because information generally will be released on a product category basis.

The General Counsel has concluded that the information is relevant to the subject of the TSCA section 6 rulemaking proceeding for the ban and phase out of the use of asbestos. Based upon the matters discussed in the notice published in the **Federal Register** on December 21, 1987 and after considering all comments, the Office of Toxic Substances remains convinced that the public interest would be served by making the described information publicly available.

Today's **Federal Register** notice informs all affected businesses that all of the information currently treated as CBI and contained in the Asbestos Exposure Assessment, the Asbestos Modeling Study, or the Regulatory Impact Analysis will be released to the public in the near future. In addition to the publication of this **Federal Register** notice, each company that provided the Agency with information claimed as CBI will receive individual notice of this release. The information treated as CBI which is contained in the Asbestos Exposure Assessment, the Asbestos Modeling Study, or the Regulatory Impact Analysis will be disclosed no sooner than 5 calendar days after the businesses have received notice of this decision.

List of Subjects in 40 CFR Part 763

Environmental protection, Hazardous substances, Reporting and recordkeeping requirements, Asbestos.

Date: March 11, 1988.

John A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

[FR Doc. 88-5832 Filed 3-15-88; 8:45 am]

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40 CFR Parts 795 and 799

[OPTS-42097; FRL-3340-9]

Isopropanol; Proposed Test Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: In response to the Interagency Testing Committee's (ITC) designation of isopropanol (CAS No. 67-63-0) 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 isopropanol be required to perform testing of this substance for subchronic toxicity, oncogenicity, mutagenicity, reproductive toxicity, developmental toxicity, neurotoxicity, and pharmacokinetics.

DATES: Submit written comments on or before May 16, 1988. If persons request an opportunity to submit oral comments by May 2, 1988, 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-42097) 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 isopropanol under section 4(a) of TSCA in response to the ITC's designation of isopropanol for health effects testing consideration. Testing is being proposed under section 4(a)(1)(B) of TSCA because the production volume of isopropanol is substantial and there is or may be substantial human exposure to it. The Agency has concluded that existing data are inadequate to assess the health risks posed by the manufacture, processing, use, or disposal of and the resulting human exposure to isopropanol and that testing 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 chemical substances and mixtures (chemicals) to be considered for testing under TSCA section 4(a) of the Act. The ITC recommended isopropanol with intent to designate for health effects testing in its 19th Report, published in the **Federal Register** of November 14, 1986 (51 FR 41417). The ITC designated isopropanol for priority consideration in its 20th Report, published in the **Federal Register** of May 20, 1987 (52 FR 19020). The ITC recommended that isopropanol be tested for chronic toxicity including oncogenicity, and for genotoxicity including mutagenicity in mammalian systems and clastogenicity. Testing for developmental and reproductive effects was deferred from consideration pending the outcome of relevant studies currently being conducted in the United Kingdom by the British Industrial and Biological Research Association (BIBRA) for the Food and Drink Federation. The ITC's rationale for recommending these tests was as follows: (1) The large production volume and many uses indicating a potential for widespread human exposure; (2) the large number of workers occupationally exposed and the possibility for general population exposure from use in commercial and household products; (3) the identification of isopropanol in leachates from a landfill site; and (4) the insufficient available data with which to assess the long-term effects of exposure. No chemical fate testing was recommended because any isopropanol released to the environment is widely dispersed and rapidly biodegraded and oxidized. Environmental effects testing was not recommended because there is sufficient information to show that isopropanol is unlikely to persist in the environment at concentrations that would be likely to cause adverse ecological effects.

B. Opportunity for Negotiating a Consent Order

EPA has issued an Interim Final Rule that amends EPA's procedural regulations in 40 CFR Part 790 for the development and implementation of testing requirements under section 4 of TSCA. The amendments establish procedures for using enforceable consent agreements to require testing under section 4 of the Act. EPA intends to use such consent agreements when a consensus exists among the Agency, affected manufacturers and/or processors, and interested members of the public about the need for and scope of testing requirements. The consent agreement provides an alternative to the test rule development process, facilitating the rapid development of test data by removing the necessity for a lengthy rulemaking process.

When EPA concludes that the Agency, the affected firms, and interested parties cannot reach a consensus on the testing requirements or other provisions to be included in the consent agreement, the Agency will proceed with rulemaking under section 4(a) of TSCA. A description of the procedures governing consent agreements and test rules appears in detail in the **Federal Register** of June 30, 1986 (51 FR 23706).

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The first step in determining the feasibility of developing a consent agreement for a specific chemical is the identification of interested parties who may wish to participate in negotiations with EPA. In the **Federal Register** of February 3, 1987 (52 FR 19020), EPA announced that the Agency was considering developing a testing consent agreement for isopropanol. The notice requested interested parties to identify themselves. The Chemical Manufacturers Association (CMA), the Environmental Conservation Board (ECB) of the Graphics Communication Industry, and the Natural Resources Defense Council (NRDC) requested participation as "interested parties" in the consent order negotiation process for isopropanol. However, consensus could not be reached on issues raised in the proposals submitted by CMA concerning the EPA science policy requirement of a two-species oncogenicity bioassay. CMA's plan was to use the results of various short-term tests (subchronic and mutagenicity) and pharmacokinetics to establish equivalency between species to negate the need for a second rodent species bioassay. CMA later proposed that there be an "independent scientific body" established to review the feasibility of CMA's approach and that this decision be binding on EPA. Both EPA and NRDC found this approach unacceptable. Since consensus was not reached as required for a consent order, the Agency decided to proceed with rulemaking under section 4(a) of TSCA.

C. Test Rule Development Under TSCA

Section 4 of TSCA provides authority for EPA to require development of data relevant to assessing the risks to health and the environment posed by exposure to a particular chemical.

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

In evaluating the ITC's testing recommendations for isopropanol, EPA considered all available relevant information including the following: Information presented in the ITC's report recommending testing consideration and public comments on the ITC's recommendations; production volume, use, exposure, and release information reported by manufacturers of isopropanol under the TSCA section 8(a) Preliminary Assessment Information Rule (40 CFR Part 712); health and safety studies submitted under the TSCA section 8(d) Health and Safety Data Reporting Rule (40 CFR Part 716) concerning isopropanol; and published and unpublished data on isopropanol available to the Agency. From its evaluation, as described in this proposed rule, EPA is proposing health effects testing for isopropanol under TSCA section 4(a)(1)(B). By this action, EPA is responding to the ITC's designation of isopropanol for priority testing consideration as required by TSCA section 4(e).

II. Review of Available Data

A. Chemical Profile

Isopropanol is a colorless, volatile, flammable liquid with a slight odor resembling that of a mixture of ethanol and acetone (Ref. 1), the air odor threshold is 22 ppm (Ref. 2). The freezing point of isopropanol is −88.5 °C and its boiling point is 82.3 °C (Ref. 1). It is miscible in water, ethanol, acetone, and benzene (Ref. 3). At 20 °C, it has a vapor pressure of 33 mmHg and a density of 0.7849 g/cm ^{3} (Ref. 1). The log octanol/water partition coefficent of isopropanol is 0.05 (Ref. 4).

Three grades of isopropanol are marketed in the United States: Anhydrous, and two aqueous solutions containing 95 volume percent and 91 volume percent of isopropanol, respectively (Ref. 1). The 91 volume percent is an azeotropic mixture with water and is usually referred to as CBM (constant-boiling-mixture) isopropanol (Ref. 1).

B. Production

Isopropanol is produced in the United States primarily by two basic commercial processes involving synthesis from propylene; the indirect hydration (sulfuric acid) process and the direct hydration process. The indirect hydration process utilizes a C_3 feedstock stream containing 40 to 60 percent propylene from refinery off-gas that is absorbed in concentrated sulfuric acid and the resulting ester then hydrolyzed. Although there are two variants of the indirect hydration process, the one currently employed by U.S. producers is the weak-acid process (Ref. 57). A strong-acid process is no longer in use. The product is packaged in drums, pails, or glass jugs or shipped in tank cars or trucks (Ref. 6).

The annual production volume of isopropanol has been in excess of 1 billion lb since 1956 (Ref. 7), and it ranked 50th for chemicals produced in the United States in 1985 (Ref. 8). Isopropanol is manufactured in the United States by four companies (Arco Chemical Company, Exxon Chemical Company, Shell Oil Company, and Union Carbide) at five locations with a combined production capacity of 2.5 billion lb per year as of January 1987 (Refs. 9 and 10). Imports increased from 48 million lb in 1980 to over 100 million lb each year from 1983 to 1986. Exports have exceeded 130 million lb each year since 1980, and increased from approximately 180 million lb per year in 1984 to 1985 to 267 million lb in 1986 (Refs. 7 and 64).

C. Uses

Estimated uses of isopropanol in 1987 were: Coating solvents, 18 percent; process solvents, 14 percent; pharmaceuticals, 14 percent; household and personal products, 14 percent; acetone production, 10 percent; miscellaneous solvents and chemical intermediates, 10 percent; and exports, 20 percent (Ref. 11).

The major use of isopropanol is as a solvent in consumer products and industrial products and procedures. As an industrial process solvent, isopropanol is used as an extractant in many procedures involving natural products such as fat, oils, gums, shellacs, waxes, drugs, spices, and flavorings (Refs. 3 and 13). Its solvent properties for a variety of oils, gums, waxes, resins, and alkaloids make it an important solvent in printing inks, paints, and varnishes (Ref. 1). While formerly the major source of demand for isopropanol, acetone production is now a relatively minor use. Acetone is now manufactured primarily as a by-product of phenol production by cumene oxidation, and is manufactured from isopropanol only as a supplementary supply source.

