

applicable to the CHAMPUS PRO program in the same manner as they apply to the Medicare PRO program. Section 1102(g) of title 10, United States Code also applies to the CHAMPUS PRO program.

(1) *Additional provision regarding confidentiality of records*—(1) *General rule.* The provisions of 10 U.S.C. 1102 regarding the confidentiality of medical quality assurance records shall apply to the activities of the CHAMPUS PRO program as they do to the activities of the external civilian PRO program that reviews medical care provided in military hospitals.

(2) *Specific applications.* (i) Records concerning PRO deliberations are generally nondisclosable quality assurance records under 10 U.S.C. 1102.

(ii) Initial denial determinations by PROs pursuant to paragraph (g) of this section (concerning medical necessity determinations, DRG validation actions, etc.) and subsequent decisions regarding those determinations are not nondisclosable quality assurance records under 10 U.S.C. 1102.

(iii) Information the subject of mandatory PRO disclosure under 42 CFR part 476 is not a nondisclosable quality assurance record under 10 U.S.C. 1102.

(m) *Obligations, sanctions and procedures.* (1) The provisions of 42 CFR 1004.1-1004.80 shall apply to the CHAMPUS PRO program as they do the Medicare PRO program, except that the functions specified in those sections for the Office of Inspector General of the Department of Health and Human Services shall be the responsibility of OCHAMPUS.

(2) The provisions of 42 USC section 1395ww(1)(2) concerning circumvention by any hospital of the applicable payment methods for inpatient services shall apply to CHAMPUS payment methods as they do to Medicare payment methods.

(3) The Director, or a designee, of CHAMPUS shall determine whether to impose a sanction pursuant to paragraphs (m)(1) and (m)(2) of this section. Providers may appeal adverse sanctions decisions under the procedures set forth in § 199.10(d).

Dated: January 2, 1990.

Linda Bynum,
Alternate OSD Federal Register Liaison
Officer, Department of Defense.

[FR Doc. 90-320 Filed 1-5-90; 8:45 am]

BILLING CODE 5010-01-0

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 795 and 799

[OPTS-42084H; FRL 3687-1]

Commercial Hexane; Pharmacokinetics Test Standard and Amended Test Requirements

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is issuing a final test rule under section 4(a) of the Toxic Substances Control Act (TSCA) that requires the pharmacokinetics testing of commercial hexane to be performed by a specified test standard. This rule amends a final test rule (53 FR 3382; February 5, 1988) issued under section 4(a)(1)(B) of TSCA that requires manufacturers and processors of commercial hexane to test it for health effects and pharmacokinetics.

DATES: In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern (daylight or standard as appropriate) time on January 22, 1990. This rule shall become effective on February 21, 1990. The incorporation by reference in this rule is approved by the Director of the Federal Register as of February 21, 1990.

FOR FURTHER INFORMATION CONTACT: Michael M. Stahl, Acting Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. EB-44, 401 M St., SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: EPA is finalizing the amended pharmacokinetics test requirements and the associated test standard in 40 CFR 795.232 for commercial hexane.

I. Background

On May 15, 1986 (51 FR 17854), EPA proposed pharmacokinetics testing of commercial hexane at 40 CFR 795.232 and 799.2155. Comments regarding the sufficiency of available pharmacokinetics data and findings supporting the insufficiency of these data were discussed in the final rule for commercial hexane (53 FR 3382; February 5, 1988). Prior to issuing the final test rule for commercial hexane, EPA determined from an internal review that inadequacies in the proposed guideline for pharmacokinetics testing would limit the ability to obtain meaningful data. When the final test rule for commercial hexane was issued, EPA made findings that required test sponsors to perform pharmacokinetics

testing but delayed initiation of testing, stating it would propose a revised test standard and reporting requirements at a later date. EPA proposed a revised test standard and reporting requirements on November 9, 1988 (53 FR 45289) proposing that pharmacokinetics testing for commercial hexane be conducted according to the inhalation and dermal pharmacokinetics test guideline described in that rule.

II. Public Comments

EPA received written comments (Refs. 1 through 3) from the American Petroleum Institute (API), the Halogenated Solvents Industry Alliance (HSIA), and Texaco, Inc. Also, a public meeting was requested by API and held on January 12, 1989 (Ref. 4). Discussion of comments received by EPA in response to the proposed pharmacokinetics test standard for commercial hexane follows:

A. Definitions

1. *Bioavailability and pharmacokinetics.* Texaco (Ref. 3) objected to the use of the term, "bioavailability" and the definition of "pharmacokinetics." Texaco recommended that EPA use the pharmacokinetics terms and definitions of the Organization for Economic Cooperation and Development (OECD) in its guideline on toxicokinetics (Ref. 5). EPA has reviewed the definitions in the OECD Toxicokinetics guideline. The definitions in the OECD guideline did not include the term "bioavailability" nor was another term used with a similar meaning. Since Texaco did not state the nature of its objection to the use of the term "bioavailability", EPA will continue to use "bioavailability" to mean the amount of administered test substance which reaches the systemic circulation and the rate at which this occurs.

The OECD guideline also does not have a definition for pharmacokinetics; it does, however, define a similar term "toxicokinetics" to mean "the study of the absorption, distribution, excretion, and metabolism of substances". This is essentially the definition EPA has for pharmacokinetics. Because Texaco did not state the nature of its objection to the proposed definition, EPA can only surmise that Texaco thinks EPA should use the term "toxicokinetics" instead of "pharmacokinetics". Since EPA has issued numerous pharmacokinetic guidelines to date, to change terminology at this point would cause considerable confusion. Therefore, EPA prefers to continue to use the term "pharmacokinetics".

