

**ENVIRONMENTAL PROTECTION AGENCY****40 CFR Parts 798 and 799****(OPTS-42065; FRL-TSH-FRL 2818-1)****2-Ethylhexanoic Acid, Proposed Test Rule****AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Proposed rule.

**SUMMARY:** Under section 4 of the Toxic Substances Control Act (TSCA), EPA is proposing that manufacturers and processors conduct health effects tests for 2-ethylhexanoic acid (EHA, CAS No. 149-57-5). The proposed health effects tests include pharmacokinetic studies, and 90-day subchronic toxicity and developmental toxicity tests. This notice constitutes EPA's response to the Interagency Testing Committee's designation of EHA for priority consideration for testing.

**DATES:** Submit written comments on or before July 16, 1985. If persons request time for oral comment by July 1, 1985. EPA will hold a public meeting on this proposed rule in Washington, DC. For further information on arranging to speak at the meeting see Unit VII of this preamble.

**ADDRESS:** Submit written comments, identified by the document control number OPTS-42065, in triplicate to: TSCA Public Information Office (TS-733), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-103, 401 M St., SW., Washington, DC 20460.

Include the document control number (OPTS-42065) on all submissions.

**FOR FURTHER INFORMATION CONTACT:** Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460. Toll Free (800-424-9085). In Washington, DC: (554-1404). Outside the USA (operator—202-554-1404).

**SUPPLEMENTARY INFORMATION:** EPA is issuing a proposed test rule under section 4(a) of TSCA in response to the Interagency Testing Committee's designation of EHA for health effects testing consideration.

**I. Background****A. ITC Recommendation**

Section 4(e) of TSCA (Pub. L. 94-489, 90 Stat. 2003 *et seq.*; 15 U.S.C. 2601 *et seq.*) established an Interagency Testing Committee (ITC) to recommend to EPA a list of chemicals to be considered for testing under section 4(a) of the Act. The

ITC may designate substances on the list for EPA's priority consideration for requiring testing.

The ITC designated EHA for priority consideration for health effects tests in its 14th Report, published in the *Federal Register* on May 29, 1984 (49 FR 22389). The ITC recommended that EHA be tested for chronic health effects including carcinogenicity. The ITC further identified, although it did not specifically recommend for testing, the following biological effects of concern to human health: acute toxicity, teratogenicity/embryo-toxicity, metabolism and toxicokinetics, genotoxicity, and other effects (peroxisome induction). These biological effects of concern were identified by the ITC because there is either insufficient information to characterize these effects or there is a structural similarity between EHA, which is known to induce peroxisomal proliferation, and other chemicals which also induce peroxisomes and are animal carcinogens.

The ITC's testing recommendations were based upon a U.S. production volume in 1977 of 11 to 61 million pounds. The ITC, using the National Occupational Hazard Survey, identified over 16,000 persons potentially exposed to EHA in different occupational settings. Also, the ITC stated that EHA is a chemical intermediate used primarily in the manufacture of 2-

ethylhexanoate metal soaps (salts of EHA) which have a variety of uses. The ITC further commented that, although EHA itself is not used in consumer products, the salts of EHA are used in various consumer products. The ITC believed that general population exposure to the 2-ethylhexanoate anion may occur from the use of products containing these salts. The ITC further stated that suspicion exists as to the potential toxicity of the 2-ethylhexyl moiety on the basis of results from carcinogenicity studies of four 2-ethylhexyl compounds [di(2-ethylhexyl) phthalate, di(2-ethylhexyl) adipate, 2-ethylhexyl sulfate, and tris (2-ethylhexyl) phosphate] and of the ability of a group of 2-ethylhexyl compounds, including 2-ethylhexanoic acid, to induce peroxisomal proliferation and hypolipidemia in rats.

No environmental effects tests were recommended by the ITC. According to the ITC, chemicals with a similar structure to EHA have been found to have a low to moderate toxicity to aquatic organisms. The ITC did not believe that EHA would be toxic to aquatic organisms at the levels at which it is likely to occur in the environment.

**B. Test Rule Development Under TSCA**

Under section 4(a)(1) of TSCA, EPA must require testing of a chemical substance to develop appropriate test data if the Administrator finds that:

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

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

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

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

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

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

EPA uses a weight-of-evidence approach in making section 4(a)(1)(A)(i) findings: both exposure and toxicity information are considered in determining whether available data

support a finding that the chemical may present an unreasonable risk. For the finding under section 4(a)(1)(B)(i), EPA considers only production, exposure and release. For the findings under sections

4(a)(1)(A)(ii) and 4(a)(1)(B)(ii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to or environmental release of the chemical. In making the finding under section 4(a)(1)(A)(iii) or 4(a)(1)(B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's process for determining when these findings apply is described in detail in EPA's first and second proposed test rules. The section 4(a)(1)(A) findings are discussed in the *Federal Register* of July 18, 1980 (45 FR 48528) and June 5, 1981 (46 FR 30300) and the section 4(a)(1)(B) findings are discussed in the *Federal Register* of June 5, 1981 (46 FR 30302).

In evaluating the ITC's testing recommendations concerning EHA, EPA considered all available relevant information including the following: information presented in the ITC's report recommending testing consideration; production volume, use, exposure, and release information reported by manufacturers of EHA 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 EHA; and published and unpublished data available to the Agency. Based on its evaluation, as described in this proposed rule, EPA is proposing health effects testing requirements for EHA under section 4(a)(1)(A). By these actions, EPA is responding to the ITC's designation of EHA for testing consideration.

#### C. Change in Process for Adopting Test Standards

In the *Federal Register* of March 26, 1982 (47 FR 13012), EPA announced an approach to adopting test rules that involved two-phase rulemaking. In the first phase of rulemaking EPA would specify the test substance, who would be responsible for testing, and the required tests. In the second phase, EPA would establish the tests methodologies (test standards) and the deadlines for submission of test data. EPA has used this approach for most of the test rules it has proposed for chemicals recommended in the first through the thirteenth ITC reports.

In December 1983 the Natural Resources Defense Council (NRDC) and the Industrial Union Department of the

American Federation of Labor-Congress of Industrial Organizations (AFL-CIO) filed an action under TSCA section 20, which challenged, among other things, the use of the two-phase process. In an August 23, 1984 Opinion and Order, the Court found that utilization of the two-phase rulemaking process was permissible. However, the Court also held that the Agency was subject to a standard of promulgating test rules within a reasonable time frame (*NRDC and AFL-CIO v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984)).

Subsequent to the issuance of this Opinion, the Agency submitted papers to the Court which indicated that, in order to expedite the test rule development process, EPA would utilize a single-phase rulemaking process for most future test rules. The Agency also indicated that EPA would publicly announce this policy in the first test rule proposal to be published in the spring of 1985 (Declaration of Don R. Clay at 12 (September 24, 1984)). In accordance with this commitment, the Agency is setting forth in the preamble of this proposed rule and elsewhere in this issue of the *FEDERAL REGISTER*, interim final guidelines and procedure for utilization of single-phase rulemaking in the test rules program.

Section 4(b)(i) specifies that test rules shall include standards for the development of test data ("test standards") and deadlines for submission of test data. Under the two-phase process, both test standards and data submission deadlines are established during the second phase of rulemaking. However, in the single-phase approach, EPA will propose the pertinent Office of Toxic Substances (OTS) guideline(s), Organization for Economic Co-operation and Development (OECD), or other suitable test guideline(s) as the required test standard(s) in the notice of proposed rulemaking; at this time EPA will also propose time frames for the submission of the test data. Industry and other commenters may suggest an alternative methodology or modifications to the guideline, i.e., the proposed test standard, during the public comment period, and such comments should state why the alternative methodology or modification is more suitable for the chemical substance in question than the EPA-proposed test standard.

Comment will also be sought on the proposed data submission deadlines. All such submissions, including alternative test methodologies, will be placed in the rulemaking record and will be available for review by the public. The final rule will promulgate as the test standards either the OTS guidelines, OECD or

other suitable guidelines, a modified version of these guidelines, the alternative methodology submitted by commenters, or a modified version of the alternative methodology. The proposed test standards and data submission deadlines will be open for discussion at any public meeting held pursuant to TSCA section 4(b)(1).

The single-phase approach offers a number of advantages over the two-phase approach. First, the Agency believes that the single-phase approach will shorten rulemaking by as much as 18 months, resulting in the expedited initiation of the required testing. Secondly, because the OTS guidelines, OECD guidelines, or other appropriate methodologies will be proposed as the test standards, the one-phase process eliminates the requirement under the two-phase approach for industry to prepare and submit test protocols. Yet, by allowing commenters to submit alternative test methodologies during the comment period, it preserves the flexibility of the two-phase process, but at reduced administrative cost.

Because of these advantages, the Agency intends to utilize single-phase rulemaking for most rules promulgated under TSCA section 4(a). However, EPA may continue to utilize the two-phase process for rules where the two-phase process may be a more expeditious route to a final test rule, e.g., in cases where no well accepted test methodology is available for inclusion in a proposed test rule.