Many consumer products have been reported to contain isopropanol, including hair sprays, liniments, lotions, cosmetics, perfumes, floor detergents, shoe polishes, insect repellants, flea and tick sprays, air fresheners, windshield deicers, windshield cleaners, paints, and polishes (Ref. 1). Many home, industrial, and medicinal products containing isopropanol rely on its germicidal properties. Included in this category are sanitizers and antiseptics such as rubbing alcohol, a 70 percent isopropanol aqueous solution (Ref. 1). Some of these uses come under the jurisdiction of the Federal Food, Drug, and Cosmetic Act and the Federal Insecticide, Fungicide, and Rodenticide Act and are not subject to TSCA.

Isopropanol is an important chemical intermediate. Commercially important

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chemicals derived from it include aluminum isopropoxide, isopropyl acetate, isopropylamine diisopropylamine, isopropyl myristate, isopropyl oleate, and isopropyl xanthate (Refs. 1 and 14). Of these, recent production figures are available only for isopropylamine, which had a production volume of 54 million lb in 1985 (Ref. 12).

Isopropanol also is added to gasoline as an antistall agent. Other automotive uses include windshield deicers and windshield washer concentrates (Ref. 14).

D. Human Exposure and Release

1. Occupational

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that there were 8,899,594 exposures in 357,173 plants, potentially exposing 5,483,862 people to isopropanol in the workplace in 1970 (Ref. 15). The National Occupational Exposure Survey (NOES) estimates that 1,857,972 workers (60 percent of whom were female) were potentially exposed to isopropanol in the workplace in 1980 (Ref. 16).

Due to its large production volume and use in so many industries and products as a solvent, considerable exposure to isopropanol is expected. An assessment of worker exposure during manufacture was performed by EPA in 1985 (Refs. 6 and 17). These results are summarized in the following Table 1.

TABLE 1.—WORKER EXPOSURE TO ISOPROPANOL DURING 1985 [1]

Exposure phase	Workers exposure [2]	Exposure type	
		Inhalation [3] (mg/m [3])	Dermal [2] (mg/day)
Manufacturing (4 sites)	20-25/day/site	50 [4]	1,300-3,900
Processing (100 sites):			
Ink	1/day/site	5-52	1,300-3,900
Coatings	5/day/site	ND [5]-120	1,300-3,900
Uses:			
Acetone mfg. (4-6 sites)	6-10/day/site	3-4 [2]	1,300-3,900
Coatings (1,000 sites)	10,000-60,000	1-10, 5-11	1,900-5,500
Inks (7,000-11,000 sites)	83,000 [6]	50-1,470, 0-8,000, 240-280	260-780
Rubbing alcohol (5,900 sites)	1,000,000 [6]	ND-110	900-2,700

[1] Source: (Ref. 18).
[2] Estimated.
[3] Measured concentration, unless indicated otherwise.
[4] Upper limit.
[5] Not detected.
[6] National Occupational Exposure Survey (NOES).

Most of these exposures occurred at concentrations that are less than the 400 ppm, 8-hour time-weighted average, which is the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL), the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit, and the American Conference of Government and Industrial Hygienists (ACGIH) Threshold Limit Value (TLV). During manufacture, human exposure to isopropanol is primarily through inhalation as a result of filling operations, sampling, and reactor cleanup (Ref. 6).

Sources of occupational exposure include:

a. Use as a solvent in the application and manufacture of surface coatings, including stain, varnish, nitrocellulose lacquers, quick-drying inks and paints, textile coatings and dyes, dopes, and polishes.

b. Use in manufacture and handling of acetone.

c. Use in organic synthesis for isopropyl derivatives, including phenols, acetates, xanthates, ether, amines, myristate, palmitate, nitrite, and glycerin.

d. Use in manufacture of personal care items including liniments, skin lotions, permanent wave lotions, and hair color rinses.

e. Use in preparation, manufacture, packaging, and consumption of disinfectants and sanitizers, including rubbing alcohol, other antiseptic solutions, skin astringents, mouth washes, and medicated sprays.

f. Use in manufacture of cleaning and degreasing agents, including stain and spot removers, glass cleaners, rug and upholstery cleaners, tar remover, liquid soap, and windshield cleaner fluid and use in manufacture of deicing, defogging and antifreeze products.

g. Use in extraction and purification of alkaloids, proteins, chlorophyll, perfumes, sulfuric acid, vitamins, kelp, pectin, resins, gums, and waxes.

h. Use in manufacture of rubber products; use as an additive in antistalling gasoline, lubricants, denatured ethyl alcohol, hydraulic brake fluids, and rocket fuel.

i. Use in manufacture of adhesives, including nitrocellulose film and microfilm cement and in manufacture of safety glass.

General dilution/ventilation and the use of personal protective equipment have been recommended by NIOSH as effective controls to reduce occupational exposure to isopropanol in each of these operations (Ref. 15).

2. Consumer and General Population

Fugitive emissions of isopropanol during production have been estimated to be 1.5 percent of production in 1976 (Ref. 19); no more recent estimates are available. Based on 1985 production figures (1.236 billion lb), this would mean that 18.5 million lb of isopropanol were lost as fugitive emissions during its manufacture. Virtually all of the isopropanol used as a solvent in inks, coatings, and related products, as well as many household and consumer products, is ultimately released to the atmosphere. The majority of these releases are in an indoor environment, potentially resulting in relatively high peak exposures, depending on the product and use circumstances, as well as longer exposures to lower levels of isopropanol after product use and before ventilation can entirely remove the chemical.

In a study to identify environmental pollutants in human milk, isopropanol was detected in all eight samples of mothers' milk from women living in four heavily industrial urban areas; no quantitation was performed (Ref. 20).

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The extent of background pollutants, common air and water pollutants, or metabolites of naturally occurring products is unknown in this study.

Isopropanol has been identified in emissions from latex paint by Tichenor (Ref. 63) in experiments conducted to study indoor pollutants from building materials and consumer products. These experiments were performed as part of the EPA indoor air quality research program to characterize sources of indoor air pollutants.

Each year 22 million lb of isopropanol, or about 2 percent of its annual production, goes into rubbing alcohol, which is used in hospitals and industrial settings as an antiseptic and disinfectant (Ref. 6). Over 1 million workers are potentially exposed in this manner (Ref. 16). Levels of exposure from not-detected to 110 mg/m ^{3} of isopropanol have been estimated from OSHA inspection at two medical centers (Ref. 6). Exposure to rubbing alcohol (70 percent isopropanol) by the general population is also widespread.

Isopropanol occurs naturally as a plant volatile, as a product of fermentation, in animal wastes, and in volcanos and has been found in wine, beer, apples, pears, grapes, and pine logs (Refs. 13, and 21 through 27). Results of a Swedish study show that isopropanol is released in vehicle exhaust (Ref. 28).

3. Environmental Releases

Evidence suggests that considerable quantities of isopropanol may be released in wastewater that enters the aquatic environment. In a comprehensive EPA survey involving 4,000 samples of wastewater from industrial and publicly owned treatment works, 84 occurrences of isopropanol were reported from 19 industrial categories (Ref. 29). Additionally, 94 to 41,000 mg/L of isopropanol have been detected in leachate from municipal landfills (Refs. 30 and 31). Positive samples of groundwater taken from landfill sites have contained 86 to 2,600 mg/L of isopropanol (Ref. 31). Levels of isopropanol ranging from 10 to 2,000 mg/L have been found in a well in South Carolina near an industrial impoundment (Ref. 32).

E. Chemical Fate

Isopropanol enters the environment almost exclusively by evaporation or when discharged in wastewater. In the atmosphere, the major degradative process is expected to be reaction with photochemically formed hydroxyl radicals. Washout by precipitation may also contribute to its removal. Biodegradation should be the dominant degradative mechanism in water and soil. Isopropanol is readily biodegraded as determined in aerobic screening tests. Volatilization from water, especially shallow rivers, will be a significant transport process, as will leaching through soil. Isopropanol is not expected to break down by chemical means in the aqueous environment. Since it is miscible with fresh water, it is expected to remain in the aqueous compartment. In salt water, where it is less soluble, isopropanol may form surface films and evaporate. While no experimental data are available on the adsorption of isopropanol to soil or sediment, this should be insignificant because its octanol/water partition coefficient is low (0.05) (Refs. 33 and 34).

F. Health Effects

1. Acute Toxicity

The Agency has reviewed several studies and has found them sufficient to reasonably predict or determine the acute toxicity of isopropanol.

Oral LD50 values in the range of 4.4 to 8.0 g/kg have been determined for isopropanol in rats, rabbits, dogs, and mice indicating isopropanol to be of a low order of acute oral toxicity. An LD50 of 5.84 g/kg by dermal exposure has been established in the rabbit. A 2-hour LC50 value of 10.39 mg/L (49.120 ppm) has been determined by inhalation in mice. Following inhalation exposure, LC50 values of 1,900 and 22,500 were determined for female and male rats respectively. Studies on the acute effects of isopropanol in humans by the oral, inhalation and dermal routes are also available. These effects include hypotension, facial flushing, dizziness, gastritis, stupor, headaches, mental depression, body ache, nausea, and mild irritation of the ear, nose, and throat. The documentation for the acute effects of isopropanol is found in the isopropanol technical support document prepared by the Syracuse Research Corporation (Ref. 62).

2. Subchronic Toxicity

The Agency has reviewed all of the available studies on the subchronic toxicity of isopropanol and has found them insufficient to reasonably predict or determine the subchronic toxicity of isopropanol. Most of these studies were not conducted according to accepted, standard protocols, or complete data were not available to the Agency for review. The available data on the subchronic toxicity of isopropanol are not suitable for risk assessment purposes. This conclusion is borne out by the summaries that follow.

