 97 billion gallons (Ref. 20). This translates into 1.53 billion gallons of cyclohexane or about 9.5 billion pounds of cyclohexane in finished gasoline in 1983. In 1980, an estimated 7.7 million tons of hydrocarbons were released by land transportation vehicles. Exhaust samples from a variety of automobiles without emission control devices were found to contain an average of 0.6 percent (weight/weight) of cyclohexane (Ref. 21). Cyclohexane has been detected but not quantified in the distillate fuel, JP–4 (Ref. 22). An estimate of the amount of cyclohexane released by the use of JP–4 cannot be made with the available information.

5. *Solvent related sources.* One pesticide grade *n*-hexane, used as a solvent in chemical analyses, contained 0.1 to 1.0 percent cyclohexane (Ref. 23). Hexane A, a relatively impure hexane, contains 0.78 volume percent cyclohexane (Ref. 7). No information on commercial uses of hexane A was available. Hexanes B and C, which are widely used, contain no measurable amounts of cyclohexane (Ref. 7). Release of cyclohexane due to the use of *n*-hexanes, therefore, is expected to be low. A Japanese study detected cyclohexane in only one of 1,179

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samples of thinners, degreasers, and miscellaneous solvents. The unspecified thinner contained 21.0 percent cyclohexane (Ref. 24).

6. *Cyclohexane in biological materials.* Cyclohexane was detected but not quantified in the hydrocarbon fraction of cigarette smoke gases (Ref. 25). This study was designed to qualitatively identify hydrocarbon components, but semi-quantitative data were obtained that suggest cyclohexane is present only in trace amounts. The origin of the cyclohexane in the tobacco was not specified. Muscat oil (from muscat grapes) was analyzed by GLC and found to contain cyclohexane (Ref. 26). It was suggested that the cyclohexane found may have been due to unspecified solvents sprayed on the fruit before harvesting.

C. Uses

The primary use of cyclohexane is as a raw material in the production of Nylon-6 and Nylon-66 (Refs. 2 and 7). Cyclohexane is oxidized to cyclohexanol or cyclohexanone followed by conversion to adipic acid, which is used in the preparation of Nylon-66 (Ref. 8). Cyclohexane can also be oxidized solely to cyclohexanone, from which caprolactam is prepared and then used in the production of Nylon-6 (Ref. 8). Approximately 58.1 percent and 26.7 percent of the total 1981 United States production of cyclohexane was used for the production of nylon or nylon-related production via adipic acid and caprolactam, respectively (Ref. 9). According to a chemical profile for cyclohexane, 54 percent of the 1983 cyclohexane production volume was used for adipic acid for the production of Nylon-66 and 26 percent was used for caprolactam for the production of Nylon-6 (Ref. 11). Exports and miscellaneous uses accounted for 19 percent and 1 percent of 1983 cyclohexane production, respectively (Ref. 11). It is assumed that solvent uses including azeotroping medium compose the bulk of these miscellaneous uses (Ref. 6). Using a 1983 cyclohexane production volume of 2.1 billion pounds (Ref. 27), as much as 21 million pounds of cyclohexane, therefore, may have been used as solvent in 1983. A recent survey by the Chemical Manufacturers Association (Ref. 28) from 12 of 35 identified users, however, indicates that 1.66 billion pounds of cyclohexane was used as an intermediate and 42.1 million pounds as a solvent (Ref. 28). Cyclohexane was received by barge (65.1 percent), pipeline (18.9 percent), rail car (15.4 percent), tank truck (0.6 percent) and drum (<0.01 percent) (Ref. 28).

Cyclohexane is increasingly used to dehydrate ethyl and isopropyl alcohols (Ref. 28). Addition of cyclohexane to ethanol:water and isopropanol:water azeotropes breaks the azeotropes, allowing the pure alcohols to be isolated. Some important alcohol azeotropes are ethanol:cyclohexane (30:70) and isopropanol:cyclohexane (22:67). Consumption of cyclohexane for non-nylon uses was estimated to be 58 million pounds in 1985. This amount was estimated to be distributed among current uses as follows: high pressure polyethylene synthesis—2 million pounds; purification of ethanol—30 million pounds; purification of isopropanol—1.5 million pounds; catalyst carriers—25 million pounds (Ref. 28). Cyclohexane serves as the solvent for the catalyst used in the production of Shell Company's Kraton thermoplastic elastomer and the solvent for the polymerization process (Ref. 28).

Minor reported uses include solvent uses for cellulose ethers, fats, oil, waxes, bitumens, resins, and crude rubber; the extraction of essential oils; uses in organic syntheses and as a recrystallation medium; as a paint or varnish remover; in fungicides (Ref. 2); and in the manufacture of solid fuels for camp stoves (Ref. 1). It is not known to what extent these uses currently occur. Cyclohexane may be found in paint removers and rubber adhesives (Ref. 29). Cyclohexane was listed on the label as a component of two consumer spray adhesives (See Unit II.D.2.), Scotch Sprayment Art and Display Adhesive and Super 77 Spray Adhesive (Ref. 30).

D. Human Exposure

1. *Occupational exposure.* Provisional data from 1981 to 1983 from the National Occupational Exposure Survey (NOES) indicate that 42,558 workers, including 12,021 females, were exposed to cyclohexane at 985 plants (Ref. 31). The level of exposure and whether this exposure was routine or intermittent were not specified.

Worker exposure standards for atmospheric cyclohexane include the permissible exposure limit of 300 ppm established by OSHA (29 CFR 1910.1000, Table Z-1), which is also the threshold limit value/time-weighted average recommended by ACGIH (Ref. 32).

The Cyclohexane Program Panel (the Panel) of the Chemical Manufacturers Association (CMA) is composed of the seven U.S. cyclohexane producers, one of which is also a processor. The following information on the exposure of cyclohexane workers in manufacturing was developed by the Panel (Ref. 10). The survey covers 11 production units at 10 manufacturing locations.

The producers report that a total of 119 workers are exposed routinely (3 or more 8 or 12-hour work days per week) and an additional 62 persons are exposed intermittently (2 or fewer 8 or 12-hour work days per week) to cyclohexane. One producer has an internal exposure limit of 150 ppm per 12-hour time-weighted-average (TWA). The others operate under the Occupational Safety and Health Administration (OSHA) 300 ppm Permissible Exposure Limit (PEL). Four of these producers operate on 8-hour shifts for maintenance personnel and a 12-hour shift for operators.

Two of the seven producers reported that no respiratory protection is used at any of the sites to minimize exposure to cyclohexane. Five producers reported use of protective clothing such as goggles, face shields, gloves, and synthetic outer garments impervious to cyclohexane. Four producers report the use of formal training programs on hazard awareness and one producer minimizes exposure by adjustment of work assignments.

Four producers have conducted area monitoring for cyclohexane or volatile organic chemicals. Monitoring data from over 5,000 samples ranged from .001 to 4,171 ppm. The arithmetic average ranged from .3 to 20 ppm from 3 producers for 8 or 12 hour shifts. The other producer reported a geometric mean of .03 to 1.65 ppm.

Additional occupational exposure information from production facilities is as follows: About 48 operating, maintenance and supervisory personnel at Texaco are potentially exposed to cyclohexane (Ref. 33). These workers were monitored at an unspecified Texaco plant and the arithmetic mean for the 56 personal 8-hour TWA samples taken was 1.77 ppm. According to Walker (Ref. 27), the Texaco plant at Port Arthur, TX, was the site of data collection in the monitoring study above. Personal monitoring data (about 3,305 samples) from about 200 workers at three Phillips facilities ranged from undetectable levels to 112.97 ppm with a geometric mean of <0.29 ppm. According to Dynamac (Ref. 17), the three Phillips plants were the Borger and Sweeney refineries in Texas and the Puerto Rico Core Refinery.