## II. 2-Ethylhexanoic Acid

### A. Human Exposure and Environmental Release

1. *Profile and production.* EHA is a colorless liquid with a mild odor. It has a vapor pressure of 0.03 torr at 20 °C, boils at 226.9 °C at 760 torr, and is 0.1 percent soluble in water at 20 °C. EHA is used exclusively as a chemical intermediate or reactant in the production of 2-ethylhexanoate metal soaps, peroxy esters, or other derivatives (Refs. 24 and 40).

There are two domestic manufacturers and three importers of EHA (Ref. 32). Eastman Kodak Co. is the primary domestic manufacturer of EHA. Union Carbide Corp. is also a domestic manufacturer of EHA; American Hoechst Corp., BASF Wyandotte, and Filo Chemical Inc. are importers of EHA. The annual U.S. supply (domestic production plus imports) of EHA is currently between 20 to 25 million pounds.

The import level of EHA is about 1 million to 2 million pounds annually.

The TSCA Inventory identified the 1977 U.S. production/importation of EHA as 11 to 61 million pounds, the same figure used by the ITC (Refs. 18, 24, and 25).

2. *Exposure during manufacturing and processing.* In evaluating the exposure of workers to EHA, the Agency considered: (a) The effectiveness of in-place engineering controls and manufacturing methods; (b) the number of workers that manufacture, handle, transport, and/or process EHA; (c) the frequency and duration of such activities; (d) typical and worst-case concentrations (estimated) of EHA which might be inhaled or dermally absorbed; and (e) the use of protective clothing to minimize dermal exposure.

Inhalation and dermal exposure to EHA are limited by engineering features and controls employed in manufacturing and processing. EHA is manufactured using enclosed, automated, continuous feed chemical processes (Refs. 18, 24, and 39). The raw materials are pumped from storage tanks to closed, continuous feed vertical reactors. After reaction, the product (EHA) is refined through distillation and pumped to storage tanks, where the EHA remains until pumped directly to another process for use, or loaded into tank cars, trucks, or drums. Waste from the distillation column is recycled to the reactor or disposed by incineration or chemical treatment. During clean-up for changeover or maintenance, the distillation column is drained, a heel of water or solvent added and put on total reflux, then the equipment is blown back. The water or solvent is drained and incinerated or treated as a chemical waste stream.

The equipment and methods used to process EHA derivatives are generally the same as those used to produce naphthenate metal soaps. The ethylhexanoate metal soaps are typically manufactured in mineral spirits by reaction of either the free metal, its oxide, or its hydrate with EHA in a closed reactor. During production the EHA and mineral spirits are charged through feed lines directly from closed storage tanks. The solids (i.e., the metal or metal oxide hydrates) are introduced by means of screw or bucket feeders equipped with dust collectors. Processing typically consists of a batch reaction followed by a neutralizing step where excess acid is stripped off. The solids from this step (not the desired salt) are removed by filtration and disposed. At the end of the neutralization step, all the EHA should have been consumed or removed from the process stream. Engineering controls for the processing equipment are

described by industry as satisfactory to comply with OSHA standards currently regulating the handling of the raw materials, including lead compounds, and the product's base solvent (Ref. 39).

The number of workers exposed to EHA is significantly less than reported by the ITC. The ITC utilized the 1970 National Occupational Hazard Survey (NOHS) which estimated that as many as 18,000 workers in 28 occupations were potentially exposed to EHA (Ref. 28). However, over 95 percent of these workers were exposed to products that contained ethylhexanoate metal soaps or other derivatives of EHA. For comparison, the National Occupational Exposure Survey (NOES), a survey that more closely represents actual observations, estimates that approximately 1,800 workers may be exposed to EHA (Ref. 27). More recent information reported to EPA indicated that approximately 400 workers are potentially exposed to EHA (Ref. 39). Industry estimates that at most 75 workers are currently involved in manufacturing and 300 in processing EHA nationwide.

During manufacturing, the duration of occupational exposure to EHA is typically less than 2 hours per day per worker. Rotation of assignments further limits exposure of any given individual. Workers may be exposed to EHA via inhalation of vapors and dermally. Exposure may occur primarily during sampling of reactors and distillation columns and loading/unloading of drums, tank cars, and trucks. EHA is manufactured at two sites, 24 hours per day, approximately 300 days per year, with on the order of 75 workers potentially exposed to EHA. The reactor and distillation column are sampled several times per day. During sampling, the 2 to 5 workers involved are collectively exposed to EHA for approximately 2 hours per day per site.

Exposure is also expected during loading/unloading of EHA. Tank cars and trucks are loaded approximately 100 days per year. This loading also involves 2 to 5 workers per site for a total of 1 to 2 hours per day per site. A small percentage of the EHA is drummed and this is done approximately 60 days per year, 1 to 2 hours per day. Occupational exposure to EHA at processing facilities is also possible. EHA is processed at an estimated 30 to 100 sites. At these sites, 1 to 3 workers are typically involved in the manufacture of EHA derivatives up to 8 hours per day, 30 to 250 days per year (Ref. 39).

Industry has not monitored EHA in the workplace nor provided estimates of

airborne concentrations. In order to estimate airborne concentrations of EHA, the Agency utilized its "Standard Parameters for Worker Exposure Models" (Ref. 39), which are based upon vapor pressure during typical activities. Actual conditions may be different; however, the results given by these models should represent the range from typical to worst-case airborne concentrations. For EHA manufacture, estimated exposure is greatest during the loading of tank cars and trucks. To estimate this worst-case exposure (0.1 to 0.2 mg/kg/day), the Agency assumed that the worker would stay on top of the tank car or truck while it is being filled, positioned immediately downwind of the vent. Actual exposure may be an order of magnitude lower (0.01 to 0.02 mg/kg/day) since the worker typically stands away from the truck during most of the time it is being filled. During sampling and processing activities, airborne concentrations of EHA are probably less than 0.01 mg/m<sup>3</sup>, resulting in inhalation of less than 0.01 mg/kg/day.

Workers who sample, load, unload, and/or drum EHA or clean the filter press in processing may also be dermally exposed. This potential is considered to be negligible by industry because gloves and other protective clothing and equipment are "routinely worn" during these activities (Refs. 24, 25, and 38). However, the Agency notes that worker hygiene procedures can vary widely throughout the industry and believes that a worker might be exposed to as much as 500 mg/kg/contact if both hands were immersed in EHA, and 100 percent of the EHA film on the hands was absorbed through the skin (Ref. 39).

3. *Exposure associated with consumer goods.* EHA is not an ingredient or constituent in any consumer product, and consumers are not exposed to manufactured EHA. Consumers, however, may be exposed to a wide variety of products that contain ethylhexanoate metal soaps or other derivatives of EHA.

The ethylhexanoate metal soaps and other derivatives of EHA have the following uses (Refs. 24 and 40):

- (a) Vinyl stabilizer (barium, cadmium, and zinc salts). Typically, the final vinyl article contains one percent of the EHA salt.
- (b) Paint and ink dryers (cobalt, lithium, zinc and manganese salts). Typically, the paint or ink would contain about 0.5 percent of the EHA salt.
- (c) Peroxide catalysts (such as t-amylperoxy 2-ethylhexanoate).
- (d) Catalyst in oxo chemical production (cobalt salt).

(e) Manufacture of plasticizer for synthetic rubbers.

(f) Promoter for curing thermoset polyester resins (cobalt salt). Typically, the final resin would contain 0.005 to 0.1 percent of the EHA salt.

Products that contain these derivatives of EHA include dried paint films, coatings and inks, PVC products, and fiberglass reinforced products. However, potential for consumer exposure to EHA from use or contact with such products is extremely low because of their expected low volatility, low water solubility, high resin solubility, and the small concentration (usually less than 1 percent) in the product. Therefore, EPA believes that there is minimum potential for EHA (or its derivatives) to migrate from the polymerized products in which they are incorporated.

Products containing EHA derivatives that are available for direct use by consumers are limited to oil base paints, varnishes, stains and polyester fiberglass resins. The Agency found no stability constant or other data to support the ITC's contention that EHA derivatives in these consumer products dissociate (hydrolyze) resulting in indirect exposure to the EHA anion. Both industry (Ref. 41) and EPA (Ref. 43) believe that significant hydrolysis does not occur during the use of these products. These derivatives are not expected to hydrolyze at the near neutral pH's maintained by buffers and the low moisture levels in these products. Potential exposure is further reduced because the amount of EHA derivatives in these products is typically less than 0.005 to 0.5 percent of the product (Ref. 16), and most of the product that might contact the skin would be removed by clean-up. Therefore, the Agency believes that indirect consumer exposure to EHA anion, even if it were to occur, would be negligible.

**4. Environmental and general population exposure.** The Agency has no reason to believe that present levels of EHA released to the environment result in human exposure from either contaminated drinking water or foods. Eastman Kodak Co. reports that more than 99.5 percent of the EHA in their process effluents is either incinerated or biodegraded on-site in a wastewater treatment plant (Refs. 24 and 25).