Daily dermal application of 50 percent isopropanol to albino rats for 187 days produced no skin injuries (Ref. 35), but experimental data are lacking for evaluation. In a 27-week study, rats were given isopropanol (0.5 to 10 percent) in their drinking water. Female rats receiving 1 or 5 percent isopropanol showed retardation of growth and body weight loss while rats in the 10 percent dose group refused to drink and died (due to unknown cause) after 7 to 28 days (Ref. 36). No effects were reported for the 0.5 percent group.

Savolainen et al. (Ref. 66) exposed 20 male Wistar rats to 300 ppm isopropanol vapors, 5 days per week, 6 hours per day for up to 21 weeks. Additional groups of 20 rats were sham-exposed (controls), sham-exposed with ethanol-water solution as sole drinking water source, or exposed to isopropanol vapors with ethanol-water solution as sole drinking water source. Within each group, 5 rats were sacrificed at intervals of 5, 10, 16, and 21 weeks for biochemical analyses of the nervous system. In addition, open field activity tests were conducted at 5-week intervals. Effects observed included reduced cerebellar superoxide dismutase and azoreductase activities in all treated groups, and elevated acid proteinase levels in the ethanol and isopropanol groups, while glial cell glutathione levels were unaltered. In rats administered either isopropanol alone or isopropanol with ethanol and sacrificed after 21 weeks, the lipid phosphorous/cholesterol ratio was slightly decreased relative to controls. The investigators proposed that the results suggest a general degeneration of nervous system tissue, but could not interpret the negative results regarding glutathione levels. Treatment-related changes in spontaneous open-field activity measures were negligible. At 15 weeks, however, isopropanol and combined isopropanol-ethanol treated rats administered caffeine prior to behavioral testing were less active than controls. This study failed to provide a comprehensive evaluation of all potential toxicologic end points.

In an oral subchronic study, Lehman et al. (Ref. 37) administered isopropanol solution to 3 dogs as a sole drinking water source, 1 hour per day for 6 months. Initially, the dogs were given a 1 percent isopropanol solution. By the end of the first month, the concentration had been raised to 4 percent and was maintained at that level until the end of the study. The dogs developed neuromuscular incoordination during the first exposure sessions; less incoordination was observed during subsequent exposures. The dogs

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received a challenge intravenous dose of isopropanol of approximately one half (2.56 cm^3) to three quarters (3.84 cm^3) of the fatal dose at the end of the 6-month period. Thirty-six hours after this dose, one dog died with evidence of minor hemorrhaging, leucodiapedisis, and microglial involvement in the brain, and hydropic changes and tubular epithelial necrosis of the kidneys. The remaining dogs were sacrificed at this time, and showed only negligible pathological changes. EPA believes this study is inadequate due to unorthodox dosing schedule, the small number of dogs used, and the lack of controls.

Two Russian studies have also described the effects of subchronic exposure to isopropanol (Refs. 38 and 39). Balkov et al. (Ref. 38) exposed an unspecified strain of rats to 20, 2.5, and 0.6 mg/m^3 isopropanol vapors continuously for 86 days. Statistically significant effects were observed only at the highest concentration. EPA believes that this study is inadequate to determine subchronic effects because the study suffered from a number of deficiencies including the lack of control animals, lack of details on experimental analysis, and use of obscure physiological measures. In the second study, Guseinov and Abasov (Ref. 39) exposed 10 male and 10 female "nonpurebred" white rats/group to 0, 0.1, or 0.5 mg/L (40 and 203 ppm) isopropanol vapors 5 days per week, 4 hours per day, for 4 months. Effects at the high concentration included increases in relative liver, spleen, and adrenal weight, vessel degeneration, changes in red and white cell counts, and a decrease in hippuric acid excretion and nonspecific cholinesterase activity. The significance of several of the observed effects is obscure, and other effects such as relative red and white cell counts in treated rats showed no consistent trend across months.

3. Chronic Toxicity

The Agency has reviewed the available studies and has found them insufficient to reasonably predict or determine the effect of long-term exposure to isopropanol. The only chronic toxicity data in animals are provided in a study by Boughton (Ref. 35) in which eight albino rats were exposed to 5 percent isopropanol in their drinking water for 304 days. There were no effects on mortality but rats developed forced breathing after several months of treatment. By 36 weeks the treated rats had a 23 percent decrease in weight gain relative to that of controls, and after 8.5 months all isopropanol-treated rats had a 16 percent increase in errors in 15 learning trials. The adequacy of the study is in question since only eight rats were treated. No other data have been found for chronic toxicity.

4. Oncogenicity

The Agency has reviewed all of the available studies on the oncogenicity of isopropanol and has found them insufficient to reasonably predict or determine the oncogenicity of isopropanol. None of the oncogenicity studies submitted to the Agency were conducted using currently accepted standard testing protocols.

Weil et al. (Ref. 40) conducted laboratory studies in six strains of mice on the tumorgenicity of isopropanol and byproducts associated with the strong-acid manufacturing process for isopropanol using different routes of exposure, but experimental details are lacking for assessment. In subcutaneous studies, mice were administered undiluted samples of 0.025 mL/animal for 20 to 40 weeks. However, the subcutaneous route of exposure is inappropriate for isopropanol, and the duration of the experiment was too short. In an inhalation study, mice were reportedly exposed to 0.0075 mg isopropanol/m^3, 5 days per week, 3 to 7 hours per day, for 5 to 8 months. In a subsequent communication, however, Weil noted that the actual metered concentration of isopropanol was a millionfold higher (7,700 mg./m^3) (Ref. 42). No increase in the incidence of tumors was observed in animals treated with isopropanol. However, an increase in the incidence of tumors was observed in the positive controls and in animals treated with some of the byproducts of the strong-acid process of isopropanol manufacture.

Van Esch (Ref. 43) administered an unspecified quantity of isopropanol to the diet of Swiss mice followed by biweekly applications of croton oil (a known tumor promoter) to the head. This treatment did not increase papilloma formation. Pyleva and Sakharov (Ref. 44) reported that application of isopropanol to the skin of CBA x C57BL mice had a "weak activating", but not a carcinogenic effect (not defined further). These studies were only available as abstracts. Other data were not reported in sufficient detail for evaluation.

Available animal data assessing oncogenicity are inadequate with regard to number of species used in the experiments, number of doses, inappropriate routes of exposure, and insufficiency of data reporting and duration of exposure, and thoroughness in reporting all test data.

5. Mutagenicity

The Agency has reviewed all of the available studies and has found them insufficient to reasonably predict or determine the genotoxicity of isopropanol. The only adequate study was one in which the NTP (Ref. 45) conducted a *Salmonella* reverse mutation assay (plate incorporation) with isopropanol. Isopropanol was tested at concentrations ranging from 100 to 10,000 ug/plate in the presence and absence of mammalian liver S9 fraction. Under the conditions of this assay, isopropanol produced no increase in the reversion frequency in *Salmonella* strains TA97, TA98, TA100, TA1535, or TA1537.

Brockman et al. (Ref. 46) reported that isopropanol had no effect on meiotic nondisjunction and subsequent aneuploidy in crossed strains of Neurospora crassa Only the maximum dose of isopropanol which was consistent with fertility was tested. This screening study is not adequate to address potential clastogenicity of isopropanol.

Isopropanol was assayed for its ability to cause transformation in Syrian hamster embryo cells infected with Simian SA7 virus (Ref. 47) and was found to be negative. At no concentration did isopropanol affect transformation rate; however, the control transformation rate was high and variable. Aristov et al. (Ref. 48) as reported in an abstract of a Russian study, showed that inhalation exposure to an unspecified concentration of isopropanol for 4 months resulted in a significantly increased number of aberrant metaphases in the bone marrow cells of albino rats. The no-effect level was 0.52 mg./m^3. Full evaluation of this study is not possible due to the lack of details presented in the abstract.

EPA has therefore concluded that there is not sufficient information to reasonably determine or predict the genotoxic potential of isopropanol for gene mutations and chromosomal aberrations in mammalian systems.

6. Reproductive Effects and Developmental Toxicity

The Agency has reviewed all of the available reproductive effects and developmental toxicity studies for isopropanol and has found them insufficient to reasonably determine or predict the potential toxicity of isopropanol. Nelson et al. (Ref. 49) recently conducted a study of the developmental toxicity effects of isopropanol in female Sprague-Dawley

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rats. Groups of 15 animals were exposed to 0 ppm, 3,500 ppm, 7,000 ppm, or 10,000 ppm isopropanol vapor 7 hours per day from days 1 to 19 of gestation. On gestation day 20, the dams were sacrificed, and the number of corpora lutea, resorptions, and live fetuses were recorded. The fetuses were removed and examined for external malformations. Half of the fetuses were analyzed for skeletal malformations, and the other half were examined for visceral malformations.

Administration of the two highest concentrations resulted in reversible maternal toxicity. Initial exposure to 10,000 ppm produced narcosis in dams, and treatment with 7,000 ppm was associated with an unsteady gait. Exposure to 10,000 ppm resulted in significant decrease in maternal body weight gain. Weight gain was slightly reduced in dams exposed to 7,000 ppm. Exposure to 3,500 ppm produced no maternal toxicity.

Effects of isopropanol exposure on developmental parameters included a dose-related decrease in fetal body weight, a reduced number of pregnancies (6/15 were not pregnant, reduced number of implantations), and an increased number of fetal resorptions (4/15 litters had total resorptions) in dams exposed to 10,000 ppm. There were significant increases in skeletal malformations among fetuses in the two higher dose groups. Fetal body weights were reduced in all treated groups. This study is inadequate due to the fact that initially there were only 15 rats per group and in the highest dose group (10,000 ppm) there were only 5 litters available for examination and evaluation.