Texaco (Ref. 34) provided monitoring data quantifying worker exposure to cyclohexane in its Port Arthur cyclohexane manufacturing plant. Worker exposure to cyclohexane ranged from an 8-hour time-weighted-average of 0.03 to one of 11.57 ppm. The mean cyclohexane concentration was 1.59 ppm. The minimum and maximum

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exposure levels were associated with operators with an unknown type of respirator exposed to "running unknown spills." Cyclohexane concentrations ranged from 0.03 to 28.0 ppm with a mean concentration of 1.73 ppm in area samples. The maximum concentration resulted from a spill in an unknown location. Short-term samples for cyclohexane ranged from 0.06 to 180.0 ppm with a mean concentration of 9.25 ppm. The maximum value was associated with a pipefitter; no specific activity or location was reported.

In the CMA Panel User Survey (Ref. 28), to which 12 of 35 identified users and processors responded, a total of 1,388 employees (assigned to production units and/or involved in distribution) in 22 locations were potentially exposed to cyclohexane. Routine exposure to cyclohexane (3 or more work schedules/week) occurred in 477 persons and intermittent exposure (2 or less work schedules/week) in 577 persons. No information was offered about the remaining 334 potentially exposed persons or the workers employed by the remaining 23 identified uses. Personal monitoring data indicated that 8 or 12 hour TWAs ranged from 0 to 50 ppm. One of the companies had internal exposure guidelines of 150 ppm based on a 12-hour TWA. Nine of 12 companies used protective clothing including gloves, goggles or face shields, respirators, rubber boots, SCBA equipment, acid suits and fireproof suits. Engineering controls used to minimize exposure to cyclohexane were closed loading (10 companies), flow check valves (7 companies), closed-loop sampling (2 companies), remote atmosphere venting (4 companies), vent to flare (7 companies), local exhaust (6 companies), vapor recovery (7 companies), dripless, self-closing valves (2 companies), double mechanical seals (6 companies) and double-sealed valves (6 companies). Three other companies reported using a variety of exposure minimization techniques including catalytic incineration; seal, flush, vent through scrubber; minimum purge coupling; floating roofs and nitrogen blanket. Other minimization techniques included administrative controls (adjustment of work assignments) (2 companies) and formal hazard awareness training programs (11 companies). The parenthetical numbers correspond to the number of companies using the various techniques.

The levels of cyclohexane in all 55 samples of workplace atmospheres of seven Standard Industrial Code (SIC) industries taken from 1981 to 1984 were <300 ppm (4 codes N.D.; 2 codes <150 ppm) (Ref. 19). The samples were taken from the following SIC industries: (a) Commercial printing, lithographic; (b) miscellaneous plastic products; (c) gaskets, packing and sealing devices; (d) architectural and ornamental metal work; (e) semiconductors and related devices; (f) orthopedic prosthetic and surgical appliances and supplies; and (g) computer programming and software.

Worker exposures to cyclohexane are also possible through its use as a laboratory chemical, particularly as a solvent for extraction and separation in preparative and analytical chemistry. Cyclohexane is sold in bottles and drums by a number of chemical companies including Fisher and Aldrich Chemical Companies (Refs. 35 and 36).

A reasonable worst-case laboratory exposure estimate was created as follows by Syracuse Research Corporation (SRC) (Ref. 6): A 500 g quantity of cyclohexane was allowed to evaporate into an unventilated laboratory of dimensions 25 m x 10 m x 5 m (i.e., 1,250 m^3 volume). This created a cyclohexane concentration in air of 400 mg/m^3, or about 120 ppm. This is an unlikely event, but one that could occur through neglect or accident, such as failure to work in an operative fume hood, or otherwise vent solvent vapors during an evaporative operation. According to SRC laboratory personnel, the air in the SRC chemistry laboratories is completely exchanged about every 2 hours, exclusive of fume hood operation. This will significantly limit the levels of cyclohexane that can be achieved, even in case of grossly incompetent laboratory technique. NIOSH (Ref. 37) notes that the odor threshold of cyclohexane is 0.41 ppm and that 300 ppm (the OSHA PEL) is somewhat irritating to the eyes. Despite this, cyclohexane is classified by NIOSH as having poor warning properties because of the sweetish nature of the odor and insufficient irritancy.

EPA has estimated 8-hour TWAs for workers in various paint and glue formulation operations ranged from 2 to 26 ppm with an average value of 7.5 ppm (Ref. 29). Inhalation exposure to cyclohexane ranged from 0.1 to 0.9 ppm in spray painting and 3.5 to 5.7 ppm in glue spraying operations, based on personal monitoring data (Ref. 29). An 8-hour TWA of 2 to 7 ppm was obtained using the volatilization model of the Chemical Engineering Branch, Office of Toxic Substances, USEPA (Ref. 38), for exposure resulting from cyclohexane volatilization from open dip and brush paint and glue application equipment. It should be noted that EPA is uncertain that cyclohexane is used in paint and glue formulations and seeks additional information on these uses (See Unit V.3 of this document). Worker exposure to cyclohexane from gasoline was estimated to range from 0.001 to 1.02 ppm, based on the typical cyclohexane content of gasoline, 8 hours exposure and methylcyclopentane data submitted to the ITC (Ref. 29).

Exposure to cyclohexane from gasoline found in a survey of 231 workers in a variety of jobs ranged from an average of 0.02 to 2.36 ppm (Ref. 39). Although maximum exposure values ranged from .08 to 9.40 ppm, in three cases the average exposure value reported was higher than the corresponding maximum exposure level, a discrepancy that leaves this information open to question.

2. *Consumer exposure.* The cyclohexane content in three rubber solvents ranged from 1.18 to 1.93 percent, commercial hexane contained from 0.4 to 2.0 percent cyclohexane and textile spirit contained from 1.9 to 4.3 percent cyclohexane (Ref. 39). Cyclohexane was listed as a component on the label of two spray adhesives: Scotch Sprayment Art and Display Adhesive (Cat. No. 6060) and Super 77 spray adhesive (Ref. 30). Cyclohexane may also be present in paints, paint removers and rubber glues and other adhesives. (See Unit V.2 and V.3 of this document.)

3. *General population exposure.* Human milk from five of eight mothers contained cyclohexane at unquantitated levels (Ref. 40). The authors suggested that the cyclohexane in the milk resulted from the mothers' exposure to environmental pollutants since they resided near chemical manufacturing plants or industrial user facilities. Krotoszynski and O'Neill suggested that the cyclohexane found but not quantified in non-smokers by GC/MS was due to exposure to the compound in the environment (Ref. 41).

A number of studies have been conducted in which cyclohexane has been detected in ambient air. Concentrations of 0.1 to 31 parts per billion (ppb) have been reported in the atmosphere of seven U.S. cities (Ref. 6) indicating that cyclohexane is widespread in urban air. This is likely due to the presence of cyclohexane in automobile exhaust. The presence of cyclohexane in air samples from rural or remote areas may be due to nonanthropogenic sources, but the available information is equivocal. Arnts and Meeks presented monitoring data from six sites in Rio Blanco county in Colorado, an area containing shale oil deposits. Cyclohexane was found in

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only one of the six sites, however, so the authors' conclusion that the hydrocarbons detected were not due to a distant urban source must be regarded as tentative (Ref. 42). No quantitative statements can be made about total human exposure to cyclohexane with the available information.

Thirteen of an unspecified number of surface water samples collected from 204 sites near industrial areas across the United States contained cyclohexane at unspecified concentrations (Ref. 43). Because of the expected rapid volatilization of cyclohexane, however, it is likely that human exposure to cyclohexane from this source will be insignificant. A cyclohexane concentration of 540 ppb was detected in a drinking water well in New York. It was not specified whether this was a maximum, minimum or average value, nor was the frequency with which cyclohexane was found in the samples taken (Ref. 44).