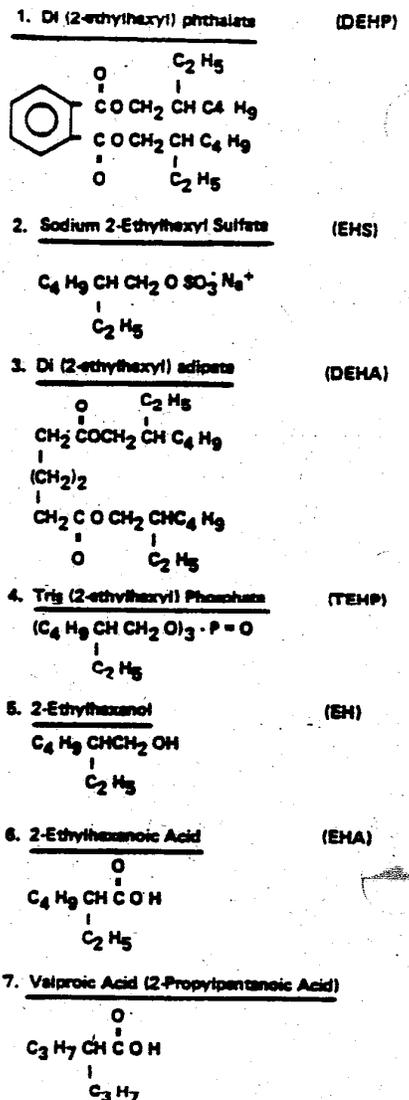
Furthermore, because of EHA's low vapor pressure, little atmospheric release is expected from venting of storage tank cars, and trucks. Union Carbide Corp. treats its process effluents containing EHA in an on-site wastewater treatment plant prior to discharge to Galveston Bay, Texas. The reported volume and frequency of this release (Ref. 39) and the anticipated concentrations of EHA discharged to the bay in treated effluents are considered insignificant. EHA should be readily biodegraded, similar to other short chain carboxylic acids. Both its persistence and bioaccumulation potential are considered to be low and of no consequence.

Environmental release of EHA from processing facilities is also considered low. Because of its metal and mineral spirit content, the filter cake waste is disposed of according to Resource Conservation and Recovery Act regulations (Ref. 38). Airborne emissions of EHA are expected to be low because of the low vapor pressure of EHA (and its derivatives) and the engineering features and controls that are generally utilized.

**5. Summary.** The Agency believes that dermal exposure to EHA may be a significant concern during manufacturing, handling, and processing operations if gloves and other protective equipment are not worn. Since all workers who may come in contact with EHA are not required to wear gloves, the Agency assumes that potential exists for exposure of up to 500 mg EHA/kg body weight/contact. The Agency also believes that airborne exposure in the workplace, consumer exposure, and general population exposure to EHA are not of sufficient magnitude to be of concern at this time.

#### B. Health Effects

**1. Similarities in chemical structure.** A variety of chemicals with structures similar to EHA have been or are currently being tested by the National Toxicology Program (NTP). These chemicals possess a similar range of biological activity. As can be seen from the chemical structures below, they all contain similar structural features.



As illustrated by the chemical structures, the first 5 chemicals have one or more 2-ethylhexyl groups while the last 2 chemicals, EHA and valproic acid, are short, branched chain carboxylic acids.

**2. Carcinogenicity.** The first four chemicals that contain the 2-ethylhexyl moiety (DEHP, EHS, DEHA, TEHP) were tested by the NTP for carcinogenic and other chronic toxic effects in 90-day and 2-year studies in male and female

Fischer 344 rats and B6C3F1 mice. All four of these chemicals caused increased occurrence of hepatocellular tumors, principally carcinomas, in female mice. DEHP and DEHA also caused hepatocellular tumors in male mice, while DEHP caused hepatocellular tumors in both male and female rats as well. These four 2-ethylhexyl containing chemicals have been shown by the NTP bioassays to be animal oncogens, though the response appears to be relatively species, sex, and site specific (Refs. 11 through 15). These studies suggest that compounds containing the 2-ethylhexyl moiety (including EHA) possess some carcinogenic hazard (Ref. 7).

3. *Other biological effects.* The 2-ethylhexyl containing chemicals (including EHA) have also illustrated a spectrum of other biological effects. EHA, DEHP, DEHA, EHS, 2-ethylhexanol, and 2-ethylhexyl aldehyde induce peroxisomal proliferation and, in addition, may be associated with hepatomegaly and hypolipidemia in rats (Refs. 9 and 17). Peroxisomal induction is primarily an enzymatic biochemical event typically associated with the liver (Ref. 9). Furthermore, there is evidence to suggest an association between peroxisomal induction and hepatocarcinogenicity in rats and mice (Refs. 9, 17, and 18). However, there is currently insufficient information to understand the nature and importance of this association.

4. *Metabolism.* In addition to peroxisomal induction, the 2-ethylhexyl type chemicals have some metabolic interrelationships. Both DEHP and DEHA are diesters that are metabolically hydrolyzed to their corresponding monoesters and 2-ethylhexanol (Refs. 28 and 30). Albro (Ref. 23) reported that within 28 hours after administration of <sup>14</sup>C-labeled 2-ethylhexanol to rats by gavage, 80 to 82 percent was excreted in urine; 8 to 9 percent in feces; and 6 to 7 percent in respirable CO<sub>2</sub>. EHA was identified as the major (61 percent) urinary metabolite of 2-ethylhexanol, while probable metabolites of EHA accounted for almost all of the remaining urinary excreted radioactivity. Only 3 percent of the 2-ethylhexanol was excreted unchanged. In contrast, sodium 2-ethylhexyl sulfate (EHS) is excreted primarily unchanged by rats with only a small percentage excreted as 2-ethylhexanol (Ref. 29). Although no confirming metabolic data are available, TEHP is probably hydrolyzed to 2-ethylhexanol as well. Thus it appears that three of the four 2-ethylhexyl containing chemicals tested by the NTP are converted to 2-ethylhexanol and EHA. The NTP is planning further

comparative feeding studies with 2-ethylhexanol, DEHP, and mono (2-ethylhexyl) phthalate to compare toxic effects and dose response relationships (Ref. 31). They are also planning a 2-year oncogenicity bioassay with 2-ethylhexanol (Ref. 42).

5. *Neurological effects.* EHA has been shown to have pronounced anticonvulsant activity similar to that of valproic acid (Ref. 22) which affects brain enzyme chemistry (Refs. 19, through 21). However, although EHA has been shown to have therapeutic anticonvulsive activity in experimental mice with induced audiogenic seizures, this is not a sufficient basis to indicate that significant neurological effects may occur in humans from exposure to EHA.

6. *Developmental toxicity.* EHA, along with 12 other short chain carboxylic acids, was tested in an *in vitro* screen using a whole rat embryo culture system (Ref. 1). EHA produced a spectrum of malformations similar to those produced by valproic acid, a known human teratogen. Valproic acid produces the same spectrum of malformations *in vivo* as it does *in vitro* (Ref. 2). Furthermore, an *in vivo* teratogenicity screen conducted on 2-ethylhexanol indicated significant adverse effects (Ref. 5). Severe maternal toxicity, however, was also observed and could have caused the adverse effects of these fetuses. The positive results of both EHA and valproic acid (and several other short chain carboxylic acids) in the same *in vitro* test, coupled with the close structural analogy between EHA, valproic acid, and 2-ethylhexanol, suggests that EHA may possess some developmental toxicity hazard.

Furthermore, a recent TSCA section 8(e) submission (Ref. 36) for [[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]thio] acetic acid, 2-ethylhexyl ester (CAS No. 80387-97-9) reported teratogenic and embryolethal effects in pregnant rats which were administered a dose of 300 mg/kg/day orally. This 2-ethylhexyl ester can be expected to be metabolized to 2-ethylhexanol which will be metabolized to EHA. If EHA is the causal agent, it may cause similar developmental toxicity effects.

7. *Acute toxicity.* The acute toxicity of EHA has been adequately characterized in the 14th ITC Report (49 FR 22389). In brief, EHA has an oral LD<sub>50</sub> equal to 3g/kg in rats; a dermal LD<sub>50</sub> equal to 6.3 ml/kg in rabbits and 6.3 g/kg (4-day contact period) in guinea pigs; and an inhalation LC<sub>50</sub> greater than 400 ppm for 6 hours in guinea pigs (Refs. 3, 4, and 6). Full-strength EHA has also been shown to

cause corneal necrosis and skin erythema in rabbits (Ref. 4).

### C. Findings

EPA is basing its proposed testing of EHA on the authority of section 4(a)(1)(A) of TSCA.

EPA finds that EHA may present an unreasonable risk of subchronic toxicity, oncogenicity, and developmental toxicity. These findings are based on potential dermal exposure of workers engaged in manufacturing, transfer, storage and processing of EHA and the suggestive evidence of toxicity discussed in Unit II. B of this preamble.