Lehman et al. (Ref. 37) conducted a three-generation reproductive study. Six female and three male white rats were given free access to 2.5 percent isopropanol in drinking water for 80 days and then mated. This procedure was repeated for the subsequent 2 generations, but only 13 first generation and 10 second generation females were maintained in the experimental protocol. Compared to control rats, first (but not second) generation progeny had reversible delays in development. These were not further defined. Deficiencies in this study include the number of animals used and the lack of details regarding the assessment of developmental toxicity.

Additional data on isopropanol reproductive toxicity were obtained from a Russian study (Ref. 50). In the first series of experiments, isopropanol was administered (probably orally) to female rats for 20 days at doses of 252 or 1,008 mg/kg. Administration of either dose for 20 days during pregnancy resulted in decreased numbers of fetuses in treated females. Treatment with the higher dose was associated with embryolethality. Furthermore, 10 out of 70 fetuses in the high dose group had visceral anomalies in comparison with 0 out of 90 control fetuses. Treatment of non-pregnant females for 45 days with the same doses resulted in statistically significant increases in the length of the estrus cycle. In a second series of studies, isopropanol was administered at 1,800 mg/kg/day to white rats for 3 months prior to pregnancy. There was a significantly higher embryolethality rate among treated rats in comparison with controls. In the chronic portion of the study, male and female rats were administered 0.018, 0.18, 1.8, and 18 mg/kg isopropanol through the drinking water for 6 months. The timing of the exposure period in relation to the mating period was unspecified. Experimental and control male and female rats were cross-mated in a 2x2 factorial design. Offspring mortality was most prevalent in the groups containing experimental females.

When data were collapsed across mating condition, the rats administered 18 mg/kg isopropanol had a 35 percent decrease in weight gain, and the treated offspring had dose-related impairments in a behavioral turning task. This study is deficient due to the limited sample sizes (5 to 7 rats per experimental cell) and ambiguous measuring techniques.

Currently BIBRA is conducting a study at the request of the Government of the United Kingdom consisting of a single-generation reproductive study in the rat with dosages at 0.5 percent, 1.0 percent, and 2 percent isopropanol in drinking water. Ten males were exposed 70 days prior to mating and 20 females were exposed 21 days prior to mating, during mating, during pregnancy, and until sacrificed. Offspring were treated with isopropanol during rearing and until killed. The test protocols for roproductive effects indicated that only 10 females were dosed. In addition, the protocol is for a one-generation study. EPA believes a two-generation study is necessary to sufficiently address the potential reproductive effects of a chemical.

A single-species teratology study in the rat with dosages at 0.5 percent, 1.5 percent and 2.5 percent isopropanol in drinking water is also being conducted at the request of the Government of the United Kingdom. EPA has reviewed the protocol for developmental toxicity in the rat and has determined that it is incomplete. The adequacy of this study will be assessed after receipt of the data.

The TSCA test guideline (40 CFR 798.4900(e)(1)(i)) stipulates that at least two mammalian species be used for testing in order to completely assess the potential developmental toxicity of a chemical. If the study conducted for the Government of the UK is regarded as adequate, then only a single-species developmental toxicity study will be required. If the study is inadequate, then developmental toxicity studies in two mammalian species will be required.

7. Neurotoxicity

The Agency has reviewed all of the available studies and has found them insufficient to reasonably predict or determine the neurotoxicity of isopropanol. The experimental evidence accumulated to date is very limited and some of the data are based upon results of tests performed using isopropanol in combination with other alcohols.

Maizlish et al. (Ref. 51) looked at 240 workers exposed to mixtures of organic solvents over a 7-year period of isopropanol exposure and determined that there was no deleterious effect on six behavioral parameters. The workers included a subset at one plant in which isopropanol was found to be 161 percent of TLV (644 ppm). The significance of the findings with regard to isopropanol is difficult to assess since it was only one component in the solvent mixtures studied.

In a laboratory study, Wallgren (Ref. 52) administered 0.043 mole/kg (2.6 g/kg) isopropanol to groups of 3- to 4-month-old rats and monitored performance on an inclined plane task. After a baseline measure, the investigators administered the alcohol and conducted six tests at 20-minute intervals. Isopropanol treatment reduced the angle at which the rats could maintain themselves to 67.7 percent of baseline values. There was no appreciable recovery 2 hours after treatment.

Leander et al. (Ref. 53) assessed schedule-controlled behavior in three male pigeons after oral administration of 5 percent isopropanol directly into the proventriculus (glandular stomach) twice weekly. Responses were reduced with increasing doses. Other related data as to response rates with varied electric shocks are inadequate due to the small number of animals and the use of isopropanol in combination with ethanol.

Boughton (Ref. 35) administered 5 percent isopropranol to male rats in their drinking water for 304 days and found no subjective behavioral signs. After 8.5 months, rats given isopropanol had a 16 percent increase in errors in

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their performance in elevated T-mazes for 15 learning trials and had increased running times. Maze performance returned to normal 1 month after treatment ended.

8. Epidemiology

Several studies pertaining to worker exposures to isopropanol have been reviewed. These studies involve workers in the manufacture of isopropanol by the "strong-acid" process. Currently the method of production being used is a closed-system weak-acid process in which propylene is reacted with sulfuric acid and the isopropyl esters are further hydrolyzed to isopropanol. To date, no epidemiology studies have been submitted to the Agency on workers involved in the manufacture of isopropanol using only the newer weak-acid process.

Weil (Ref. 40) investigated the incidence of cancers in workers involved in isopropanol manufacture. Of the various substances to which the workers may have been exposed, only propylene, isopropyl ether, sulfur dioxide, and isopropanol were sufficiently volatile to be inhaled in large quantities. Although an increase in sinus tumors was observed, NIOSH (Ref. 42) concluded that the increase could not be associated with a specific compound and that the entire manufacturing process should be regulated as a "cancer hazard process" Eckardt (Ref. 54) reported that, after appropriate industrial hygiene controls and the weak-acid process were initiated, no cancers were found for a period of more than 20 years. Similar results were obtained in a second plant after conversion to the closed-system weak-acid process. NIOSH (Ref. 55) has since reaffirmed that a carcinogen appeared to have been present in the strong-acid process. Evidence was provided by Wright (Ref. 56) that this carcinogen was likely to have been diisopropyl sulfate.

As reviewed in IARC (1977) (Ref. 13), enhanced incidence of respiratory tract cancer has been reported in two plants manufacturing isopropanol by the strong-acid process. In one plant in which isopropyl oils were formed as byproducts, 7 neoplasms were found among 71 men who had worked for more than 5 years between 1928 and 1950. A conservative estimate is that the incidence of paranasal sinus cancer in this group of workers is more than 3 times that expected in the general population. In another isopropyl alcohol manufacturing factory, in operation in the United States since 1927, two sinus cancers and two intrinsic laryngeal cancers occurred among a total of 11 cancers in 779 employees. All cancer cases occurred in subjects who had worked in the factory for more than 9 years. The incidence of sinus and laryngeal cancers in this group was reported to be 21 times that expected in the general population aged 45 to 54 years.

Additional occupational studies at Shell Oil Refineries in Texas and England (Refs. 57 through 60) were conducted to further assess the impact of the isopropanol production process on worker mortality, with particular emphasis on excess cancer deaths. The group consisted of 124 employees who worked in the isopropanol production unit (strong-acid process) and were transferred subsequently to the epichlorohydrin production area. Analysis of the mortality incidence among 433 isopropanol production workers, who worked in the unit for at least one quarter, showed two deaths from buccal and pharyngeal cancer. The two cases of buccal and pharyngeal cancers were diagnosed in the workers who were subsequently exposed to epichlorohydrin, but 4 out of 7 of the respiratory cancer deaths were in individuals exposed to both production processes. The mixed exposure, the lack of concurrent control data (workers exposed to neither production process), the short followup times, and the low incidence of tumor-related deaths make interpretation of the results difficult.

Alderson and Rattan (Ref. 61) conducted an epidemiological study of workers at a plant that manufactured isopropanol by the strong-acid process. Nine neoplasms were found among 262 men who had worked for more than 1 year between 1950 and 1975. Neoplasms were found at the following sites; 1 in nose and nasal sinus, 1 in esophagus, 2 in lung and pleura, 2 in kidneys and adrenals, and 2 in brain and central nervous system (CNS). Only the single case of nose and sinus cancer was deemed to be of statistical significance. These studies were performed on workers in a manufacturing process that is no longer in use and its relevance to the current process is unknown. To date, no epidemiological studies have been submitted to the Agency for workers employed in the weak-acid process of manufacture of isopropanol.

9. Metabolism and Pharmacokinetics

The Agency has reviewed all of the available studies and has found them insufficient to reasonably predict or determine the metabolism and pharmacokinetics of isopropanol (Ref. 62).

The studies reviewed encompass absorption, tissue distribution, biotransformation, and elimination data mainly in rats, dogs, rabbits, and humans. No data are available for the mouse. The data provide evidence that isopropanol is readily absorbed by the oral, inhalation, and dermal routes of exposure, and that the major metabolic pathway is transformation to acetone by alcohol dehydrogenase (ADH). Elimination of both parent compound and the major metabolite occurs predominantly through the lungs and in the urine.

The studies appear to provide sufficient data to qualitatively assess the biotransformation of isopropanol. However, none of the studies reviewed provide sufficient quantitative data to assess percent absorption, mechanism of elimination, or a materials balance for the relevant species by the oral or inhalation routes of exposure. The Agency is unable to use these data to extrapolate toxic effects from lower species to human, from high to low doses, or from route to route (Ref. 67). Such data are needed to fully assess the metabolism and pharmacokinetics of isopropanol.

III. Findings

Under TSCA section 4(a)(1)(B), EPA finds that isopropanol is produced in substantial quantities and that there is or may be substantial human exposure from its manufacture, processing, disposal, and use.

Approximately 1 billion lb of isopropanol has been produced yearly since 1956 (Ref. 7).