4. *Non-human populations.* No data were available which indicate the level of cyclohexane exposure in nonhuman populations. Since the majority of cyclohexane is released in urban areas and estimations suggest complete partitioning to the atmosphere, the cyclohexane levels to which organisms, particularly aquatic species, may be exposed are expected to be low.

E. Environmental Releases

Release of cyclohexane to the environment occurs mainly from the use of products in which cyclohexane is an inadvertent component. In 1980, an estimated 92.4 to 92.8 million pounds of cyclohexane was released primarily by hydrocarbon emissions from land transportation vehicles and to a lesser extent by oil spills (Ref. 6). About 0.2 percent of the annual production of cyclohexane or 1,050,000 pounds/year of cyclohexane may have entered the environment in the years 1979 to 1980 as fugitive emissions or evaporative losses from refineries, but an unspecified amount of this cyclohexane is flared (Ref. 17). The amount of cyclohexane released in this way cannot, therefore, be estimated.

The CMA provided the following estimates for environmental release of emissions from producers (Ref. 10). The CMA panel used EPA AP-42 equations (Ref. 45) and 600/2-79-044 (fugitive) guidelines (Ref. 46) to generate these numbers.

Source	Emissions (metric tons/yr)
Fugitive	147.21
Storage	23.29
Production	26.04
Barge loading	58.9
Total	257.44

In the same submission, the CMA reported that one producer reports a cyclohexane level of less than 1 ppm in the effluent from waste water treatment plants and one other reports a measured level less than 0.5 ppm (Ref. 10).

The CMA user survey (Ref. 28) provided the following information. Cyclohexane emissions were estimated at 372,000; 202,000; 970,000; and 1,053,000 kg/yr for fugitive, storage, production, and residuals in product, respectively. Disposal methods included off-site incineration (2,043,163.6 kg), flaring (1,198,181.82 kg), boiler fuel (13,636.6 kg), deep well injections (<454.5 kg), direct release to air (43,181.8 kg), and handling by a waste disposal firm followed by incineration or landfilling (1,363.6 kg). None of the companies supplied data on cyclohexane levels in waste water treatment plant effluents.

Potential sources of cyclohexane release that cannot be quantified are cigarette smoke, the deliberate venting of waste hydrocarbon gases and dumping of formation waters (water produced with oil and gas) associated with offshore crude oil production operations, and the use and disposal of solvents containing cyclohexane.

F. Health Effects

1. *Pharmacokinetics.* The Agency has reviewed several cyclohexane intravenous, oral, and inhalation absorption, distribution, metabolism and elimination studies (Refs. 47 through 60) and concluded that no further pharmacokinetic testing is necessary except for dermal absorption. However, it is possible that the chronic toxicity study proposed in this document will show some unusual target organ and/or possible mechanism of action that will require further metabolic studies.

Jeffcoat performed intravenous and oral studies on the absorption, distribution, metabolism and excretion of ^{14}C-cyclohexane in adult male Fischer 344 rats (Ref. 47). The results indicated that cyclohexane had a short residence time. The elimination half-lives of total ^{14}C for plasma and tissues were on the order of 10 to 15 hours. Eighty percent of the intravenous dose was excreted via the lung in 24 hours. Greater than 61 percent of the oral dose was excreted via the lungs in 12 hours. Approximately 14 percent of the intravenously administered dose and from 12 to 29 percent of the oral dose was excreted via the urine in 72 hours. Cyclohexane, cyclohexanol and cyclohexanone were detected only as trace quantities in the urine. The chemical structures of the three major metabolites detected by HPLC were not determined, but the author stated that they elute from the column "in the region typical of conjugates."

Results from oral, inhalation and dermal toxicity studies of cyclohexane in rabbits by Treon et al. (Refs. 48 and 49) indicated that cyclohexane metabolites are excreted in the urine as sulfate and glucuronic acid conjugates.

Elliott et al. (Ref. 50) studied the urinary metabolites of ^{14}C-cyclohexane in adult female chinchilla rabbits. The compound was administered in water by gavage. When a dose of 300 to 400 mg cyclohexane/kg (higher dose group) was administered, 35 to 45 percent of the dose was detected in expired air. Approximately 10 percent of the dose was detected as carbon dioxide; the remainder was unchanged cyclohexane. At a very small dose (0.3 mg/kg, low dose), 5.5 percent of the administered dose was detected in expired air as carbon dioxide. No unchanged cyclohexane was found. The two metabolites found in the urine were glucuronide conjugates of cyclohexanol, (30 to 40 percent of the high dose and 60 percent of the low dose) and (±) transcyclohexane-1,2-diol, (5 to 8 percent of the high dose and 17 percent of the low dose).

Cyclohexane has also been found in five out of eight human breast milk samples collected from women in Bayonne, NJ (2/2); Jersey City, NJ (1/2); Pittsburgh, PA (2/2); and Baton Rouge, LA (0/2) (Ref. 40).

2. *Acute toxicity.* Acute toxicity data for cyclohexane are summarized below. The data are sufficient to reasonably determine or predict the acute effects of cyclohexane except for dermal sensitization.

a. *Acute oral toxicity.* Phillips Petroleum Company has provided the results of an acute oral toxicity study performed with rats (in groups of five males, five females; strain not reported) conducted by Hazleton Laboratories (Ref. 61). A single oral dose of 5 g/kg body weight (bw) was administered to the animals by gavage, followed by observation at 1, 2 and 4 hours post-dosing. Animals were observed twice daily for a further 14 days. No animals died during the study, and all animals gained weight over the 14-day observation period. Clinical observations of depression, salivation

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and soft feces seen 1, 2, and 4 hours post-dosing were not noted from day 2 through termination of the study. Necropsies performed on all 10 rats revealed no gross pathology findings in any animal. This result indicates that the acute oral lethal dose for cyclohexane is greater than 5 g/kg bw in the rat.

Kimura et al. (Ref. 62) investigated the acute oral toxicity of cyclohexane to rats of different age groups over a 7-day observation period. LD_{50} values of <0.78, 6.2, 30.3, and 12.8 g/kg cyclohexane were reported for neonate (24 to 48 hours old), immature (14 days old), young adult (80 to 160 g) and adult (300 to 470 g) rats, respectively. Rabbits administered a single oral dose of 1 to 10 g/kg cyclohexane exhibited overt signs of intoxication including severe diarrhea and increased respiration (Ref. 48). The minimum lethal dose of cyclohexane was between 5.5 and 6 g/kg (Ref. 48).

b. *Acute inhalation toxicity.* Phillips provided the results for an acute inhalation toxicity study performed with rats (five/sex) conducted by Hazleton Laboratories (Ref. 64). The mean analytical concentration was reported to be 21,250.0 ppm (S.D. 925.82) in methane equivalents, or 4,044 ppm (13.9 mg/L) cyclohexane. The duration of exposure was 4 hours, and animals were observed for a further 14 days before sacrifice and necropsy. Over the 4-hour exposure, tremors, hyperactivity, rapid respiration and prostration were noted in all animals. Ataxia was observed in one animal. During the post-exposure observation period, all females appeared normal, one male exhibited localized alopecia (noted on days 1 to 10), and one male (the report does not state whether this is the same or a different animal) exhibited sores around the left eye (noted on days 8 to 10). No exposure-related trends were reported in either mean body weights or gross pathology. This result indicates that the acute inhalation lethal dose for cyclohexane is greater than 4,044 ppm (13.9 mg/L) in rats.