Inadequate data exist to characterize the pharmacokinetics, subchronic toxicity, and developmental toxicity of EHA. In addition, the dermal exposure of an estimated 400 workers during the manufacturing, transfer, storage, and processing of EHA has not been sufficiently characterized to conclude that there is no unreasonable risk from this exposure to EHA. Furthermore, the potential health hazard of EHA is significant because of: (1) its structural similarity to several chemicals that have been associated with such health effects; (2) the metabolic interrelationships of certain of these chemicals to EHA; and (3) the suggestive evidence that chemicals such as EHA that induce peroxisomal proliferation may have oncogenic potential. The available data on the health effects of concern are inadequate to reasonably predict or determine the health risks posed by present exposure to EHA.

The National Toxicology Program's planned testing of 2-ethylhexanol (Ref. 42) should resolve much of the uncertainty over the oncogenic potential of EHA since EHA is the principal metabolite/excretion product of animals dosed with 2-ethylhexanol (Refs. 23 and 37). The Agency, therefore, is not proposing a 2-year bioassay of EHA at this time since such testing would most likely not be necessary given the current knowledge of the pharmacokinetics and metabolism of 2-ethylhexanol to EHA and the proposed pharmacokinetic testing of EHA. EHA has also been nominated for genotoxicity testing by the NTP (Ref. 10). NTP's genotoxicity testing may include the *Salmonella* assay, cytogenetic testing of chromosomal aberrations, and sister chromatid exchange in Chinese hamster ovary cells.

Data are not available to characterize the pharmacokinetics, subchronic toxicity, and developmental toxicity of EHA. The Agency is unaware of any ongoing or planned testing in these areas of concern. Therefore, the Agency finds that the testing specified below is necessary to characterize these risks.

#### D. Proposed Testing and Test Standards

On the basis of these findings, the Agency is proposing pharmacokinetic tests, 90-day subchronic tests, and developmental toxicity tests as a basis for determining the health risks of EHA.

The Agency is proposing that the following health effects test guidelines be adopted as test standards for the purposes of the proposed tests for EHA.

The Agency believes that the metabolism test standards developed by OTS for this proposed rule (Ref. 8) is appropriate for determining and comparing the pharmacokinetics of EHA for both the oral and dermal routes of administration. Data from these studies on the absorption, distribution, excretion, and metabolism of EHA are necessary to aid in the evaluation of test results from other toxicology studies and to determine the comparability of oral and dermal dosing.

The purpose of these studies is to determine: (1) The bioavailability of EHA after dermal administration, (2) whether or not the biotransformation of EHA is qualitatively and quantitatively the same after dermal and oral administration, (3) whether or not the biotransformation of EHA is changed qualitatively or quantitatively by repeated dosing, and (4) the extent of transport of EHA and its metabolites to the fetus.

The Agency proposes that 7 to 9 week old Fischer 344 rats and 5 to 7 week old Hartley guinea pigs be used for these studies. Fischer 344 rats are proposed for subchronic testing of EHA and have been used extensively by NTP for testing ethylhexyl containing chemicals. They have also been used extensively in percutaneous absorption studies. Hartley guinea pigs are proposed because their skin resembles human skin. Two doses will be required in these studies, a "low" dose and a "high" dose. When administered orally, the "high" dose level should ideally induce some overt toxicity such as weight loss. The "low" dose level should correspond to a no-effect level. The same "high" and "low" dose will be administered orally and dermally. The proposed studies evaluate blood levels, urinary and fecal excretion, biotransformation, and placental transport of EHA when administered dermally and/or orally. In addition, the extent to which washing removes dermally applied EHA is also evaluated.

The Agency believes that this OTS metabolism test methodology represents the state-of-the-art and forms the basis for a valid and scientifically acceptable test standard. This test standard is

proposed under § 798.450 of 40 CFR Chapter I.

The Agency believes that the subchronic exposure oral toxicity test standard developed by OTS for this proposed rule is appropriate for determining the subchronic toxicity of EHA. This test permits the determination of the no-observed-effect level, the characterization of toxic effects associated with continuous or repeated exposure for a period of 90 days, and provides information on target organs.

The subchronic test is conducted by administering a chemical substance such as EHA orally for 90 days in graduated daily doses to several groups of experimental animals, one dose level per group. During the period of administration the animal are observed daily to detect signs of toxicity. Animals which die during the period of administration are necropsied, and at the conclusion of the test all surviving animals are sacrificed and histopathological examinations are conducted on the tissues. Given the test results of Moody and Reddy (Refs. 9 and 17), the subchronic toxicity evaluation should pay particular attention to hepatotoxicity and serum lipid alterations. In addition, Fischer 344 rats and B6C3F1 mice are proposed for this testing since results from these tests will allow comparison with subchronic and other testing of 2-ethylhexanol by NTP.

The Agency believes that this subchronic toxicity test methodology represents the state-of-the-art and forms the basis for a valid and scientifically acceptable test standard. This test standard is proposed under § 789.75 of 40 CFR Chapter I.

The Agency believes that either the OTS test guideline entitled "Developmental Toxicity (HG-Organ/Tissue-Developmental Toxicity-Oral, OTS Health Effects Test Guidelines)" or the OECD test guideline entitled "Teratogenicity", No. 414, adopted May 12, 1981 is appropriate for determining the developmental hazard of EHA. Both developmental toxicity test guidelines using the oral route of administration have been designed to determine the potential of a chemical substance such as EHA to induce structural and/or other abnormalities in the fetus which may arise from exposure of the mother to the chemical substance during pregnancy.

The developmental toxicity test is conducted by administering a chemical substance such as EHA orally in graduated doses, for at least that part of the pregnancy covering the period of organogenesis, to several groups of pregnant experimental animals, one

dose level being used per group. Shortly before the expected date of delivery, the pregnant females are sacrificed, the uteri removed, and the contents examined for structural malformations, *in utero* death, growth retardation, and functional deficits. The Agency proposes two modifications to this protocol:

1. Rats and a non-rodent mammalian species should be utilized instead of rats and mice. EPA recommends rabbits as the non-rodent species. The Agency believes that multispecies testing is a more sensitive means of detecting developmental hazards than single species testing (Refs. 33, 34, and 35). Testing EHA in the rat and a non-rodent mammalian species will provide the Agency with the data needed to reasonably determine or predict whether EHA poses a risk of developmental toxicity to humans.

2. EPA does not specify the strains or precise ages of the animals to be used; it recommends that young adult rats and rabbits be used. The Agency is unaware of specific strains of test animals which might be sensitive to EHA for developmental effects.

The Agency believes that either the OTS or OECD oral developmental toxicity test guideline represents the state-of-the-art methodology and forms the basis for a valid and scientifically acceptable test standard for evaluating the developmental toxicity of a chemical substance such as EHA. Both guidelines have been reviewed to ensure that they reflect the most current scientific approach to developmental toxicity testing.

#### E. Test Substance

EPA is proposing that EHA of at least 99 percent purity be used as the test substance. EHA of this purity is commercially available at nominal cost. EPA has specified a relatively pure substance for testing because the Agency is interested in evaluating the effects attributable to EHA itself. Radiolabeled <sup>14</sup>C-EHA will be needed for the pharmacokinetics testing.

#### F. Persons Required to Test

Section 4(b)(3)(B) of TSCA specifies that the activities for which the Administrator makes section 4(a) findings (manufacture, processing, distribution, use and/or disposal) determine who bears the responsibility for testing. Manufacturers are required to test if the findings are based on manufacturing ("manufacture" is defined in section 3(7) of TSCA to include "import"). Processors are required to test if the findings are based on processing. 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 the manufacture, transport, storage, and processing of EHA may present an unreasonable risk to human health, EPA is proposing that persons who manufacture or process, or intend to manufacture or process EHA at any time from the effective date of the final test rule to the end of the reimbursement period be subject to the pharmacokinetic, subchronic toxicity, and developmental toxicity testing requirements contained in this proposed rule. The end of the reimbursement period is proposed to be 5 years after the submission of the last final report required under the test rule.

Because TSCA contains provisions to avoid duplicative testing, not every person subject to this rule must individually conduct testing. Section 4(b)(3)(A) of TSCA provides that EPA may permit two or more manufacturers or processors who are subject to the rule to designate one such person or a qualified third person to conduct the tests and submit data on their behalf. Section 4(c) provides that any person required to test may apply to EPA for an exemption from the requirement.

EPA promulgated in the *Federal Register* of October 10, 1984 (49 FR 39774) procedures for the granting of exemptions under TSCA section 4(c) for use with two-phase rulemaking. Elsewhere in this issue to the *Federal Register*, EPA is promulgating interim final exemption procedures for use with single-phase rulemaking. These new procedures differ only slightly from those previously adopted. In brief, when both manufacturers and processors are subject to a test rule, processors will be granted an exemption without filing exemption applications if manufacturers perform all of the required testing. Manufacturers are required to submit either a letter of intent to perform testing or an exemption application.