There is substantial human exposure to isopropanol in the workplace. The National Occupational Hazard Survey (NOHS) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974 estimated that there were 8,899,594 exposures in 357,173 plants, potentially exposing 5,483,862 people to isopropanol in the workplace in 1970. The National Occupational Exposure Survey (NOES) estimates that 1,857,972 workers, 60 percent of whom were female, were potentially exposed to isopropanol in the workplace in 1980.

Isopropanol is used as a solvent and is a component of numerous industrial products, consumer products, and commercial sprays. The above uses may result in widespread exposure to workers and consumers. The Agency believes that exposures associated with the manufacture, processing, disposal, and use of isopropanol and its products provide a sufficient basis for a finding of

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substantial human exposure under TSCA section 4(a)(1)(B) for isopropanol.

On the basis of findings given in Unit II of this document, EPA finds that existing data are insufficient to reasonably determine or predict the subchronic, chronic, oncogenic, genotoxic, reproductive, developmental, and neurotoxic effects of human exposure to isopropanol resulting from its manufacture, processing, disposal, and use and that testing is necessary to develop such data. EPA also finds that there are insufficient data to reasonably predict and compare the absorption, distribution, metabolism, and excretion of isopropanol in the body as a result of oral or inhalation exposure due to isopropanol's manufacture, processing, and use, and that an oral-inhalation comparative pharmacokinetic study of isopropanol is necessary to develop such data. EPA believes that the data generated from this testing will be relevant to a determination as to whether the manufacture, processing, disposal, and use of isopropanol 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 795 and 798. All persons conducting tests would conduct tests in accordance with the TSCA Good Laboratory Practice (GLP) Standards (40 CFR 792).

On the basis of the findings presented in Unit III, the Agency is proposing that isopropanol be tested under TSCA section 4(a)(1)(B) for: (1) Subchronic inhalation toxicity, 40 CFR 798.2450; (2) oncogenicity by inhalation, 40 CFR 798.3300; (3) reproductive toxicity by gavage, 40 CFR 798.4700; (4) developmental toxicity by gavage, 40 CFR 798.4900; (5) neurotoxicity by inhalation, 40 CFR 798.6050, 798.6200, and 798.6400; (6) developmental neurotoxicity by gavage, 40 CFR 795.250; (7) genotoxicity, 40 CFR 798.5300, 798.5275, 798.5200, 798.5375, 798.5385, 798.5450, and 798.5460; and (8) pharmacokinetics, 40 CFR 795.231.

To assess the degree of toxicological activity of isopropanol upon various target organs, the Agency is proposing that isopropanol be tested for subchronic toxicity by inhalation, 40 CFR 798.2450. To assess the neurotoxic effects of repeated inhalation exposures to isopropanol, the Agency is proposing a subchronic neurobehavioral toxicity evaluation consisting of a neuropathologic evaluation of tissues perfused *in situ*, 40 CFR 798.6400, a functional observation battery, 40 CFR 798.6050, and measurement of motor activity, 40 CFR 798.6200. This proposed battery of neurotoxic evaluation may be combined with the subchronic test 40 CFR 798.2450. To assess the effects of acute neurotoxic inhalation exposures to isopropanol, the Agency is proposing an acute neurobehavioral toxicity evaluation consisting of a functional observations battery, 40 CFR 798.6050, and measurement of motor activity, 40 CFR 798.6200.

To fully assess the developmental neurotoxicity potential of isopropanol the Agency is proposing a developmental neurotoxicity evaluation, 40 CFR 795.250, based upon the TSCA section 4(a)(1)(B) finding. In addition, the Agency is concerned because other simple short-chain alcohols have shown developmental neurotoxic effects. Data on ethanol indicate that it is not only a known developmental toxicant but that it is also a developmental neurotoxicant (Ref. 49). Furthermore, *t*-butanol has been shown to produce developmental neurotoxic effects in animal species (Ref. 49).

Due to substantial exposure to isopropanol and a lack of data regarding potential chronic toxicity or oncogenic effects, the Agency believes that the oncogenicity part of the test program is justified without waiting for results of gene mutation tests. The Agency is thus proposing a 2-year inhalation bioassay in two species, 40 CFR 798.3300. 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 isopropanol 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.

The Agency is proposing testing for reproductive effects, 40 CFR 798.4700, and developmental toxicity, 40 CFR 798.4900, because of the widespread human exposure and lack of data to reasonably predict these effects. EPA is proposing that these two tests be done by gavage.

To assess the potential for isopropanol to cause gene mutations, the Agency is proposing that testing be conducted for gene mutations in cells in culture, 40 CFR 798.5300. If the results of the cells in culture test are positive, a *Drosophila* sex-linked recessive lethal assay (SLRL) would be conducted using the method, 40 CFR 798.5275. A positive result in the SLRL assay would trigger a mouse specific locus test, 40 CFR 798.5200. If the cells in culture test is negative, no further testing would be required. If the SLRL assay is negative, the mouse specific locus test would not be required.

To assess the potential for isopropanol to cause chromosomal aberrations, the Agency is proposing that an *in vitro* cytogenetic assay be conducted on isopropanol, 40 CFR 798.5375. If the results of the *in vitro* test are positive, a dominant-lethal assay would be required, 40 CFR 798.5450. A positive result in the dominant-lethal assay would trigger a heritable translocation assay, 40 CFR 798.5460. If the *in vitro* cytogenetics assay is negative, the *in vivo* bone marrow assay, 40 CFR 798.5385, would be required. Should the *in vivo* bone marrow test results prove negative, no further chromosomal aberrations testing would be required. A positive result in the in *vivo* bone marrow test would trigger the dominant-lethal assay 40 CFR 798.5450. Again, if the dominant-lethal test is positive, a heritable translocation assay, 40 CFR 798.5460 would be conducted.

If the results from the dominant-lethal assay and/or the SLRL are positive, EPA would hold a public program review prior to requiring initiation of the heritable translocation and/or mouse specific locus testing. Public participation in this program review would be in the form of written public comments or a public meeting. Request for public comments or notification of a public meeting would be published in the **Federal Register**. Should the Agency determine, based on the weight of the evidence then available, that proceeding to the heritable translocation test and/or mouse specific locus assay is no longer warranted, the Agency would propose to repeal that test requirement and, after public comment, would issue a final amendment to rescind the requirement.

For a more detailed discussion concerning mutagenicity tiered testing and program review, see the final test rule for the C_9 aromatic hydrocarbon fraction (50 FR 20662; May 17, 1985).

EPA is proposing a tiered testing approach to evaluate whether isopropanol elicits heritable gene mutations. Positive results in SLRL would trigger the requirement for conducting a mouse visible specific locus (MVSL) test. EPA believes that the MVSL is necessary, when these lower-tier tests are positive, to establish

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definitively whether a substance is capable of eliciting heritable gene mutations. Under the approach proposed, EPA would consider the positive results in the lower-tier tests in a public program review, together with other relevant information, during which interested persons would be able to give their views to the Agency. If, after the review, EPA determined that the MVSL was still appropriate, EPA would notify the test sponsors by letter or **Federal Register** notice that they must conduct the test. If EPA determined that the test was no longer necessary, EPA would propose to amend the rule to delete the test requirement.

Other test rules have included the requirement for the MVSL, including those for the C_9 aromatic hydrocarbon fraction (50 FR 20662), diethylenetriamine (50 FR 21398), and four fluoroalkenes (52 FR 21516). EPA based the requirement in those rules, in part, on information and assumptions about the cost of conducting the test and the availability of laboratories capable of performing the test. The information and assumptions have since proven to be incorrect. Accordingly, EPA is in the process of reexamining the MVSL requirement for all those chemical substances for which the MVSL has been required or proposed to be required. In particular EPA is reviewing whether any laboratories are available to perform the MVSL for industry in accordance with the TSCA Good Laboratory Practice Standards at 40 CFR Part 792 and the cost of such testing. EPA is also reviewing possible alternative tests to the MVSL for which costs may be lower or laboratory availability may be more certain.

Once EPA completes its evaluation of this additional information, EPA will publish a notice in the **Federal Register** concerning the MVSL for isopropanol and other substances subject to proposed and final TSCA section 4 test rules. This notice will provide up-to-date information on the cost of MVSL testing, availability of laboratories to perform the MVSL, and possible alternative tests to the MVSL together with their costs and laboratory availability. The notice will also address EPA's intentions about any changes to the MVSL requirements in the various test rules and will provide an opportunity for public comment. If, after this exercise, EPA concludes that the MVSL is appropriate for isopropanol, EPA will include the MVSL requirements with any appropriate modifications in the final rule.

To fully assess the potential toxicity of isopropanol for quantitative risk assessment purposes, the Agency is proposing metabolism and pharmacokinetics testing by the oral and inhalation routes of exposure. The Agency believes this testing of isopropanol is necessary to reduce uncertainties associated with the extrapolation of test data from high to low doses, from species to species, and from one route of exposure to another. Pharmacokinetic data in rats are being proposed to determine comparative, dose-dependent, oral and inhalation absorption, tissue distribution, bioaccumulation, metabolism, and excretion data. These data are needed for extrapolation purposes. The necessary extrapolations can only be made on the basis of metabolism and pharmacokinetics data obtained from studies performed by both routes of isopropanol administration. Repeated dose studies are needed in order to learn whether multiple exposures modify the metabolism and/or pharmacokinetics of isopropanol.

Although there is some human and rat data provided, these data are not adequate to support the required extrapolations. The Agency is proposing that pharmacokinetics studies be conducted for isopropanol as described in proposed 40 CFR 795.231.

The Agency is proposing that the TSCA health effects test guidelines be employed as the test standards for the purpose of the proposed tests for isopropanol. The TSCA test guidelines for health effects testing specify generally accepted minimum conditions for determining the health effects for substances like isopropanol 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 2, 1982), has found no reason to conclude that these guidelines need to be modified significantly.