A precis of the acute toxic effects of inhalation exposures to cyclohexane reported in the earlier literature is presented in Patty (Ref. 65). Overt signs of intoxication exhibited in mice exposed to 18,000 ppm included trembling within 5 minutes, disturbed equilibrium within 15 minutes and complete recumbency within 25 minutes of continuous exposure. Atmospheric concentrations of 18,000 ppm cyclohexane produced slight trembling in guinea pigs over an unspecified period of exposure, disturbed equilibrium (11 minutes) and complete recumbency (18 to 25 minutes) in cats, and slight trembling (6 minutes), disturbed equilibrium (15 minutes) and complete recumbency (30 minutes) in rabbits. Following a single exposure of rabbits to cyclohexane vapors, Deichmann and LeBlanc (Ref. 66) reported no visible effects at 3,330 ppm and lethargy, narcosis, increased respiration and convulsions at 12,600 and 18,500 ppm over an 8-hour observation period. Death was observed within 1 hour in rabbits exposed to 26,572 ppm cyclohexane (Refs. 49 and 66). Rabbits exhibited severe, rapid, "running-like" movements of the feet, tremors and rapid narcosis preceding death.

c. *Acute dermal toxicity.* No mortality was reported following dermal application of cyclohexane to rabbits (Ref. 67). Six rabbits (New Zealand White/Dutchland strain; three per sex) were used. Cyclohexane was applied dermally to clipped skin under a non-absorbent binder at a dose level of 2,000 mg/kg bw. Animals were observed at 1, 2 and 4 hours post-application and then twice daily for 14 days. By 2 hours post-application, all animals were reported to appear normal and remained normal throughout the 14-day observation period. Animals gained weight during the observation period. No gross pathology was observed upon necropsy. This result indicates that the acute dermal lethal dose for cyclohexane is greater than 2,000 mg/kg bw in rabbits.

d. *Acute intravenous toxicity.* Braier (Ref. 68) reported the toxic effects of intravenous injections of cyclohexane to groups of 10 rabbits. Complete mortality was observed following a single injection of 0.23 g/kg, 10 percent mortality occurred at 0.15 g/kg, and no mortality occured at 0.12 g/kg. No clinical symptoms were reported prior to death.

e. *Acute subcutaneous toxicity.* Braier (Ref. 68) reported that a single subcutaenous injection of 0.78 g/kg in male and female rabbits caused granulopenia in all animals over a 6-day observation period, although bone marrow remained normal.

f. *Dermal irritation.* A primary skin irritation study in rabbits was also provided by Phillips Petroleum Company (Ref. 69). Six rabbits (three male, three female) were exposed to cyclohexane (0.5 mL under a non-absorbent binder) for 24 hours. An intact and an abraded skin site were employed on each animal. No erythema, edema or other dermal effects were reported at 24 or 72 hours after compound administration. The primary irritation score was reported to be zero.

Dermal irritation scores in rabbits were also presented as part of the acute dermal toxicity study by Phillips (Ref. 67). The dose was 2,000 mg/kg. Two out of three male rabbits exhibited very slight erythema on days 1 and 3 after application of cyclohexane. All three female rabbits exhibited erythema ranging from very slight (two out of three) to well-defined (one out of three) on day 1. On day 3, two females exhibited erythema. No erythema was noted in any rabbit on day 7. Very slight edema was observed in all female rabbits and one of three males on day 1. Slight edema was observed in one other male on day 1. No edema was observed on day 3. Epidermal scaling was reported in one female on day 10.

g. *Eye irritation.* Phillips Petroleum Company has submitted washed and unwashed primary eye irritation studies in rabbits (Refs. 70 and 71). Each study employed six rabbits (three male, three female). The dose of cyclohexane employed was 0.1 mL instilled into the conjunctival sac of the left eye. After cyclohexane administration, animals were observed and scored at 1, 24, 48 and 72 hours, and at 4 and 7 days. When eyes were washed (Ref. 70), conjunctival redness was observed in four animals (one male, three females) at the 1-hour observation period. This redness was not observed at 24 hours. No corneal opacity, iritis, conjunctival chemosis or discharge was observed in any of the animals. When eyes were not washed (Ref. 71), conjunctival redness was observed in five animals (three male, two female) at 1 hour after cyclohexane administration. Conjunctival chemosis was observed in one rabbit (male), corneal opacity involving ≦25 percent of the cornea was observed in another rabbit (male) and iritis was observed in another (male). No ocular lesions were observed at 24 hours. The overall eye irritation index was 1.3 for washed eyes and 3.7 for unwashed eyes at 1 hour. At 24 hours through 7 days, the primary irritation score was 0.0 for both washed and unwashed eyes.

h. *Dermal Sensitization.* No data on the dermal sensitization of cyclohexane have been found in the literature or have been reported under the TSCA section 8(d) rule (50 FR 47538) for this chemical.

3. *Subchronic toxicity.* The Agency has reviewed several subchronic studies on cyclohexane and found them insufficient to reasonably determine or predict the subchronic toxicity of cyclohexane. Treon et al. (Ref. 49) exposed rabbits (four/group) to cyclohexane by inhalation. Exposure concentrations ranged from 1.47 mg/L (435 ppm) for 1,040 hours (26 weeks) to 62.6 mg/L (18,600 ppm) for 60 hours. Exposure regimens were 6 or 8 hours/day, 5 days/week over a 2-, 5-, 10-, or 26-week period (see following Table 1).

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Table 1 -- MULTIPLE EXPOSURE INHALATION TOXICITY TESTS WITH CYCLOHEXANE (Ref 49)

Species	Exposure Level ppm	Exposure Level mg/L	Duration of Observation	Effects/Comments
Rabbits	7400 12,600 18,600	25 1 42 1 62 6	6 hours/day, 5 days/week, 2 weeks	7,400 ppm; lethargy, light narcosis, increased respiration and diarrhea Mortality: 1/4; weight gain (16 g/animal) 12,600 ppm; spasmodic convulsions, lethargy, light narcosis, increased respiration, diarrhea and salivation Mortality: 1/4; weight loss (260 g/animal) 18,600 ppm; rhythmic "running-like" movements of feet, tremors, spasmodic jerking, narcosis, paresis of legs, salivation, conjunctival congestion and labored respiration Mortality: 3/4; weight loss (188 g/animal)
Rabbits	9,200	31 1	6 hours/day, 5 days/week, 5 weeks	Tremors, lethargy, paresis of legs, incoordination, increased respiration and salivation Mortality: 3/4; weight loss (311 g/animal)
Rabbits	430 790 3,300	1 5 2 7 11 2	6 hours/day, 5 days/week 10 weeks	No grossly observable effects; minor microscopic changes detected in the liver and kidney at 790 ppm No mortality; weight gain at 430 and 3,300 ppm (531 and 262 g/animal, respectively) Weight loss at 790 ppm (115 g/animal) considered not compound related
Rabbits	435	1 5	8 hours/day, 5 days/week, 26 weeks	No observable effects Weight gain (531 g/animal)
Monkey	1,200	4 2	6 hours/day, 5 days/week, 10 weeks	Weight loss: 333 g Only one animal used; no other observable effects

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This study has a number of design flows that limit its usefulness including: (1) The small numbers of animals used (4/group; minimum requirement is 20/group); (2) survivors were sacrificed and necropsied 2 months after exposure ended rather than immediately allowing for possible recovery or reversibility of effects (3) while hemoglobin concentration and erythrocyte and leucocyte counts were measured, other important clinical markers (e.g., clinical biochemistry such as electrolyte balance and liver and kidney function) were not reported.

Treon et al. (Ref. 48) applied repeated doses of cyclohexane to the clipped anterior abdominal skin of a single rabbit for 14 days (total dose was 180.2 g/kg). Increased injury to the skin was noted during the exposure period. Within a week following the last application, healing had occurred. No narcosis or convulsions were observed. Upon autopsy, unspecified toxic changes in the heart, liver and kidney were noted, accompanied by chronic bronchitis and some vascular degeneration in the lung.