EPA is not proposing to require the submission of equivalence data as a condition for exemption from the proposed testing for EHA. As noted in Unit II. E of this preamble, EPA is interested in evaluating the effects attributable to EHA itself and has specified a relatively pure substance for testing.

#### G. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its final TSCA good laboratory practice (GLP) standards, which appear in 40 CFR Part 792.

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. Specific reporting requirements for each of the proposed test standards follow:

The pharmacokinetic tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final test rule. Interim progress reports shall be provided quarterly.

The subchronic toxicity tests shall be completed and the final results submitted to the Agency within 15 months of the effective date of the final test rule. Interim progress reports shall be provided quarterly.

The developmental toxicity tests shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final test rule. Interim progress reports shall be provided quarterly.

NTP's experience with testing other ethylhexyl moiety substances and the Agency's experience with Negotiated Testing Agreements with industry suggests that the proposed time allowances and reporting requirements are reasonable.

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

#### H. Issue

This proposed rule identifies various OTS developed test standards and an OTS or OECD test guideline as a test standard for health effects testing of EHA. The Agency is soliciting comments as to whether these health effects test standards and guidelines are appropriate and applicable for the testing of EHA. The Agency also requests comments on the adequacy of this testing, and the reporting times for the identified health effects tests.

#### III. Enforcement Provisions

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

Additional, TSCA section 15(4) makes it unlawful for any person to fail or refuse to permit entry or inspection as required by section 11. Section 11 applies to any "establishment, facility, or other premises in which chemical substances or mixtures are manufactured, processed, stored, or held before or after their distribution in commerce . . ." The Agency considers a testing facility to be a place where the chemical is held or stored and, therefore, subject to inspection. Laboratory audits/inspections will be conducted periodically in accordance with the authority and procedures outlined in TSCA section 11 by duly designated representatives of the EPA for the purpose of determining compliance with any final rule for EHA. These inspections may be conducted for purposes which include verification that testing has begun, that schedules are being met, that reports accurately reflect the underlying raw data and interpretations thereof, and that the TSCA GLP standards and the test standards established in the rule are being complied with.

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

Violators of TSCA are subject to criminal and civil liability. Persons who submit materially misleading or false information in connection with the requirement of any provision of this rule may be subject to penalties which may be calculated as if they never submitted their data. Under the penalty provision of section 16 of TSCA, any person who violates section 15 could be subject to a civil penalty of up to \$25,000 for each violation with each day of operation in violation constituting a separate violation. This provision would be applicable primarily to manufacturers or processors that fail to submit a letter of intent or an exemption request and that continue manufacturing or processing after the deadlines for such submissions. Knowing or willful violations could lead to the imposition of criminal penalties of up to \$25,000 for each day of violation and imprisonment for up to 1 year. In determining the amount of penalty, EPA will take into account the seriousness of

the violation and the degree of culpability of the violator as well as all the other factors listed in section 16. Other remedies are available to EPA under section 17 of TSCA, such as seeking an injunction to restrain violations of TSCA section 4.

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

#### IV. Economic Analysis of Proposed Rule

To evaluate the potential economic impact of test rules, EPA has adopted a two-stage approach. All candidates for test rules go through a Level I analysis. This consists of evaluating each chemical or chemical group on four principal market characteristics: (1) Demand sensitivity, (2) cost characteristics, (3) industry structure, and (4) market expectations. The results of the Level I analysis, along with the consideration of the costs of the required tests indicate whether the possibility of a significant adverse economic impact exists. Where the indication is negative, no further economic analysis is done for the chemical substance or group. However, for those chemical substances or groups where the Level I analysis indicates a potential for significant economic impact, a more comprehensive and detailed analysis is conducted. This Level II analysis attempts to predict more precisely the magnitude of the expected impact.

Based upon the Level I analysis, total testing costs for the proposed rule for EHA are estimated to range from \$185,600 to \$491,700. The Level I economic analysis (Ref. 16) suggests that the potential for adverse economic effects due to the estimated test costs is low. Annualized costs should be \$48,100 to \$127,400 and should increase the price 0.2 to 0.6 cents per pound which is equivalent to 0.4 to 1 percent of the current base price.

#### V. 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 tests facilities and personnel to handle the additional demand for testing services created by section 4 test rules and test programs negotiated with industry in place of rulemaking. Copies of the study, "Chemical Testing Industry: Profile of Toxicological Testing (PB 82-140773)", can be obtained through the National Technical Information Service (NTIS).

On the basis of this study, the Agency believes that there will be available test facilities and personnel to perform the testing in this proposed rule.

#### VI. Guidelines

The OTS developmental toxicity testing guideline cited in this proposed test rule is available from the NTIS, 5285 Port Royal Rd., Springfield, VA 22161 (703-487-4657). This OTS guideline is within NTIS publication PB 84-233295 which costs \$11.00. The OECD teratogenicity testing guideline cited in this proposed test rule is available from the OECD Publication and Information Center, Suite 1207, 1750 Pennsylvania Ave. NW., Washington, DC, 20003 (202-724-1857). This guideline is within OECD Guidelines for Testing Chemicals, publication ISBN-9264-12229-4, which costs \$80.00. These guidelines are included in the docket for this proposed rule. The pharmacokinetics and subchronic toxicity test standards are contained in the proposed test rule and will be codified under § 798.460 and § 798.75 of 40 CFR Chapter I.

#### VII. Public Meetings

If persons indicate to EPA that they wish to present comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analysis, EPA will hold a public meeting in Washington, DC. Persons who wish to present comments at the meeting should call the TSCA Assistance Office (TAO): Toll Free: (800-424-9065); in Washington, DC: (554-1404); Outside the U.S.A. (operator 202-554-1404), by July 1, 1985. The meeting will not be held if members of the public do not indicate that they wish to make oral presentations. This meeting will be scheduled after the deadline for submission of written comments, so that issues raised in the written comments can be discussed by EPA and the public commenters. 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 the 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.

#### VIII. Rulemaking Record

EPA has established a record for this rulemaking, (OPTS-42065). This record includes basic information considered by the Agency in developing this proposal and appropriate Federal Register notices. The Agency will supplement the record with additional information as it is received.

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 EHA to the Priority List. (49 FR 22389, May 29, 1984).

(b) Notice of final rule of EPA's TSCA good laboratory practice standards (48 FR 53922, November 29, 1983).

(c) Notice of final rule on two-phase test rule development and exemption procedures (49 FR 39774, October 10, 1984).

(d) Notice of interim final rule on single-phase test rule development and exemption procedures.

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

(f) Notices relating to the availability of OTS health effects test guidelines (49 FR 39911, October 11, 1984; 48 FR 44898, September 30, 1983).

(g) Notices requiring TSCA section 8(a) and 8(d) reporting for EHA (49 FR 22284, 49 FR 22286, May 29, 1984).

(2) Support documents: consisting of:

(a) Study of availability of test facilities and personnel.

(b) EHA economic analysis.

(3) Records of minutes of informal meetings.

(4) Communications before proposal consisting of:

(a) Written public and intra- or interagency memoranda and comments.

(b) Summaries of telephone conversations.

(c) Reports—published and unpublished factual materials.

(5) Test guidelines proposed as standards.

##### B. References

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- (4) Union Carbide. Unpublished summary toxicity data submitted to the Interagency Testing Committee by T.R. Tyler. Union Carbide Corp. September 26, 1983.
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- (9) Moody, D.E., and Reddy, J.K. Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. *Toxicology and Applied Pharmacology*, 45:497-504, 1978.
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- (11) U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. Carcinogenesis Bioassay of Di(2-Ethylhexyl)phthalate (CAS No. 117-81-7) in F344 Rats and B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> Mice (Feeding Study). National Toxicology Program. Technical Report Series No. 217.
- (12) U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. Carcinogenesis Bioassay of Di(2-ethylhexyl)adipate (CAS No. 103-23-1) F344 Rats and B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> Mice (Feed Study). National Toxicology Program. Technical Report Series No. 212.
- (13) U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. Carcinogenesis Bioassay of Sodium 2-Ethylhexyl Sulfate (CAS No. 126-92-1) in F344N Rats and B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> Mice (Feed Study). Draft NTP Technical Report. Prepared for the Board of Scientific Counselors. September 22, 1982.
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- (25) Chemical Manufacturers Association. Letter from E.J. Moran to C.R. McCormack on Production, Exposure and Health Effects of 2-Ethylhexanoic Acid. August 1, 1984.
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- (41) Eastman Kodak Co. Letter From R.D. Gerwe to F. Benenati on Hydrolysis Potential of 2-Ethylhexanoic Acid. February 27, 1985.
- (42) Department of Health and Human Services. Memorandum. Nomination of Additional Compounds Containing the 2-Ethylhexyl Moiety for Mutagenicity Testing. D.A. Canter, National Toxicology Program. National Institutes of Health. May 2, 1983. (Note: Table 1 lists carcinogenicity status.)
- (43) USEPA. U.S. Environmental Protection Agency. Memorandum. Hydrolytic Stability of 2-Ethylhexanoic Acid. F.L. Metz, Chemist, Industrial Chemistry Branch, Economics and Technology Division, Office of Toxic Substances. February 12, 1985.