B. Test Substance

EPA is proposing that isopropanol (CAS No. 67-63-0) 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 isopropanol itself. EPA believes that this grade of isopropanol is readily available for testing purposes.

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 in commerce, 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, disposal, and use of isopropanol, EPA is proposing that persons who manufacture and/or process, or who intend to manufacture and/or process isopropanol, 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. While EPA has not identified any byproduct manufacturers of isopropanol, such persons would be covered by the requirements of this test 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 proposed rule would 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 a 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 isopropanol would 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, Subpart E.

Manufacturers, including importers, subject to this rule would be 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

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letters and applications are described in 40 CFR Part 790.

Processors subject to this rule, unless they are also manufacturers, would 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 would pass an appropriate portion of the costs of testing on to processors through the pricing of their products or reimbursement mechanisms. If manufacturers fail to submit notices of intent to test or fail to sponsor all the required tests, the Agency would 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 isopropanol.

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

D. Reporting Requirements

As required in 40 CFR 799.10, all data developed under the final rule would 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 would be 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 isopropanol in the following Table 2.

TABLE 2.—PROPOSED TESTING, TEST STANDARDS, AND REPORTING REQUIREMENTS FOR ISOPROPANOL

Test	Test standard (40 CFR citation)	Reporting deadline for final report[1]	Interim (6-month) reports required
Subchronic Toxicity:			
1. Subchronic inhalation toxicity	§ 798.2450	15	2
Chronic Toxicity:			
2. Oncogenicity	§ 798.3300	53	8
Specific Organ/Tissue Toxicity:			
3. Reproduction and fertility effects	§ 798.4700	24	4
4. Developmental toxicity	§ 798.4900	12	1
Gene Toxicity-Gene Mutations:			
5. Mammalian cells in culture	§ 798.5300	6	.....
6. *Drospophila* sex-linked recessive lethal	§ 798.5275	18	2
7. Mouse specific locus	§ 798.5200	[2] 48	7
Chromosomal Aberrations:			
8. *In vitro* cytogenetics	§ 798.5375	15	2
9. *In vivo* cytogenetics	§ 798.5385	15	2
10. Dominant lethal assay	§ 798.5450	24	3
11. Heritable translocation assay	§ 798.5460	[2] 24	3
Acute Neurotoxicity:			
12. Functional observation battery	§ 798.6050	15	2
13. Motor activity	§ 798.6200	15	2
Subchronic Neurotoxicity:			
14. Functional observation battery	§ 798.6050	15	2
15. Motor activity	§ 798.6200	15	2
16. Neuropathology	§ 798.6400	15	2
17. Developmental neurotoxicity screen	§ 795.250	15	2
Pharmacokinetics:			
18. Pharmacokinetics (oral and inhalation)	§ 795.231	15	2

[1] Number of months after the effective date of the final rule, except as indicated.
[2] Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or FEDERAL REGISTER notice that, following public program review of all of the then existing data for isopropanol, the Agency has determiend that the required testing must be performed.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by the final rule, the Agency would 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 final 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 the final test rule, an exporter of isopropanol would report to EPA the first export or intended export of isopropanol to a particular country in a calendar year. EPA would notify the foreign country concerning the test rule for the chemical.

V. Issues for Comment

1. This proposed rule specifies TSCA test guidelines as the test standards for health effects testing of isopropanol. The Agency is soliciting comments as to whether these test guidelines are appropriate and applicable for the testing of isopropanol.

2. Also regarding the testing of isopropanol, the Agency requests comment on:

a. The adequacy of the proposed testing to characterize the health effects of isopropanol.

b. The reporting requirements for the specified health effects tests.

c. Any alternative approaches that should be considered.

3. The Agency requests comment on the route of exposure for the testing program. The Agency is proposing that most of the proposed tests be conducted by inhalation because it is the most relevant route for human exposure to isopropanol under TSCA. The reproductive effects test, developmental toxicity, and developmental neurotoxicity tests, however, are being

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proposed by gavage due to the technical difficulties in performing these tests by inhalation for isopropanol.

4. The Agency is proposing pharmacokinetics testing in the rat to determine comparative dose-dependent oral and inhalation absorption, tissue distribution, bioaccumulation, metabolism, and excretion data. The Agency believes that these data are useful for dose selection and for high to low dose extrapolations, route to route extrapolations, and animal species to human extrapolations.

The Agency requests comment on:

a. Selection of the rat for the pharmacokinetic studies

b. Need for pharamacokinetic data in the mouse for bioassay dose-selection and for risk assessment.

c. Need for and time-course of the elements required in the pharamacokinetic standard. Specifically, should absorption, distribution, and excretion data be completed prior to the subchronic studies? Should the metabolic fate studies run concurrently, or sequentially after the results of the subchronic toxicity studies are completed?

VI. Economic Analysis of the 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 isopropanol: (1) Price sensitivity of demand; (2) market expectations; (3) industry cost characteristics; and (4) industry structure. 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 examines the magnitude and distribution of the expected impact.

Total testing costs for the proposed testing of isopropanol are estimated to range from $2.7 to $3.8 million. In order to predict the financial decision-making practices of manufacturing firms, these costs have been annualized. Annualized costs are compared with annual revenue as an indication of potental 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 test costs, using a 7 percent cost of capital over a period of 15 years, range from $291,000 to $414,000. Based on 1986 production of 1.3 billion lb, the unit test costs range from $0.00022 to $0.00032 per pound. These costs are equivalent to 0.097 to 0.139 percent of the current price of $0.23 per pound.

EPA believes that the potential for adverse economic impact resulting from the costs of testing is low. This conclusion is based on the following observations:

1. The annualized cost of testing is very low, at approximately 0.14 percent of product prices in the upper bound case.

2. Demand for isopropanol does not appear to be sensitive to a price increase in this range.

Refer to the economic analysis which is contained in the public record for this rule making for a complete discussion of test cost estimation and potential for economic impact resulting from these costs (Ref. 12).

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 National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (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 specified in this proposed rule.

EPA has reviewed the availability of contract laboratory facilities to conduct the neurotoxicity testing requirements (Ref. 65) and believes that facilities will be made available for conducting these tests. The laboratory review indicates that few laboratories are currently conducting these tests according to TSCA test guidelines and TSCA GLP standards. However, the barriers faced by testing laboratories to gear up for conducting these tests are not formidable. Laboratories will need to invest in testing equipment and personnel training, but EPA believes that these investments will be recovered as the neurotoxicity testing program under TSCA section 4 continues. EPA's expectations of laboratory availability were borne out under the testing requirements of the C_9 aromatic hydrocarbon fraction test rule (50 FR 20675; May 17, 1985). Pursuant to that rule, the manufacturers were able to contract with a laboratory to conduct the testing according to TSCA test guidelines and TSCA GLP standards.

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 of Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): (202) 554-1404 by May 2, 1988. No meeting will be held unless members of the public 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 will 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. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42097). This record contains the basic information considered by the Agency in developing this proposal and appropriate **Federal Register** notices. The Agency will supplement this record with additional relevant information.

This record includes the following information:

A. Supporting Documentation

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

(a) Notice containing the ITC designation of isopropanol to the Priority List (51 FR 41417); November 14, 1986) and all comments on isopropanol received in response to that notice.

(b) Rules requiring TSCA sections 8 (a) and (d) reporting on isopropanol (51 FR 41328; November 14, 1986).

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

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

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

(f) Interim Final Rule: Procedures Governing Testing Consent Agreements and Test Rules Under the Toxic Substances Control Act (51 FR 23706, June 30, 1986).

(2) Support documents consisting of:

(a) Technical support document for proposed rule.

(b) Economic impact analysis of proposed rule for isopropanol.

(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 including Chemical Testing Industry: Profile of Toxicological Testing (October, 1981).

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X. Other Regulatory Requirements

A. Excecutive Order 12291

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

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

B. Regulatory Flexibility Act

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

C. Paperwork Reduction Act

The information collection requirements contained in this proposed rule have been approved under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and have been assigned OMB number 2070–0033. Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs of OMB marked "Attention Desk Officer for EPA." The final rule will respond to any OMB or public comments of the information collection requirements.

List of Subjects in 40 CFR Parts 795 and 799

Chemicals, Environmental protection, Hazardous substances, Testing Laboratories, Provisional testing, Recordkeeping and reporting requirement.

Dated: March 9, 1988.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

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

PART 795—[AMENDED]

1. In Part 795:

A. The authority citation for Part 795 continues to read as follows:

Authority: 15 U.S.C. 2603.

b. By adding § 795.231 to read as follows:

§ 795.231 Pharmacokinetics of isopropanol.

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

(1) Ascertain whether the pharmacokinetics and metabolism of isopropanol ("test substance") are

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similar after oral and inhalation administration.

(2) Determine bioavailability of the test substance after oral, dermal, and inhalation administration.

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

(b) *Definitions.* (1) "Bioavailability" refers to the rate and relative amount of administered test substance which reaches the systemic circulation.

(2) "Metabolism" means the study of the sum of the processes by which a particular substance is handled in the body, and includes absorption, tissue distribution, biotransformation, and excretion.

(3) "Percent absorption" means as 100 times the ratio between total excretion of radioactivity following oral or inhalation administration and total excretion of radioactivity following intravenous administration of test substance.

(4) "Pharmacokinetics" means the study of the rates of absorption, tissue distribution, biotransformation, and excretion.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species.* The rat shall be used for pharmacokinetics testing because it has been used extensively for metabolic and toxicological studies.

(ii) *Test animals.* For pharmacokinetics testing, adult male and female rats (Fisher 344 or strain used for major toxicity testing), 7 to 9 weeks of age, shall be used. The animals should be purchased from a reputable dealer and shall be identified upon arrival at the testing laboratory. 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 test group shall contain at least 4 animals of each sex for a total of at least 8 animals.