In a study reported by Naruse (Ref. 53), 20 mice (sex and strain not clear from the report, but probably male ddY mice), initial weight approximately 15 g each, were exposed to vapors of adhesive D (36.3 percent cyclohexane, 15.3 percent acetone, 7.1 percent isopropyl acetate, 6.8 percent *n*-hexane, 1.5 percent methylcyclopentane, 1.0 percent 3-methylpentane, 0.8 percent 2,3-dimethylbutane and 2-methylpentane, and 0.5 percent toluene) in air at 18 °C for 1 hour, 6 days/week over 120 days. Mice exposed to adhesive D exhibited a significant ($p<0.01$) inhibition of body weight gain and significantly ($p<0.01$) decreased food and water consumption when compared with controls. The liver/body weight ratio was significantly ($p<0.01$) increased with respect to controls; other organ/body weight ratios were not significantly different. No gross or microscopic abnormalities were reported in any organs. The significance of these findings with respect to cyclohexane is impossible to assess because cyclohexane was only one of several constituents of the chemical mixture tested.

4. *Neurotoxicity.* EPA concludes that the neurotoxicity data on cyclohexane are not sufficient to reasonably determine or predict the neurotoxicity of cyclohexane. The experimental evidence accumulated to date, relative to cyclohexane's neurotoxic potential, is very limited. Cyclohexane has been shown to be a central nervous system (CNS) depressant in rabbits (Ref. 49). Observed effects have included dizziness, nausea, and unconsciousness (Ref. 72). At high vapor concentrations, convulsions in rabbits have also been reported (Refs. 49 and 73). No definitive experimental data appear to exist in the published literature on the potential of cyclohexane to induce neuropathological changes, following long-term chronic exposure.

In one animal study (Ref. 74) six to nine rats were intermittently exposed to cyclohexane (9 to 10 hours/day, 5 to 6 days/week) via inhalation for up to 30 weeks at concentrations of 1,500 and 2,500 ppm. Post-exposure histologic examination of both tissue and sectional preparations from the peripheral nervous system did not reveal any pathologic alteration; however, the CNS was not examined. In the same study, rats treated with *n*-hexane at 2,500 ppm for 30 weeks and 5,000 ppm for 14 weeks developed solvent-induced giant axonal neuropathies.

This study indicates that cyclohexane did not induce neuropathic changes under experimental conditions in which *n*-hexane induced extensive peripheral neuropathy. Although the study design included use of a highly pertinent exposure route, monitoring of atmospheric test concentrations and exposure durations of up to 30 weeks, several important deficiencies must be noted. Numbers of test animals were somewhat low (6 to 9/treatment). Most important, the lack of weight gain effects or other evidence of signs of toxicity in the cyclohexane-treated group suggests that a high enough dose was not tested. Therefore, while it appears from the data that cyclohexane does not change the peripheral nerves of rats at exposure levels that produce extensive nerve damage in *n*-hexane-treated groups, it cannot be inferred that higher cyclohexane concentrations would be non-neurotoxic as well or that the tested exposure levels do not cause CNS effects (i.e. not examined). For any repeated exposure study to provide adequate evidence of a substance or mixture's lack of potential to cause a specific effect, EPA believes that a dose effect range should be obtained that demonstrates both frank toxicity and no effect levels. Because, no toxicity was demonstrated this study is inadequate to predict the neurotoxic potential of cyclohexane.

EPA has also reviewed four neurotoxicity studies where cyclohexane was a component of a mixture. EPA finds that these studies are inadequate. Egan et al. (Ref. 75) exposed male rats nearly continuously to vapors of a mixture of hexane isomers containing 109 mg/m^3 cyclohexane (31.7 ppm) but only 5.3 mg/m^3 (1.5 ppm) *n*-hexane for up to 6 months. The purpose of the study was to determine whether components of commercial hexane other than *n*-hexane contribute to the neuropathic properties of this mixture. The 6-month exposure failed to reveal any compound-related clinical or histopathological effects on the central or peripheral nervous systems.

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, the study was not designed to investigate the chronic neurotoxic potential of cyclohexane itself. The presence of multiple hexane isomers allows the possibility of antagonistic interactions affecting expression of neurotoxicity. In addition, EPA believes that the doses used were too low to adequately demonstrate lack of neurotoxic potential of cyclohexane, in view of the lack of observable clinical effects obtained.

In two American Petroleum Institute (API) studies (Refs. 76 and 77) the general objective of both studies was to evaluate the potential synergistic effects of C_6 isomers found in commercial hexanes on the chronic inhalation toxicity of *n*-hexane, emphasizing neurotoxic effects. The use of test mixtures of hexane isomers precludes the use of these data to determine the toxicity of cyclohexane, which was a relatively minor component of the isomer mixture.

Franchini et al. (Ref. 78) exposed 49-day-old Ubbart chickens to five mixtures (A–E) containing 2.1 to 17.1 percent cyclohexane by painting on shaved thoracic skin (about 10 cm^2) daily for up to 65 days (initially, 1 g/kg bw/day). All of the test mixtures contained *n*-hexane, a demonstrated neuropathic agent. Untreated animals (five) were used as controls. The report states that the dose was gradually increased as body weight increased, but no further explanation was given. Histological and microstructure analyses were made of spinal cord cervical and lumbar swellings and of sciatic nerves. Chickens from A and B groups showed no symptoms of paralysis. Microscopic examination of sciatic nerve fiber bundles, however, revealed ball-shaped swellings and demyelination. Four out of five chickens in C group (the only solvent containing tricresylphosphate, a known neurotoxin) were completely paralyzed by the treatment, and deterioration of the

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myelin sheath was seen upon microscopic examination. In groups D and E also, four out of five animals were paralyzed. In group D, the myelin sheath was observed to be swollen and frequently broken. Microscopic findings for group E animals were not reported. The significance of these findings with respect to cyclohexane is difficult to assess since cyclohexane was only one component in the complex mixtures.

5. *Developmental toxicity.* No data on the developmental toxicity of cyclohexane have been found in the literature or have been reported under the TSCA section 8(d) rule (50 FR 47538) for this chemical.

6. *Reproductive toxicity.* No data on the reproductive effects of cyclohexane have been found in the literature or have been reported under the TSCA section 8(d) rule (50 FR 47538) for this chemical.

7. *Mutagenicity.* Negative results on cyclohexane were reported in the following: (a) Gene mutation assays in *S. typhimurium* reverse mutation assay with and without metabolic activation (Refs. 79 and 80) and in the mouse lymphoma forward mutation assay (Refs. 81 and 82); (b) in the *in vivo* bone marrow cytogenetics tests in rat: chromosomal analysis (Ref. 83); (c) in a sister chromatid exchange assay in Chinese hamster ovary (Ref. 84); (d) in an unscheduled DNA synthesis assay (Ref. 85); and (e) in a DNA binding assay at 10 nM (Ref. 86). An equivocal result was reported in the DNA binding assay at 100 nM (Ref. 86). EPA concludes that although there are some deficiencies in the reporting of some of the studies, these do not appear to be sufficient reason to question the results. Cyclohexane has not demonstrated mutagenic activity in any of the reported studies. The one equivocal report in the DNA binding assay (Ref. 86) is in a study whose overall use as a predictive assay for carcinogenesis has not been validated. Therefore, the reported equivocal response does not change the overall evaluation that cyclohexane is not mutagenic in these assays.

Given the negative results in all assays in which cyclohexane was tested, including the negative response in a rat bone marrow cytogenetics assay, EPA has concluded that it is not necessary to test cyclohexane for its ability to induce chromosomal aberrations *in vitro* in the *in vitro* mammalian cytogenetics test: chromosomal aberration in cultured mammalian cells. These tests fulfill the Agency's requirements for first tier mutagenicity testing. Therefore, no further mutagenicity testing for this agent is necessary.

8. *Carcinogenicity.* EPA concludes that existing data are not sufficient to reasonably predict the carcinogenicity of cyclohexane. There have been no carcinogenicity studies conducted using currently accepted standard testing protocols. It should be noted, however, that pure cyclohexane was used as a vehicle control in 3 dermal oncogenicity studies (Refs. 87 through 89). A 50/50 cyclohexane/acetone mixture was used as a vehicle control in one dermal oncogenicity study (Ref. 90) and cyclohexane mixed with test compound as a 80/20 percent mixture in another dermal oncogenicity study (Ref. 91). Three of these studies (Refs. 89 through 91) were submitted to EPA by the CMA. While no oncogenic response was reported for cyclohexane in these studies, a number of shortcomings prevent their use for judging oncogenicity.