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the OPTS Reading Rm. E-107, 401 M St., S.W., Washington, DC from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

#### IX. Other Regulatory Requirements

##### A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "Major" and, therefore, subject to the requirement of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. First, the total cost of all the proposed testing for EHA is \$125,000 to \$332,000 over the testing and reimbursement period. Second, the cost of the testing is not likely to result in a major increase in users' costs or prices. Finally, based on our present analysis, EPA does not believe that there will be any significant adverse effects as a result of this rule.

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

##### B. Regulatory Flexibility Act

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

##### C. Paperwork Reduction Act

The Office of Management and Budget (OMB) has approved the information collection requirements contained in the proposed rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.* and has assigned OMB control number 2070-0033. 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 package will respond to any OMB or public

comments on the information collection requirements.

##### List of Subjects in 40 CFR Parts 798 and 799

Testing, Environmental Protection, Hazardous Material, Chemicals, Reporting and recordkeeping requirements.

Dated: May 7, 1985.

John A. Moore,  
Assistant Administrator.

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

1. By adding new Part 798, consisting at this time of Subpart B, § 798.75, and Subpart F, § 798.460, to read as follows:

#### PART 798—HEALTH EFFECTS TEST STANDARDS

Sec.

Subpart A—[Reserved]

Subpart B—General Toxicity Testing

798.75 Subchronic oral toxicity test standard.

Subparts C—E—[Reserved]

Subpart F—Special Studies

798.460 Pharmacokinetic test standard.

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

Subpart A—[Reserved]

Subpart B—General Toxicity Testing

§ 798.75 Subchronic oral toxicity test standard.

(a) *Purpose.* In the assessment and evaluation of the toxic characteristics of a chemical, the determination of subchronic oral toxicity may be carried out after initial information on toxicity has been obtained by acute testing. The subchronic oral study has been designed to permit the determination of the no-observed effect level and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. The test is not capable of determining those effects that have a long latency period for development (e.g., carcinogenicity and life shortening). It provides information on health hazards likely to arise from repeated exposure by the oral route over a limited period of time. It will provide information on target organs, the possibilities of accumulation, and can be of use in selecting dose levels for chronic studies and for establishing safety criteria for human exposure.

(b) *Definitions.* (1) Subchronic oral toxicity is the adverse effects occurring as a result of the repeated daily exposure of experimental animals to a chemical by the oral route for a part

(approximately ten percent for rats) of a life span.

(2) Does is the amount of test substance administered. Does is expressed as weight of test substance (g, mg) per unit weight to test substance per unit weight of food or drinking water.

(3) No-effect level/No-toxic-effect level/No-adverse-effect level/No-observed-level is the maximum dose used in a test which produces no observed adverse effects. A no-observed-effect level is expressed in terms of the weight of a substance given daily per unit weight of test animal (mg/kg). When administered to animals in food or drinking water, the no-observed-effect level is expressed as mg/kg of food or mg/ml of water.

(4) Cumulative toxicity is the adverse effects of repeated doses occurring as a result of prolonged action on, or increased concentration of the administered substance or its metabolites in susceptible tissue.

(c) *Principle of the test method.* The test substance is administered orally in graduated daily doses to several groups of experimental animals, one dose level per group, for a period of 90 days. During the period of administration the animals are observed daily to detect signs of toxicity. Animals which die during the period of administration are necropsied. At the conclusion of the test all animals are necropsied and histopathological examinations carried out.

(d) *Test procedures—(1) Animal selection—*

(i) *Species and strain.* A variety of rodent species may be used, although the rat is the preferred species. Commonly used laboratory strains should be employed. The commonly used non-rodent species is the dog, preferably of a defined breed; the beagle is frequently used. If other mammalian species are used, the tester shall provide justification/reasoning for their selection.

(ii) *Age.* (A) Young adult animals shall be employed. At the commencement of the study the weight variation of animals used shall not exceed  $\pm 20$  percent of the mean weight for each sex.

(B) Dosing of rodents shall begin as soon as possible after weaning, ideally before the rats are 6, and in any case, not more than 8 weeks old.

(C) Dosing of dogs shall commence after acclimatization, preferably at 4-6 months and not later than 9 months of age.

(iii) *Sex.* (A) Equal numbers of animals of each sex should be used at each dose level.

(B) The females should be nulliparous and non-pregnant.

(iv) *Numbers.* (A) At least 20 rodents (10 females and 10 males) shall be used at each dose level.

(B) At least eight non-rodents (4 females and 4 males) shall be used at each dose level.

(C) If interim sacrifices are required, the number shall be increased by the number of animals scheduled to be sacrificed before the completion of the study.

(2) *Control groups.* A concurrent control group is required. This group shall be an untreated or sham treated control group or, if a vehicle is used in administering the test substance, a vehicle control group. If the toxic properties of the vehicle are not known or cannot be made available, both untreated and vehicle control groups are required.

(3) *Satellite group.* A satellite group of 20 rodents (10 animals per sex) shall be treated with the high dose level for 90 days and observed for reversibility, persistence, or delayed occurrence of toxic effects for a post treatment period of not less than 28 days.

(4) *Dose levels and dose selection.* (i) In subchronic toxicity tests, it is desirable to have a dose response relationship as well as no-observed-toxic-effect level. Therefore, at least three dose levels with a control and, where appropriate, a vehicle control (corresponding to the concentration of vehicle at the highest exposure level) shall be used. Doses should be spaced appropriately to produce test groups with a range of toxic effects. The data shall be sufficient to produce a dose response curve.

(ii) The highest dose level in rodents shall result in toxic effects but not produce an incidence of fatalities which would prevent a meaningful evaluation; for non-rodents there should be no fatalities.

(iii) The lowest dose level shall not produce any evidence of toxicity. Where there is a usable estimation of human exposure the lowest dose level shall exceed this.

(iv) Ideally, the intermediate dose level(s) should produce minimal observable toxic effects. If more than one intermediate dose is used, the dose levels should be spaced to produce a graduation of toxic effects.

(v) For rodents, the incidence of fatalities in low and intermediate dose groups and in the controls should be low, to permit a meaningful evaluation of the results; for non-rodents, there should be no fatalities.

(5) *Exposure conditions.* The animals shall be dosed with the test substance

on a 7-day per week basis over a period of 90 days. However, based primarily on practical considerations, dosing by gavage or capsule studies on a 5-day per week basis shall be acceptable.

(6) *Observation period.* (i) Duration of observation shall be for at least 90 days.

(ii) Animals in the satellite group scheduled for follow-up observations shall be kept for not less than 28 days without treatment to detect recovery from, or persistence of, toxic effects.

(7) *Administration of the test substance.* (i) The test substance shall be administered in the diet or in capsules. Alternatively for rodents it may be administered by gavage or in the drinking water.

(ii) All animals shall be dosed by the same method during the entire experimental period.

(iii) Where necessary, the test substance is dissolved or suspended in a suitable vehicle. If a vehicle or diluent is needed, ideally it should not elicit important toxic effects itself nor substantially alter the chemical or toxicological properties of the test substance. It is recommended that wherever possible the usage of an aqueous solution be considered first, followed by consideration of a solution of oil, and then by possible solution in other vehicles.

(iv) For substances of low toxicity, it is important to ensure that when administered in the diet the quantities of the test substance involved do not interfere with normal nutrition. When the test substance is administered in the diet, either a constant dietary concentration (ppm) or a constant dose level in terms of the animals' body weight shall be used; the alternative used shall be specified.

(v) For a substance administered by gavage or capsule, the dose shall be given at similar times each day, and adjusted at intervals (weekly or bi-weekly) to maintain a constant dose level in terms of animal body weight.

(8) *Observation of animals.* (i) Each animal shall be handled and its physical condition appraised at least once each day.

(ii) Additional observation shall be made daily with appropriate actions taken to minimize loss of animals to the study (e.g. necropsy or refrigeration of those animals found dead and isolation or sacrifice of weak or moribund animals).

(iii) Signs of toxicity shall be recorded as they are observed including the time of onset, degree and duration.

(iv) Cage-side observations shall include, but not be limited to, changes in skin and fur, eyes and mucous membranes, respiratory, circulatory,

autonomic and central nervous systems, somatomotor activity and behavior pattern.

(v) Measurements shall be made weekly of food consumption or water consumption when the test substance is administered in the food or drinking water, respectively.

(vi) Animals shall be weighed weekly.

(vii) At the end of the 90-day period all survivors in the non-satellite treatment groups shall be sacrificed. Moribund animals shall be removed and sacrificed when noticed.