(iii) *Animal care.*—(A) Animal care and housing should be in accordance with DHEW Publication No. (NIH)-78-23, 1978, entitled "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 24±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 and shall be acclimated to the experimental environment for a mimimum of 48 hours prior to treatment.

(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.*

(2) *Administration of test substances*—(i) *Test substance.* The use of radioactive test substance is required for all studies. Ideally, the purity of both radioactive and nonradioactive test substance should be greater than 99 percent. The radioactive and nonradioactive substances shall be chromatographed separately and together to establish purity and identity. If the purity is less than 99 percent or if the chromatograms differ significantly, EPA should be consulted.

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

(B) *Oral.* Two doses of test substance shall be used in the oral portion of the study, a low dose and a high dose. The high dose should ideally induce some overt toxicity, such as weight loss. The low dose level should correspond to a no observed effect level. The oral dosing shall be accomplished by gavage or by administering the encapsulated test substance. If feasible, the same high and low doses should be used for oral and dermal studies.

(c) *Inhalation.*—Two concentrations of the test substance shall be used in this portion of the study, a low concentration and a high concentration. The high concentration should ideally induce some overt toxicity, while the low concentration should correspond to a no observed level. Inhalation treatment should be conducted using a "nose-cone" or "head only" apparatus to prevent ingestion of the test substance through "grooming".

(iii) *Dosing and sampling schedule.* After administration of the test substance, each rat shall be placed in a separate metabolic unit to facilitate collection of excreta. For the inhalation studies, excreta from the rats shall also be collected during the exposure periods. At the end of each collection period, the metabolic cages shall be cleaned to recover any excreta that might adhere to the cages. All studies, except the repeated dose study, shall be terminated at 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(A) *Intravenous study.* Group A shall be dosed once intravenously at the low dose of test substance.

(B) *Oral studies.* (*1*) Group B shall be dosed once *per os* with the low dose of the test substance.

(*2*) Group C shall be dosed once *per os* with the high dose of the test substance.

(C) *Inhalation studies.* A single 6-hour exposure period shall be used for each group.

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

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

(D) *Repeated dosing study.* Group F shall receive a series of single daily oral low doses of nonradioactive test substance over a period of at least 7 consecutive days. Twenty-four hours after the last nonradioactive dose, a single oral low dose of radioactive test substance shall be administered. Following dosing with radioactive substance, the rats shall be placed in individual metabolic units as described above. The study shall be terminated 7 days after the last dose, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(3) *Types of studies*—(i) *Pharmacokinetics studies.* Groups A through F shall be used to determine the kinetics of absorption of the test substance. In groups administered the substance by intravenous or oral routes, (i.e., Groups A, B, C, F), the concentration of radioactivity in blood and excreta shall be measured following administration. In groups administered the substance by the inhalation route (i.e., Groups D and E) the concentration of radioactivity in blood and excreta shall be measured at selected time intervals during and following the exposure period. In addition, in the groups administered the substance by inhalation (i.e., Groups D and E), the concentration of test substance in inspired air shall be measured at selected time intervals during the exposure period.

(ii) *Metabolism studies.* Groups A through F shall be used to determine the metabolism of the test substance. Excreta (urine, feces and expired air) shall be collected for identification and quantification of test substance and metabolites.

(4) *Measurements*—(i) *Pharmacokinetics.* For animals from each group shall be used for these purposes.

(A) *Bioavailability.* The levels of radioactivity shall be determined in whole blood, blood plasma or blood serum at 15 minutes, 30 minutes, 1 hour, 2 hours, 8 hours, 24 hours, 48 hours, and 96 hours after initiation of dosing.

(B) *Extent of absorption.* The total quantities of radioactivity shall be determined for excreta collected daily for 7 days, or after at least 90 percent of

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the radioactivity has been recovered in the excreta.

(C) *Excretion.* The quantities of radioactivity eliminated in the urine, feces, and expired air shall be determined separately over appropriate time intervals. The collection of the intact test substance or its metabolites, including carbon dioxide, may be discontinued when less than one percent of the dose is found to be exhaled as radioactive carbon dioxide in 24 hours.

(D) *Tissue distribution.* At the termination of each study, the quantities of radioactivity in blood and in various tissues, including bone, brain, fat, gonads, heart, kidney, liver, lungs, muscle, skin, and residual carcass of each animal shall be determined.

(E) *Changes in pharmacokinetics.* Results of pharmacokinetics measurements (i.e., biotransformation, extent of absorption, tissue distribution, and excretion) obtained in rats receiving the single low oral dose of test substance (Group B) shall be compared to the corresponding results obtained in rats receiving repeated oral doses of test substance (Group F).

(F) *Biotransformation.* Appropriate qualitative and quantitative methods shall be used to assay urine, feces, and expired air collected from rats. Efforts shall be made to identify any metabolite which comprises 5 percent or more of the dose eliminated.

(G) *Changes in biotransformation.* Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of radioactive substances in excreta from the rats receiving a single oral dose (Group B and C) with those in the excreta from rats receiving repeated oral doses (Group F).

(ii) [Reserved]

(d) *Data and reporting.* The final test report shall include the following:

(1) *Presentation of results.* Numerical data shall be summarized in tabular form. Pharmacokinetics data shall also be presented in graphical form. Qualitative observations shall also be reported.

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

(3) *Reporting results.* In addition to the reporting requirements as specified in the EPA Good Laboratory Practice Standards (40 CFR 792.185), the following specific information shall be reported:

(i) Species and strains of laboratory animals;

(ii) Chemical characterization of the test substance, including:

(A) For the radioactive test substance, information on the site(s) and degree of radiolabeling, including type of label, specific activity, chemical purity, and radiochemical purity.

(B) For the nonradioactive substance, information on chemical purity.

(C) Results of chromatography.

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

(iv) Percent absorption of the test substance after oral and inhalation exposures to rats.

(v) Quantity and percent recovery of radioactivity in feces, urine, expired air, and blood.

(vi) Tissue distribution reported as quality of radioactivity in blood and in various tissues, including bone, brain, fat, gonads, heart, kidney, liver, lung, muscle, skin and in residual carcass of rats.

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

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

(ix) Pharmacokinetic model(s) developed from the experimental data.

PART 799—[AMENDED]

2. In Part 799:

a. The authority citation for Part 799 continues to read as follows:

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

b. By adding § 799.2325 to read as follows:

§ 799.2325 Isopropanol.

(a) *Identification of of test substance.* (1) Isopropanol (CAS No. 67-63-0) shall be tested in accordance with this section.

(2) Isopropanol 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 (including import or byproduct manufacture) or process isopropanol, other than as an impurity, from (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 Parts 790 and 792 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 isopropanol in accordance with § 798.2450 of this chapter.

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

(B) Progress reports shall be submitted to EPA for the subchronic inhalation toxicity test at 6-month intervals beginning 6 months after the effective date of the final rule until submission of the final report.

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

(ii) *Reporting requirements.* (A) The oncogenicity test shall be completed and the final report submitted to EPA 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 until submission of the final report.

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

(ii) *Reporting Requirements.* (A) The reproduction and fertility effects test shall be completed and the final report submitted to EPA within 24 months of the effective date of the final rule.

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

(4) *Developmental toxicity*—(i) *Required testing.* A developmental toxicity test shall be conducted by gavage with isopropanol in accordance with § 798.4900 of this chapter.

(ii) *Reporting Requirements.* (A) The developmental toxicity test shall be completed and the final report submitted to EPA within 12 months of the effective date of the final rule.

(B) A progress report shall be submitted 6 months after the effective date of the final rule.

(5) *Mutagenic effects—gene mutations*—(i) *Required testing.* (A) A gene mutation test in mammalian cells shall be conducted with isopropanol in accordance with § 798.5300 of this chapter.

(B)(*1*) A sex-linked recessive lethal test in *Drosophila melanogaster* shall be

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conducted with isopropanol in accordance with § 798.5275 of this chapter except for the provisions in paragraphs (d)(5) (ii) and (iii), unless the results of the mammalian cells in the culture gene mutation test conducted pursuant to paragraph (c)(5)(i)(A) of this section are negative.

(*2*) For the purpose of this section the following provisions also apply:

(*i*) *Route of administration.* The route of administration shall be by exposure to isopropanol vapors.

(ii) [Reserved]

(C)(*1*) A mouse specific locus test shall be conducted with isopropanol by inhalation in accordance with § 798.5200 of this chapter except for the provisions in paragraphs (d)(5) (ii) and (iii), if the results of the sex-linked recessive lethal test conducted pursuant to paragraph (c)(5)(i)(B) of this section are positive and if, after a public program review, EPA issues a **Federal Register** notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

(*2*) For the purpose of this section the following provisions also apply:

(*i*) *Dose levels.* The duration of exposure shall be for 6 hours per day.

(*ii*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(ii) *Reporting requirements.* (A) The gene mutation tests shall be completed and final report submitted to EPA as follows:

(*1*) The gene mutation in mammalian cells assay within 6 months of the effective date of the final rule.

(*2*) The sex-linked recessive-lethal test in *Drosophila melanogaster* within 18 months of the effective date of the final rule.

(*3*) The mouse specific-locus test within 48 months of the date of EPA's notification of the test sponsor by certified letter or **Federal Register** notice under paragraph (c)(5)(i)(C) of this section that testing shall be initiated.

(B) Progress reports shall be submitted to EPA for the *Drosophila* sex-linked recessive lethal test at 6-month intervals beginning 6 months after the effective date of the final rule until the submission of the final report.

(C) Progress reports shall be submitted to EPA for the mouse specific locus assay at 6-month intervals beginning 6 months after the date of EPA's notification of the test sponsor that testing shall be initiated until submission of the final report.