These include small doses employed (less than 20 to 100 μl, 16–78 μg; 2 to 3 times per week), failure to use pure cyclohexane, use of insufficient number of animals, use of animals of only one sex, failure to expose animals for their entire lifetime, use of only one rodent species. More importantly, none of the investigations was designed to directly address the carcinogenicity of cyclohexane. Hence, because of the intended purpose of each study, these investigations must be considered inadequate for evaluating cyclohexane's carcinogenic potential. Table 2 lists summary of these studies.

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TABLE 2--SUMMARY OF EXISTING CYCLOHEXANE DATA

Route	Species	Sex	Dose or Exp. level	Duration of Exposure	Comments	(Ref)
Dermal	C3Hf/Bd mice	30 M, 30 F	50 µl cyclohexane was vehicle control	3x/wk for 60 weeks	Middle distillates were tested. Looked at nephrotoxicity. Cyclohexane was vehicle control. Skin tumor in 1/60 mice. No macroscopic renal lesions. 42 of 336 in treatment group had renal lesions. Exposure regimen not adequate. Animals not exposed during entire life span.	87
Dermal	C3H mice	35 M	0, 60 µl	2x/wk 50 weeks	Promoting activity of pristine ($C_{19}H_{40}$) and several n-alkanes in cyclohexane. All animals were treated with the initiating carcinogen DMBA. Cyclohexane was vehicle control and solvent. Benign and malignant tumor rate of cyclohexane exposed animals not significant from controls. Animals not exposed during entire lifetime. Exposure regimen not adequate. Only male mice used.	88
					Carcinogenic activity of di- and trifunctional alpha-chlor ethers and 1,4-Dichlorobutene-2 in ICR/Ha Swiss mice	
Dermal	ICR/Ha Swiss mice	50 F	100 µl	3x/wk 72 weeks	Cyclohexane was vehicle control. Only female mice used. Exposure regimen not adequate.	89
Dermal	C0-1 and C3H/HeJ mice	50 M	50 µl Cyclohexane/ acetone	2x/wk 18 months	Asphalt volatiles were applied as 50 percent solutions in cyclohexane/acetone. Cyclohexane/acetone vehicle control. Exposure regimen not adequate. Only male mice were used.	90
Dermal	Swiss mice	50 F	20 µl (one drop) of 20/ 80 mixture	3x/wk 60 weeks	Promotion activity following single dose of DMBA of various alkanes and alkanols prepared as a 20 percent (w/v) solution in cyclohexane studied. Exposure regimen not adequate. Only female mice were used. 3 agents (n-hexane, octane, and hexanol) dissolved in cyclohexane were inactive	91

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III. Findings

Under TSCA section 4(a)(1)(B), EPA finds that cyclohexane is produced in substantial quantities and that there is or may be substantial human exposure from its manufacture, processing, and use. Approximately 1.8 billion pounds of cyclohexane was produced in 1985 (Ref. 10). In addition, according to the National Occupational Exposure Survey of 1981 to 1983 (NOES), 42,558 workers including 12,021 women were potentially exposed to the compound in the workplace at 985 plants in 1980 (Ref. 31). Cyclohexane is used as a solvent and may be a component of paint remover and rubber adhesives and textile solvents. It also appears on the label as a component of at least two spray adhesives, Scotch Sprament Art and Display Adhesive and Super 77 spray adhesive, and may occur in other consumer products. The above uses may result in widespread exposure to workers and consumers.

While EPA believes that there may be substantial human exposure to cyclohexane in finished gasoline, EPA is not considering exposure from finished gasoline as part of its basis for finding substantial human exposure to cyclohexane. The Agency believes that exposures associated with the manufacture and processing of cyclohexane, solvent uses and other uses provide sufficient basis for a finding of substantial human exposure under TSCA section 4(a)(1)(B)(i) for cyclohexane.

EPA finds, as discussed in Unit II of this document, that existing data are not sufficient to reasonably determine or predict the subchronic, oncogenic, reproductive, developmental, and neurotoxic effects as well as dermal absorption and dermal sensitization following exposure to cyclohexane resulting from its manufacture, processing, and use. EPA further finds that testing is necessary to develop such data. EPA believes that the data resulting from this testing will be relevant to a determination as to whether the manufacture, processing, and use of cyclohexane does or does not present an unreasonable risk of injury to human health.

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 40 CFR Parts 796, 797, and 798 of this chapter. Revisions to these guidelines are published elsewhere in this issue of the **Federal Register**. The test guideline cited under § 795.250 of this chapter was proposed in the **Federal Register** of May 15, 1986 (51 FR 17890). The test guideline in § 795.226 of this chapter is proposed and published with this rule for cyclohexane. All persons conducting tests must submit plans, and conduct tests in accordance with the TSCA Good Laboratory Practice (GLP) Standards (40 CFR Part 792).

On the basis of the findings presented above for health effects testing, the Agency is proposing that cyclohexane be tested under TSCA section 4(a)(1)(B) for: (1) Subchronic inhalation toxicity as specified in § 798.2450 of this chapter; (2) oncogenicity by inhalation as specified in § 798.3300 of this chapter; (3) reproductive toxicity by inhalation as specified in § 798.4700 of this chapter; (4) developmental toxicity by inhalation as specified in § 798.4350 of this chapter; (5) neurotoxicity by inhalation as specified in §§ 798.6050, 798.6200, 798.6400, 798.6500 and 795.250 of this chapter; (6) dermal absorption as specified in § 795.226 of this chapter; and (7) dermal sensitization as specified in § 798.4100 of this chapter.

Acute neurological effects are of concern because such effects may increase accident proneness, impair self-rescue, or reduce work efficiency (Ref. 92). This is of particular concern to the 42,558 workers potentially exposed to cyclohexane (Ref. 10). In order to assess the acute neurologic effects of inhaled cyclohexane 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 cyclohexane, the Agency is proposing a subchronic neurobehavioral toxicity evaluation, consisting of a 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 cyclohexane'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 cyclohexane 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 cyclohexane during pregnancy and lactation, the Agency is proposing that cyclohexane be tested for developmental neurotoxicity (§ 795.250), if warranted after the results of the other neurotoxicity tests and the reproductive effects tests are reviewed by the Agency. If the Agency decides that the developmental neurotoxicity test is warranted, it will reopen the comment period, review the comments, and if the Agency still concludes that the testing is warranted, it will finalize the developmental neurotoxicity test in a separate **Federal Register** notice.

In order to assess the degree of toxicological activity of cyclohexane upon various target organs, the Agency is proposing that cyclohexane be tested for subchronic toxicity by inhalation (§ 798.2450). Because of the widespread exposures to cyclohexane, the Agency believes that it is necessary to assess the oncogenic potential of cyclohexane and is thus proposing a 2-year inhalation bioassay in two species (§ 798.3300). Testing for developmental toxicity (§ 798.4350) and reproductive effects (§ 798.4700) is being proposed because of widespread human exposure and lack of data to reasonably predict these effects. EPA is proposing that the above tests be done via inhalation because this is the major route of exposure. EPA is also proposing a dermal absorption test (§ 795.226) and dermal sensitization test (§ 798.4100). Dermal exposure to cyclohexane is of concern to EPA because of cyclohexane's solvent uses. No data are available on dermal sensitization and EPA believes that a dermal absorption test will be needed in its assessment of cyclohexane (see Unit II.E.1 of this document).

The Agency is proposing that the TSCA health effects test guidelines be employed as the test standards for the purposes of the proposed tests for cyclohexane. The TSCA test guidelines for health effects testing specify generally accepted minimal conditions for determining the health effects for substances like cyclohexane 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 guidelines need to be modified significantly.