(9) *Clinical examinations.* (i) The following examinations shall be made on at least five animals of each sex in each group for rodents and all animals when non-rodents are used as test animals.

(A) Certain hematology determinations shall be carried out at least three times during the test period: just prior to initiation of dosing (baseline data), after approximately 30 days on test, and just prior to terminal sacrifice at the end of the test period. The following hematology determinations shall be carried out: hematocrit, hemoglobin concentration, erythrocyte count, total and differential leucocyte count, and a measure of clotting potential such as clotting time, prothrombin time, thromboplastin time, or platelet count.

(B) Certain clinical biochemistry determinations shall be carried out at least three times during the test period: just prior to initiation of dosing (baseline data), after approximately 30 days on test, and just prior to terminal sacrifice at the end of the test period. The following clinical biochemical test areas shall be carried out: electrolyte balance, carbohydrate metabolism, and liver and kidney function. The selection of additional tests shall be influenced by observations on the mode of action of the substance. Suggested additional determinations include: calcium, phosphorus, chloride, sodium, potassium, fasting glucose (with period of fasting appropriate to the species/breed), serum glutamic-pyruvic transaminase (now known as serum alanine aminotransferase), serum glutamic oxaloacetic transaminase (now known as serum aspartate aminotransferase), ornithine decarboxylase, gamma glutamyl transpeptidase, urea nitrogen, albumen, blood creatinine, total bilirubin and total serum protein measurements. Other determinations which may be necessary for an adequate toxicological evaluation include analyses of lipids, hormones, acid/base balance, methemoglobin and cholinesterase activity. Additional

clinical biochemistry may be employed where necessary to extend the investigation of observed effects. Non-rodents shall be fasted for a period (not more than 24 hours) before taking blood samples.

(ii) The following examinations shall be made on at least five animals of each sex in each group for rodents and all animals on test for non-rodents.

(A) Ophthalmological examination, using an ophthalmoscope or equivalent suitable equipment, shall be made prior to the administration of the test substance and at the termination of the study. If changes in the eyes are detected, all animals shall be examined.

(B) Urinalysis is required only when there is an indication based on expected or observed toxicity.

(10) *Gross necropsy.* (i) all animals shall be subjected to a full gross necropsy which includes examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents.

(ii) At least the liver, kidneys, adrenals, and gonads shall be weighed wet, as soon as possible after dissection to avoid drying. In addition, for the rodent, the brain; for the non-rodent, the thyroid with parathyroids also shall be weighed wet.

(iii) The following organs and tissues, or representative samples thereof, shall be preserved in a suitable medium for possible future histopathological examination: all gross lesions; brain-including sections of medulla/pons, cerebellar cortex and cerebral cortex; pituitary; thyroid/parathyroid; thymus; lungs; trachea; heart; sternum with bone marrow; salivary glands; liver; spleen; kidneys/adrenals; pancreas; gonads; uterus; accessory genital organs (epididymis, prostate, and, if present, seminal vesicles); aorta, (skin), (non-rodent gall bladder); esophagus; stomach; duodenum; jejunum; ileum; cecum; colon; rectum; urinary bladder; representative lymph node; (mammary gland), (thigh musculature), peripheral nerve; (eyes); (femur including articular surface); (spinal cord at three levels—cervical, midthoracic and lumbar); and, (rodent-exorbital lachrymal-glands).

(11) *Histopathology.* (i) Full histopathology shall be performed on the organs and tissues, listed under paragraph (d)(10) (ii) and (iii) of this section of all rodents in the control and high dose groups, all non-rodents, and all rodents that died or were killed during the study.

(ii) Histopathology shall be performed on all gross lesions in all animals.

(iii) Histopathology shall be performed on target organs in all animals.

(iv) Histopathology shall be performed on the tissues mentioned in brackets under paragraph (d)(10)(iii) of this section if indicated by signs of toxicity or target organ involvement.

(v) Histopathology shall be performed on lungs, liver and kidneys of all animals. Special attention to examination of the lungs of rodents should be made for evidence of infection since this provides a convenient assessment of the state of health of the animals.

(vi) For the satellite group of rodents, histopathology shall be performed on tissues and organs identified as showing effects in the treated groups.

(e) *Data and reporting*—(1) *Treatment of results.*

(i) Data shall be summarized in tabular form, showing for each test group the number of animals at the start of the test, the number of animals showing lesions, the type of lesions, and the percentage of animals displaying each type of lesion.

(ii) All observed results, quantitative and incidental, shall be evaluated by an appropriate statistical method. Any generally acceptable statistical methods may be used; the statistical methods should be selected during the design of the study.

(2) *Evaluation of the study results.* (i) The findings of a subchronic oral toxicity study should be evaluated in conjunction with the findings of preceding studies and considered in terms of the toxic effects and the necropsy and histopathological findings. The evaluation shall include the relationship between the dose of the test substance and the presence or absence, the incidence and severity, of abnormalities, including behavioral and clinical abnormalities, gross lesions, identified target organs, body weight changes, effects or mortality and any other general or specific toxic effects. The test shall provide a satisfactory estimation of a no-effect level.

(ii) In any study which demonstrates and absence of toxic effects, further investigation to establish absorption and bioavailability of the test substance shall be considered.

(3) *Test report.* In addition to the reporting requirements as specified in the TSCA Good Laboratory Practice Standards, 40 CFR Part 792, Subpart J, the following specific information shall be reported:

(i) *Group animal data.* Tabulation of toxic response data by species, strain, sex, and exposure level for:

(A) Number of animals dying.

(B) Number of animals showing signs of toxicity.

(C) Number of animals exposed.

(ii) *Individual animal data.*

(A) Time of death during the study or whether animals survived to termination.

(B) Time of observation of each abnormal sign and its subsequent course.

(C) Body weight data.

(D) Food consumption data when collected.

(E) Hematological tests employed and all results.

(F) Clinical biochemistry tests employed and all results.

(G) Necropsy findings.

(H) Detailed description of all histopathological findings.

(I) Statistical treatment of results where appropriate.

#### Subparts C-E—[Reserved]

#### Subpart F—Special Studies

##### § 798.460 Pharmacokinetic test standard.

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

(1) The bioavailability of 2-ethylhexanoic acid (EHA) after dermal administration.

(2) Whether or not the biotransformation of EHA is qualitatively and quantitatively the same after dermal and oral administration.

(3) Whether or not the biotransformation of EHA is changed qualitatively or quantitatively by repeated dosing.

(4) The extent of transport of EHA and its metabolites to the fetus.

(b) *Definitions.* (1) Bioavailability refers to the rate and extent to which the administered compound is absorbed, i.e., reaches the systemic circulation.

(2) Relative percent of percutaneous absorption is defined as 100 times the ratio between total urinary excretion of compound following topical administration and total urinary excretion of compound following oral administration.

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

(i) *Species.* The species utilized for investigating EHA shall be the rat, a species for which historical data on the toxicity and carcinogenicity of several compounds are available and which is used extensively in percutaneous absorption studies, and the guinea pig, a species whose skin resembles human skin.

(ii) *Animals.* Adult female Fischer 344 rats and Hartley guinea pigs shall be used. The rats shall be 7 to 9 weeks old and weigh 125 to 175 grams, and the guinea pigs, 5 to 7 weeks old and weigh

400 to 500 grams. Prior to testing the animals shall be selected at random for each group. Animals showing signs of ill health shall not be used. For studying EHA transport to the fetus, pregnant rats shall be used in accordance with the OTS or OECD guideline on teratogenicity.

(iii) *Animal care.* (A) The animals should be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms should be maintained at a temperature of  $25 \pm 2$  °C and humidity of  $50 \pm 10$  percent with a 12 hour light/dark cycle per day. The rats and guinea pigs should be kept in a quarantine facility for at least 7 days prior to use.

(B) During the acclimatization period, the rats and guinea pigs should be housed in cages on hardwood chip bedding. All animals shall be provided with conventional laboratory diets and water *ad libitum*.

(2) *Administration of EHA*—(i) *Test compound.* These studies require the use of both non-radioactive EHA and  $^{14}\text{C}$ -labeled EHA. Both preparations are needed to investigate under paragraph (a)(2) of this section. The use of  $^{14}\text{C}$ -EHA is required to investigate under paragraphs (a) (1), (2) and (4) of this section because it will facilitate the work, improve the reliability of quantitative determinations, and increase the probability of observing the presence of previously unidentified metabolites.

(ii) *Dosage and treatment.* (A) Two doses shall be used in the study, a "low" dose and a "high" dose. When administered orally, the "high" dose level should ideally induce some overt toxicity such as weight loss. The "low" dose level should correspond to a no-effect level.

(B) The same "high" and "low" doses shall be administered orally and dermally.

(C) Oral dosing shall be performed by gavage or by administering encapsulated EHA.