(6) *Mutagenic effects—chromosomal aberrations*—(i) *Required testing.* (A) An *in vitro* cytogenetics test shall be conducted with isopropanol in accordance with § 798.5375 of this chapter.

(B)(*1*) An *in vivo* cytogenetics test shall be conducted with isopropanol in accordance with § 798.5385 of this chapter except for the provisions in paragraphs (d)(5) (iii) and (iv), if the *in vitro* test conducted pursuant to paragraph (c)(6)(i)(A) of this section is negative.

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(*ii*) *Treatment schedule.* The duration of exposure shall be for 6 hours per day for 5 consecutive days with one sacrifice time or for 6 hours per day for 1 day with 3 sacrifice times.

(C)(*1*) A dominant lethal assay shall be conducted with isopropanol in accordance with § 798.5450 of this chapter except for the provisions in paragraphs (d)(5) (ii) and (iii), unless both the *in vitro* and *in vivo* cytogenetics tests conducted pursuant to paragraphs (c)(6)(i) (A) and (B) of this section are negative.

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) Route of administration. Animals shall be exposed to isopropanol by inhalation.

(*ii*) *Treatnemt schedule.* The duration of exposure shall be for 6 hours per day for 5 consecutive days.

(D)(*1*) A heritable translocation test shall be conducted with isopropanol in accordance with § 798.5460 of this chapter except for the provisions in paragraphs (d)(5) (ii) and (iii), of the results of the dominant lethal assay conducted pursuant to paragraph (c)(6)(i)(C) of this section are positive and if, after a public program review, EPA issues a **Federal Register** notice or sends a certified letter to the test sponsor specifying that the testing shall be initiated.

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) *Route of administration.* Animals shall be exposed to isopropanol by inhalation.

(*ii*) [Reserved]

(ii) *Reporting requirements.* (A) The chromosomal aberration tests shall be completed and the final reports submitted to EPA as follows:

(*1*) The *in vitro* cytogenetics test within 15 months of the effective date of the final rule.

(*2*) The *in vivo* cytogenetics test within 15 months of the effective date of the final rule.

(*3*) The dominant lethal assay within 24 months of the effective date of the final rule.

(*4*) The heritable translocation test within 24 months of the date of EPA's notification of the test sponsor by certified letter or **Federal Register** notice under paragraph (c)(6)(i)(D) of this section that testing shall be initiated.

(B) Progress reports shall be submitted to EPA for the *in vitro* cytogenetics, the *in vivo* cytogenetics, and the dominant lethal assays at 6-month intervals beginning 6 months after the effective date of the final rule until submission of the applicable final report.

(C) Progress reports shall be submitted to EPA for the heritable translocation assay at 6-month intervals beginning 6 months after the date of EPA's notification of the test sponsor that testing shall be initiated until submission of the final report.

(7) *Neurotoxicity*—(i) *Required testing.* (A)(*1*) A functional observation battery shall be conducted with isopropanol in accordance with § 798.6050 of this chapter except for the provisions in paragraphs (d) (5) and (6).

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) *Duration and frequency of exposure.* For subchronic study, animals shall be dosed for 6 hours per day, 5 days per week for 90 days. For acute study, animals shall be dosed for 4 to 6 hours once.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(B)(*1*) A motor activity test shall be conducted with isopropanol in accordance with § 798.6200 of this chapter except for the provisions in paragraphs (d)(5) and (6).

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) *Duration and frequency of exposure.* For subchronic study, animals shall be dosed for 6 hours per day, 5 days per week for 90 days. For acute study, animals shall be dosed for 4 to 6 hours once.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(C)(*1*) A neuropathology test shall be conducted with isopropanol in accordance with § 798.6400 of this chapter except for the provisions in paragraphs (d)(5) and (6).

(*2*) For the purpose of this section, the following provisions also apply:

(*i*) *Duration and fequency of exposure.* Animals shall be dosed for 6 hours per day, 5 days per week for 90 days.

(*ii*) *Route of exposure.* Animals shall be exposed to isopropanol by inhalation.

(D) A developmental neurotoxicity test shall be conducted with isopropanol in accordance with § 795.250 of this chapter.

(ii) *Reporting requirements.* (A) The functional observation battery, motor activity, neuropathology, and

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developmental neurotoxicity tests shall be completed and the final reports submitted to EPA within 15 months of the effective date of the final rule.

(B) Progress reports shall be submitted to EPA for the functional observation battery, motor activity, neuropathology, and developmental neutoxicity tests at 6-month intervals beginning 6 months after the effective date of the final rules until submission of the applicable final report.

(8) *Pharmacokinetic studies*—(i) *Required testing.* An oral and inhalation pharmacokinetic test shall be conducted with isopropanol in accordance with § 795.231 of this chapter.

(ii) *Reporting requirements.* (A) The pharmacokinetic test shall be completed and the final report submitted to EPA within 15 months of the effective date of the final rule.

(B) Progress reports shall be submitted to EPA for the pharmacokinetics test at 6-month intervals beginning 6 months after the effective date of the final rule until submission of the final report.

(d) *Effective dates.* (1) This test rule shall be effective 44 days after date of publication of the final rule in the Federal Register.

(2) The guidelines and other test methods cited in this section are referenced as they exist on the effective date of the final rule.

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

[FR. Doc. 88-5721 Filed 3-15-88; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

42 CFR Parts 405, 431, 433, 434, 456, 462, 466, 473, 476, and 489

[HSQ-135-P]

Medicare and Medicaid Programs; Changes to Peer Review Organizations Regulations

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed rule.

SUMMARY: This rule sets forth several proposed changes to the regulations governing Peer Review Organizations. Some of these changes are the result of the passage of legislation (that is, the Consolidated Omnibus Budget Reconciliation Act of 1985, enacted on April 7, 1986 and the Omnibus Budget Reconciliation Act of 1986, enacted on October 21, 1986). Other changes are of a technical nature and are intended to clarify and correct the regulations concerning issues that have arisen in the course of implementing the Peer Review Organization program.

DATE: Comments will be considered if we receive them at the appropriate address, as provided below, no later than 5:00 p.m. on May 16, 1988.

ADDRESS: Mail comments to the following address: Health Care Financing Administration, Department of Health and Human Services, Attention: HSQ-135-P, P.O. Box 26676, Baltimore, Maryland 21207.

If you prefer, you may deliver your comments to one of the following addresses:

Room 309-G, Hubert H. Humphrey Building, 200 Independence Avenue SW., Washington, DC, or

Room 132, East High Rise Building, 6325 Security Boulevard, Baltimore, Maryland.

In commenting, please refer to file code HSQ-135-P. Comments received timely will be available for public inspection as they are received, generally beginning approximately three weeks after publication of a document, in Room 309-G of the Department's offices at 200 Independence Avenue, SW., Washington, DC, on Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (phone: 202-245-7890).

FOR FURTHER INFORMATION CONTACT: Patricia Booth (301) 966-6859.

SUPPLEMENTARY INFORMATION:

I. Legislative History

The Peer Review Improvement Act of 1982 (Title I, Subtitle C of the Tax Equity and Fiscal Responsibility Act of 1982 (Pub. L. 97-248)) amended Part B of Title XI of the Social Security Act (the Act) to establish the Utilization and Quality Control Peer Review Organization (PRO) program. The 1982 legislation provided that PROs assume the responsibilities that previously had been assigned to Professional Standard Review Organizations and fiscal intermediaries. Those responsibilities include the review of health care services funded under Medicare (Title XVIII of the Act) to determine whether those services are medically necessary, are furnished at the appropriate level of care, and are of a quality that meets professionally recognized standards. In addition, PROs monitor and validate a sample of diagnostic and procedural information supplied by hospitals to fiscal intermediaries regarding the inpatient hospital prospective payment system.

To carry out their responsibilities, PROs acquire information from the medical records of patients and from other records maintained by health institutions, practitioners and claims payment agencies. In addition, they generate information regarding the quality and appropriateness of health care services. PROs use this information to develop and review profiles (practice patterns) that enable them to focus on suppliers of health care (for example, practitioners and hospitals) and specific aspects of Medicare payment (for example, the assignment of discharges to diagnosis-related groups (DRG) in the hospital prospective payment system) for the purpose of assessing the quality of care being furnished, and to recommend corrective action. PROs transmit their determinations to intermediaries responsible for making payments under the Act.

The PRO legislation contained several provisions affecting data collection and disclosure. Section 1160 of the Act contains the majority of a PRO's statutory responsibilities concerning the disclosure of information. This section recognizes both the need to protect the interests of patients, health care practitioners, and providers of health care in the confidentiality of their medical records and the need to disclose certain information.

On April 17, 1985, we published in the **Federal Register** several final rules that implemented the PRO program (50 FR 15312-15374). The PRO regulations are located in various parts of Title 42 of the CFR (that is, Parts 405, 462, 466, 473, 476, 489, and 1004). As the result of the passage of the Consolidated Omnibus Budget Reconciliation Act of 1985 (Pub. L. 99-272) on April 7, 1986 and of the Omnibus Budget Reconciliation Act of 1986 (Pub. L. 99-509) on October 21, 1986, we are proposing several conforming changes to those regulations and, in addition, several technical changes, the need for which have become clear as we have gained experience with the PRO progam.

II. Proposed Changes

A. Assistants at Cataract Surgery

Section 9307(a) of Pub. L. 99-272 added a new exclusion of coverage provision that now appears as section 1862(a)(15) of the Act. That section now provides that payment for the services of an assistant at surgery in a cataract operation is not allowed unless, before the surgery is performed, the appropriate PRO (under Part B of Title XI of the Act), or in cases where a PRO does not exist, the appropriate carrier (under section 1842 of the Act) has approved the use of the assistant in the

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