B. Test Substance

EPA is proposing under TSCA section 4(a)(1)(B) that cyclohexane (CAS No. 110-82-7) 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 cyclohexane itself. EPA believes that this grade of cyclohexane is readily available for testing purposes. Radiolabeled cyclohexane of greater than 99 percent purity will be needed for the dermal absorption test.

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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 "import"). 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 substance 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 cyclohexane, EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process cyclohexane, other than as an impurity, at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the testing requirements in this proposed rule. 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 cyclohexane will form the reimbursement pool and sponsor the required testing. EPA promulgated procedures for applying 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 cyclohexane.

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 tests for cyclohexane in the following Table 3:

TABLE 3.—REPORTING REQUIREMENTS

Test	Reporting deadline for final report[1]	Number of interim (6-mo) reports required
Testing for cyclohexane:		
A. Subchronic inhalation toxicity: § 798.2450	15	2
B. Oncogenicity: § 798.3300	53	8
C. Reproduction and fertility effects: § 798.4700	29	4
D. Inhalation developmental toxicity: § 798.4350	15	2
E. Neurotoxicity tests: §§ 798.6050, 798.6200, 798.6400, and 798.6500	15	2
F. Developmental neurotoxicity test: § 795.250	[2] 15	2
G. Dermal Sensitization: § 798.4100	12	1
H. Dermal Absorption: § 795.226	12	1

[1] Number of months after the effective date of the final rule.
[2] Number of months after the effective date of the final rule which would require the developmental neurotoxicity test.

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. In brief, as of the effective date of this test rule, an exporter of cyclohexane must report to EPA the first export or intended export of cyclohexane 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. Laboratory inspections and data audits will be conducted periodically in accordance with the authority and

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procedures outlined in TSCA section 11 by duly designated EPA representatives to determine compliance with any final rule for cyclohexane. 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 violated 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 as stated in 40 CFR 790.48(b). Knowing and willful 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. The authors of the EPA monitoring study (Ref. 40) 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 cyclohexane needed to assess potential adverse health effects upon neonates, who may be exposed to cyclohexane through mother's milk, and whose developing neurological sytems may be more susceptible to damage from exposure to this compound? What test methods should be used for such testing?

2. Cyclohexane is listed as a component on the label of two spray adhesives, Scotch Sprament Art and Display Adhesive, Cat. No. 6060 and Super 77 spray adhesive (Ref. 30). EPA seeks additional information on cyclohexane in these two consumer products or any other consumer products. EPA seeks information on how widespread consumer exposure to cyclohexane might be.

3. EPA is uncertain whether and to what extent cyclohexane is used in paint formulations, rubber glues, and paint removers. EPA seeks additional information on these uses. EPA also seeks additional information on human exposure to cyclohexane used as a laboratory solvent.

4. EPA solicits comments on whether or not manufacturers and processors of cyclohexane who do so in the course of producing gasoline or other motor or heating fuels should be subject to this rule.

5. This rule proposes oncogenicity testing for cyclohexane. EPA has often used a tiered approach to oncogenicity testing when making exposure findings under section 4(a)(1)(B). EPA and others have found shorter term tests, i.e. subchronic tests and mutagenicity screening tests, very useful for determining the priority of oncogenicity testing needs. However, EPA believes that in the case of cyclohexane, with its potential for substantial worker and consumer exposure, a 2-year bioassay is necessary to give the Agency the degree of assurance required for regulatory decision-making. EPA seeks comment on the appropriateness of this approach.

VI. Economic Analysis of Proposed Rule

To assess the potential economic impact of this rule, EPA has prepared an economic analysis 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 cyclohexane: (1) Price sensitivity of demand, (2) industry cost characteristics, (3) industry structure, and (4) market expectations. If these indications are negative, 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.

Total testing costs for the proposed testing of cyclohexane are estimated to range from $2,052,300 to $2,651,850. In order to predict the financial decisionmaking practices of manufacturing firms, these costs have been annualized. Annualized costs are compared with annual revenue as an indication of potential impact. The annualized costs represent equivalent constant costs which would have to be recouped each year of the payback period in order to finance the testing expenditure in the first year. The annualized testing costs range from $225,330 to $291,160, using a 7 percent cost of capital estimate over a period of 15 years.

Based on 1985 production of 1.8 billion pounds, the unit test costs range from $0.0001 to $0.0002 per pound. In relation to the selling price of $0.14 per pound for cyclohexane, these costs are equivalent to 0.09 to 0.12 percent of price.

Based on these costs and the uses of cyclohexane, the economic analysis indicates that the potential for significant adverse economic impact as a result of this test rule is low. This conclusion is based on the following observations:

1. The estimated unit test costs are very low, 0.12 percent of current price in the upper bound case.

2. The overall demand for cyclohexane appears relatively inelastic with respect to price in all of its major uses.

3. The market expectations for cyclohexane are moderate, with demand

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projected to grow at a rate of 3 to 7 percent annually.

Refer to the economic analysis included in the rulemaking record for a complete discussion of test cost estimation and 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 after the close of the public comment period in Washington, D.C. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): (202) 554-1404 by July 6, 1987. 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-42094). 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 recommendation with intent to designate cyclohexane (50 FR 47603; November 19, 1985).

(b) Notice containing the ITC designation of cyclohexane to the Priority List (51 FR 18359; May 19, 1986).

(c) Rules requiring TSCA section 8(a) and 8(d) reporting on cyclohexane (50 FR 47538; November 19, 1985).

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

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

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

(g) Notice of final rule revising TSCA test guidelines.

(2) Support documents consisting of:

(a) Cyclohexane technical support document for proposed rule.

(b) Economic impact analysis of NPRM for cyclohexane.

(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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(89) Van Duren, B.L., Goldschmidt, B.M., and Seidman I. "Carcinogenic Activity of di- and trifunctional a-chloroethers and of 1, 4-dichlorobutene-2 in ICR/HA Swiss Mice." *Cancer Research* 35:2553-2357 (1975). Submitted by the Chemical Manufacturers Association, Washington, DC to the Environmental Protection Agency, Office of Toxic Substances, Washington, DC (October 1, 1986).

(90) Thayer, P.S., Menzies, K.T., and Von Thurman, P.C. "Roofing asphalts, pitch and uvl Carcinogenesis." Prepared by Arthur D. Little, Inc., Cambridge, MA for the National Institute for Occupational Safety and Health, Cincinnati, OH (1981). Submitted by the Chemical Manufacturers Association, Washington, DC to the Environmental Protection Agency, Office of Toxic Substances, Washington, DC (September 17, 1986).

(91) Sice, Jean. "Tumor-promoting activity of n-alkanes and 1-alkanols." *Toxicology and Applied Pharmacology* 9:70-74 (1966). Submitted by the Chemical Manufacturers Association, Washington, DC to the Environmental Protection Agency, Office of Toxic Substances, Washington, DC (October 1, 1986).

(92) Wood, Ronald. American Psychological Association. Response to the Chemical Manufacturers Association Testing Proposal for cyclohexane of September 17, 1986. Submitted to the Environmental Protection Agency, Office of Toxic Substances, Washington, DC (October 15, 1986).

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

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, Recordkeeping and reporting requirements.

Dated: May 1, 1987.

Victor J. Kimm,

Acting Assistant Administrator for Pesticides and Toxic Substances.

PART 795—[AMENDED]

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

1. In Part 795:

a. The authority citation continues to read as follows:

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

b. Section 795.226 is added to read as follows:

§ 795.226 Dermal absorption for compounds that are volatile and metabolized to carbon dioxide.

(a) *Purpose.* The purpose of these studies is to: Determine the extent of absorption of test substance after dermal administration.

(b) *Definitions.* Percent of dermal absorption is defined as 100 times the ratio between total excretion of compound following dermal administration and total excretion following intravenous administration.