(D) For dermal treatment, the doses shall be applied at a volume adequate to deliver the prescribed doses. The backs of the rats and guinea pigs should be lightly shaved with an electric clipper shortly before treatment. The dose shall be applied with a micropipette on a specific area (2 cm<sup>2</sup> for rats, 5 cm<sup>2</sup> for guinea pigs) on the freshly shaven skin. The dosed areas shall be occluded with an aluminum foil patch which is secured in place with adhesive tape.

(iii) *Washing efficiency study.* Before initiation of the dermal absorption studies described in paragraphs (c)(2)(iv) (A) and (B) of this section, an initial washing efficiency experiment

shall be performed to assess the extent of removal of the applied EHA by washing with soap and water. Four rats and 4 guinea pigs should be lightly anesthetized with sodium pentobarbital. These animals shall then be treated with dermal doses of test compound at the low dose level. Soon after application (5 to 10 min) the treated animals shall be washed with soap and water then housed in individual metabolism cages for excreta collection. Urine and feces shall be collected at 8, 24, and 48 hours following dosing. Collection of excreta shall continue every 24 hours if significant amounts of EHA and metabolites continue to be eliminated.

(iv) *Determination of bioavailability.*

(A) *Rat studies.*

(1) Eight animals shall be dosed once orally with the low dose of  $^{14}\text{C}$ -EHA.

(2) Eight animals shall be dosed once orally with the high dose of  $^{14}\text{C}$ -EHA.

(3) Eight animals shall be dosed once dermally with the low dose of  $^{14}\text{C}$ -EHA.

(4) Eight animals shall be dosed once dermally with the high dose of  $^{14}\text{C}$ -EHA.

(5) In the oral studies, the animals shall be placed in individual metabolic cages for collection of excreta at 8, 24, 48, 72 and 96 hours following administration.

(6) In the dermal studies, doses of  $^{14}\text{C}$ -EHA shall be kept on the skin for the duration of the study (96 hours). After application, the animals shall be placed in metabolism cages for excreta collection. Urine and feces shall be collected at 8, 24, 48, 72 and 96 hours.

(B) *Guinea pig studies.* The same procedures shall be followed as specified in paragraph (c)(2)(iv)(A) (1) through (6) of this section.

(v) *Repeated dosing study.* Four rats shall receive a series of single daily oral doses of non-radioactive EHA over a period of at least 14 days, followed at 24 hours after the last dose by a single oral dose of  $^{14}\text{C}$ -EHA. Each dose shall be at the low dose level.

(vi) *Study of placental transport.* A single low dose of  $^{14}\text{C}$ -EHA shall be administered orally to four pregnant rats during the period of organogenesis.

(3) *Observation of animals*—(i) *Bioavailability*—

(A) *Blood levels.* The levels of total  $^{14}\text{C}$  shall be determined in whole blood, blood plasma or blood serum at 8, 24, 48, 72, and 96 hours after dosing rats as specified in paragraph (c)(2)(iv)(A)(1) of this section and guinea pigs as specified in paragraph (c)(2)(iv)(B) of this section. Four animals from each group shall be used for this purpose.

(B) *Urinary and fecal excretion.* The quantities of total  $^{14}\text{C}$  excreted in urine and feces by rats dosed as specified in

paragraph (c)(2)(iv)(A) of this section and guinea pigs dosed as specified in paragraph (c)(2)(iv)(B) of this section shall be determined at 8, 24, 48, 72 and 96 hours after dosing, and if necessary, daily thereafter until at least 90 percent of the dose has been excreted or until 7 days after dosing (whichever occurs first). Four animals from each group shall be used for this purpose.

(ii) *Biotransformation after oral and dermal dosing.* Appropriate qualitative and quantitative methods shall be used to assay urine specimens collected from rats dosed as specified in paragraph (c)(2)(iv)(A) of this (c)(2)(iv)(B) of this section. Any metabolite which comprises greater than 10 percent of the dose shall be identified.

(iii) *Change(s) in biotransformation.* Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of  $^{14}\text{C}$ -labeled components of urine collected at 24 and 48 hours after dosing rats as specified in paragraph (c)(2)(iv)(A)(1) of this section with those in the urine collected at 24 and 48 hours after the  $^{14}\text{C}$ -EHA dose in the repeated dosing study. Any metabolite which comprises greater than 10 percent of the dose shall be identified.

(iv) *Placental transport.* Reference shall be made to OTS or OECD guidelines on teratogenicity to assist in deciding when fetuses should be removed for  $^{14}\text{C}$  assay. The percentage dose transferred to the whole fetus shall be determined. If EHA is found to cause developmental toxicity as specified in § 799.2050(c)(3) of this chapter, an effort shall be made to identify the proximate teratogen transferred to the fetus.

(d) *Data and Reporting*—(1)

*Treatment of results.* Data shall be summarized in tabular form.

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

(3) *Test report.* In addition to the reporting requirements as specified in the TSCA Good Laboratory Practice Standards, 40 CFR 792 Part, Subpart J, the following specific information shall be reported:

(i) Species, strain, and supplier of laboratory animals.

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

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

(iv) Relative percent absorption by the dermal route for rats and guinea pigs administered low and high doses of

<sup>14</sup>C-EHA, assuming 100 percent absorption of the oral doses.

(v) Quantity of isotope, together with percent recovery of the administered dose, in feces, urine, and blood.

(vi) Biotransformation pathways and quantities of EHA and metabolites in urine collected after administering single high and low oral and dermal doses to rats and guinea pigs.

(vii) Biotransformation pathways and quantities of EHA and metabolites in urine collected after administering repeated low doses of EHA to rats.

(viii) Extent of placental transfer of radioactivity from <sup>14</sup>C-EHA to fetuses as a percent of dose transferred to the whole fetus.

2. The authority citation for Part 79 continues to read as follows:

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

3. In Part 799, Subpart B, by adding § 799.2050 to read as follows:

§ 799.2050 2-Ethylhexanoic acid.

(a) *Identification of test substance.* (1) 2-Ethylhexanoic acid (CAS No. 149-57-5) (hereinafter "EHA") shall be tested in accordance with this section.

(2) EHA of at least 99 percent purity shall be used as the test substance.

(b) *Persons required to submit study plans, conduct tests and submit data.* All persons who manufacture or process EHA other than as an impurity from the effective date of this section (44 days after the publication date of the final rule in the Federal Register) to the end of the reimbursement period shall submit an exemption application, or shall submit a letter of intent to conduct testing, study plans, conduct tests, and submit data as specified in this section. Subpart A of this Part, and Parts 790 and 798 of this chapter. The end of the reimbursement period shall be 5 years after the submission of the last final report required under this test rule. Information collection requirements are approved by the Office of Management and Budget under control number 2070-0033.

(c) *Health Effects Testing—(1) Pharmacokinetics.*

(i) *Required testing.* Metabolism studies of the oral and dermal routes of exposure shall be conducted with EHA in accordance with the test standard specified in § 798.460 of this chapter.

(ii) *Reporting requirements.* (A) Study plans shall be provided to the Agency at least 30 days prior to initiating testing.

(B) Interim progress reports shall be provided to the Agency on a quarterly basis beginning 90 days after the effective date of the final test rule.

(C) The final report of results shall be submitted to the Agency no later than 1

year from the effective date of the final test rule.

(2) *Subchronic Toxicity—(i) Required testing.* Subchronic toxicity tests shall be conducted with EHA using Fischer 344 rats and B6C3F1 mice in accordance with the test standard specified in § 798.75 of this chapter. Non-rodents need not be tested for subchronic toxicity.

(ii) *Reporting requirements.* (A) Study plans shall be provided to the Agency at least 30 days prior to initiating testing.

(B) Interim progress reports shall be provided to the Agency on a quarterly basis beginning 90 days after the effective date of the final test rule.

(C) The final report of results shall be submitted to the Agency no later than 15 months from the effective date of the final test rule.

(3) *Developmental toxicity—(i) Required testing.* Developmental toxicity tests shall be conducted with EHA using one rodent and one non-rodent mammalian species in accordance with either the OTS Health Effects Guideline for HG-Organ/Tissue-Dev Tox or the OECD guideline entitled "Teratogenicity", No. 414, Adopted May 12, 1981. The OTS guideline is available in U.S. Environmental Protection Agency Publication No. EPA 560/6-84-002 which is sold by the NTIS (Accession No. PB 84-233295). The OECD guideline is available in OECD Publication No. ISBN 92-84-12221-4 and is sold by the OECD Publication and Information Center. These documents also are available for inspection at both the Office of the Federal Register Information Center and the OPTS Reading Room (docket no. OPTS-42065). This incorporation by reference was approved by the Director of the Federal Register on [date]. These materials are incorporated as they exist on the effective date of this rule; a notice of any change will be published in the Federal Register.

(ii) *Reporting requirements.* (A) Study plans shall be provided to the Agency at least 30 days prior to initiating testing.

(B) Interim progress reports shall be provided to the Agency on a quarterly basis beginning 90 days after the effective date of the final test rule.

(C) The final report of results shall be submitted to the Agency no later than 18 months from the effective date of the final test rule.

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