(c) *Test Procedures*—(1) *Animal selection*—

(i) *Species.* The rat and guinea pig shall be used.

(ii) *Test animals.* Adult male and female Fischer 344 rats shall be used. At 7 to 9 weeks of age, the male rats should weigh 125 to 175 g and the female rats 110 to 150 g. Guinea pigs, 5 to 7 weeks old, shall also be used. The animals should be purchased from a reputable dealer and shall be identified 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. In all studies, unless otherwise specified, each experimental group shall contain at least 4 animals of each sex for a total of at least 8 animals.

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

(B) The animals should be housed in environmentally controlled rooms with at least 10 air changes per hour. The rooms shall be maintained at a temperature of 25±2 °C and humidity of 50±10 percent with a 12-hour light/dark cycle per day. The animals shall be kept in a quarantine facility for at least 7 days prior to use.

(C) During the acclimatization period, the animals should be housed in suitable cages. 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 of Test Substance*—(i) *Test compound.* The use of radioactive test substance is required for all studies outlined in paragraph (c)(2)(ii) of this section. Ideally, the purity of both radioactive and nonradioactive test substance should be greater than 99 percent. If the purity is less than 99 percent or if the radioactive and nonradioactive compounds differ significantly, the EPA should be consulted.

(ii) *Dosage and treatment*—(A) *Intravenous.* The "low" dermal dose of test substance, in an appropriate vehicle, shall be administered intravenously to four rats of each sex and to four guinea pigs of each sex.

(B) *Dermal.* For dermal treatment, the "low" and "high" doses shall be dissolved in a suitable vehicle and applied at a volume adequate to deliver the doses. The backs of the animals should be lightly shaved with an electric clipper 24 hours before treatment. The chemical shall be applied to the intact shaven skin (approximately 2 cm^2 for rats, 5 cm^2 for guinea pigs). To prevent losses of test substance by evaporation, the use of a stainless skin depot glued to the backs of the animals with a cyanoacrylate adhesive is recommended. The depot is fitted with a screw cap to prevent the escape of vapor and with a basket of activated charcoal to adsorb compound which vaporizes (Ref. 1).

(*1*) *Washing efficiency study.* Before initiation of the dermal absorption studies described in this section, an initial washing efficiency experiment shall be conducted to assess the removal of the applied test substance by washing the exposed skin area with soap and water and an appropriate solvent. The low dose of test substance shall be applied to 4 rats and 4 guinea pigs. After application (2 to 5 minutes), the areas shall be washed with soap and water and an appropriate solvent (2 rats, 2 guinea pigs). The amounts recovered in the washings shall be determined to assess efficacy of test substance removal by washing the skin.

(*2*) [Reserved].

(iii) *Dosing and sampling schedule*—(A) *Rat studies*—(*1*) *Intravenous study.* (*i*) Group A is to be dosed once intravenously at the low dose of test substance. The rats shall be placed in individual metabolic units (Ref. 2) for collection of urine, feces and expired air at 8, 24, 48, 72 and 96 hours after dosing. The metabolic units are to be cleaned after the final collection period to remove any excreta that might adhere to the units.

(*ii*) [Reserved].

(*2*) *Dermal studies* The test substance shall be kept on the skin for a minimum of 6 hours.

(*i*) Group B shall be dosed once dermally with the low dose of test substance.

(*ii*) Group C shall be dosed once dermally with the high dose of test substance. During and after the exposure period, each animal shall be placed in an individual metabolic unit for the collection of urine, feces and expired air at 8, 24, 48, 72 and 96 hours after dosing. The metabolic units are to be cleaned after the final collection period to remove any excreta that might adhere to the units. At the time of removal of the skin depot, the treated area and the steel depot shall be washed with an appropriate solvent to remove any test substance. Also, the test substance shall be desorbed from the activated charcoal with a suitable solvent. The washings and extracts shall be assayed to recover residual test substance. 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 test substance.

(B) *Guinea pig studies.* (*1*) Group D is to be dosed once intravenously at the low dose of test substance. The guinea pigs shall be placed in individual metabolic units for the collection of urine, feces and expired air as for Group A.

(*2*) *Dermal studies.* The studies conducted on groups B and C as specified in paragraph (c)(2)(iii)(A)(*2*) of this section shall be repeated using four guinea pigs per group.

(*i*) Group E shall be dosed once dermally with the low dose of test substance.

(*ii*) Group F shall be dosed once dermally with the high dose of test substance.

(*iii*) *Measurements—Excretion.* The quantities of radioactivity excreted in the urine, feces, and expired air shall be determined at appropriate time intervals as described above 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).

(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 EPA Good Laboratory Practice Standards (40 CFR Part 792, Subpart J) the following specific information shall be reported:

(i) Species and strains of laboratory animals;

(ii) Information on the site(s) and extent of test substance labeling, including specific activity, chemical purity, radiochemical purity and results of chromatography;

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

(iv) Percent of absorption of test substance after dermal exposures to rats and guinea pigs;

(v) Quantity and percent recovery of test substance in feces, urine, and expired air. In dermal studies on rats and guinea pigs, include recovery data for skin, skin washings, and residual compound in the skin depot and charcoal.

(e) *References.* For additional background information on this test guideline the following references should be consulted:

(1) Susten, A.S., Dames, B.L., Niemeier, R.W., "In *vivo* percutaneous absorption studies of volatile solvents in hairless mice. I. Description of a skin-depot." *Journal of Applied Toxicology* 6:43-46. (1986).

(2) Jeffcoat, A.R. Research Triangle Institute. Absorption, distribution, metabolism and excretion of cyclohexane. Project report No. 5. Research Triangle Park, N.C. National Institute of Environmental Health Sciences. Contract NOI-ES-1-5007. (1984)

PART 799—[AMENDED]

2. In Part 799:

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a. The authority citation continues to read as follows:

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

b. Section 799.1295 is added to read as follows:

§ 799.1295 Cyclohexane.

(a) *Identification of test substance.* (1) Cyclohexane (CAS No. 110-82-7) shall be tested in accordance with this section.

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

(ii) *Reporting requirements.* (A) 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.

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

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

(ii) *Reporting requirements.* (A) 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.

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

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

(ii) *Reporting requirements.* (A) 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.

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

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

(ii) *Reporting requirements.* (A) The inhalation developmental toxicity test shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final rule.

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

(5) *Neurotoxicity*—(i) *Required testing.* Inhalation neurotoxicity tests shall be conducted with cyclohexane in accordance with §§ 798.6050, 798.6200, 798.6400, and 798.6500 of this chapter.

(ii) *Reporting requirements.* (A) The neurotoxicity tests shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final rule.

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

(6) *Developmental neurotoxicity*—(i) *Required testing.* An inhalation developmental neurotoxicity test shall be conducted with cyclohexane in accordance with 795.250 of this chapter.

(ii) *Reporting requirements.* (A) The developmental neurotoxicity test (conditional) shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final rule which would require the developmental neurotoxicity test.

(B) Progress reports shall be submitted to the Agency for the developmental neurotoxicity test (conditional) at 6-month intervals beginning 6 months after the effective date of the final rule which would require the developmental neurotoxicity test.

(7) *Dermal Absorption*—(i) *Required testing.* Dermal absorption test shall be conducted with cyclohexane in accordance with § 795.226 of this chapter.

(ii) *Reporting requirements.* (A) The dermal absorption test shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

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

(8) *Dermal Sensitization*—(i) *Required testing.* (A) Dermal sensitization test shall be conducted with cyclohexane in accordance with § 798.4100 of this chapter.

(B) [Reserved].

(ii) *Reporting requirements.* (A) The dermal sensitization test shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final rule.

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

(d) *Effective date.* (44 days after publication of the final rule in the **Federal Register**).

(Approved by the Office of Management and Budget under control number 2070-0033)

[FR Doc. 87-11127 Filed 5-19-87; 8:45 am]
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