2. *Metabolism.* API (Ref. 1) and Texaco (Ref. 3) did not agree with EPA's definition of metabolism and recommended that the OECD definition in its Toxicokinetics guideline (Ref. 5) be used. EPA reviewed the OECD definition of metabolism and has decided to significantly modify its proposed definition of metabolism to bring it more in line with the OECD definition and the definitions in other OTS guidelines. This change is made in § 795.232(b)(2) of the final rule.

3. *Percent absorption.* API (Ref. 1) and Texaco (Ref. 3) objected to the definition of "percent absorption". Texaco recommended that the OECD definition in its guideline for Toxicokinetics (Ref. 5) be used. API commented that the percent absorbed cannot be accurately calculated by the method in the proposed definition and recommended that absorption be estimated by comparing the total area under the curve in the plasma versus time curve, after administration of the test material via inhalation or dermal routes, to that found after intravenous administration of the test material (Ref. 1). EPA considered this comment and has deleted the definition of "percent absorbed" (Ref. 6).

4. *Low dose.* API disagreed that the low dose should be a no observed effect level (NOEL), arguing that the NOEL would be a variable quantity depending on the endpoint of interest. API recommended that the low dose in the inhalation study be 1/10 of the high dose. EPA agrees that 1/10 of the high dose is a reasonable level for the low dose (Ref. 6). This change is made in § 795.232(b)(4) of the final rule.

5. *High dose.* API (Ref. 1) and HSIA (Ref. 2) disputed the description of the inhalation high dose as one which "should ideally induce some overt toxicity". API and HSIA believe that metabolic pathway and bioavailability are dose-dependent, and that a dose that induces overt toxicity could alter the normal pharmacokinetics profile, the understanding of which, along with the effect of the route of exposure, is the primary purpose of the study. API argued that the high dose should be based on either the results of subchronic studies or on the physical/chemical properties of the compound. API recommended that the high dose be the same as the highest dose in the chronic bioassay or the MTD (Ref. 4), which for safety reasons is some fraction of the lower explosive limit (LEL). EPA agrees that the high dose must not exceed the LEL and that the criterion of toxicity is appropriate only if the signs are observed at a level below the LEL (Ref.

6). EPA also realizes that toxicity may not be observed below the LEL and has modified the definition of high dose as one which "ideally should induce minimal toxicity". The purpose of retaining some criterion of toxicity in defining the high dose is to parallel the criteria for high dose in the other required studies, thereby allowing the use of pharmacokinetics data in the interpretation of effects seen at high dose levels in those studies. The change in criterion for high dose from "overt" to "minimal" toxicity is in § 795.232(b)(5) of the final rule.

B. Test Procedures, Animal Selection

1. *Species.* API, HSIA, and Texaco (Refs. 1 through 3) commented that EPA did not justify the proposed requirement to perform the dermal absorption test in female guinea pigs in addition to rats. API commented that such testing does not further the primary purpose of the testing, i.e., to compare *n*-hexane and methylcyclopentane pharmacokinetics across different routes of exposure. API believes that the rat should be used because the dermal absorption studies will be most valuable when associated with an oncogenicity study, which is also required to be performed in the rat. API (Ref. 4) also commented that there is little difference in the skin permeability of the rat and the guinea pig. In this case EPA agrees with the commenters and has, therefore, deleted requirements for conducting pharmacokinetics studies using guinea pigs for commercial hexane (Ref. 6); these studies will now be done in the rat only.

2. *Animal strains.* API (Ref. 1) commented that EPA failed to specify which animal strain to use. EPA recognizes that animal strain was not discussed in § 795.232(c)(1)(iii) and has, therefore, changed its heading to "Test animals". The requirement of a specific animal strain for the pharmacokinetics tests is addressed under § 799.2155(c)(8) of the final rule.

3. *Animal care.* API (Ref. 1) objected to the proposed requirement that the test environment be maintained at 24±2 degrees centigrade and 50±10 percent humidity. API recommended that laboratories should conform to the American Association for the Accreditation of Laboratory Animal Care (AAALAC) codes and that the temperature and humidity required should be appropriate for the species. EPA believes that the Department of Health and Human Services (DHHS) guidelines (Ref. 11) as summarized in this section are adequate. The section requires that the test environment conditions appropriate for rats be used,

i.e., 18 to 26 degrees centigrade and 40 to 70 percent relative humidity.

C. Test Procedures, Administration of Test Substances

1. *Test substances.* API (Ref. 1) and Texaco (Ref. 3) commented that the radiolabeled test substances and unlabeled test substances cannot be identical in chemical composition, because they will differ in isotope composition and slight impurities. API and Texaco recommended deletion of the phrase "shall be identical in chemical composition." EPA agrees and has deleted this phrase. However, the unlabeled test material used throughout the pharmacokinetics study, including that to which radiolabeled compound is added, shall be from the same lot number (Ref. 6).

HSIA commented that EPA has proposed that the measurements of pharmacokinetic body fluids be performed with radiolabeled test substance, but that equally useful measurements can be made with unlabeled test substance, permitting the identification of relevant metabolites. If the testing laboratory can demonstrate that the sensitivity of the analytical method for unlabeled material is equal to or greater than the sensitivity of radiochemical methods, then EPA will allow the use of unlabeled material for the bioavailability measurements.

2. *Dosage and treatment.* HSIA (Ref. 2) commented that there should be greater flexibility in determining the number, selection, and comparison of routes of administration. EPA proposed the inhalation and dermal routes of administration because they are the most common routes of human exposure to commercial hexane. The intravenous route is necessary to establish a control for 100 percent absorption (Ref. 6).

3. *Dosage and treatment, intravenous.* API (Ref. 1) and Texaco (Ref. 3) commented that the proposed requirement to administer the same low dose intravenously as was administered dermally and by inhalation may not be possible because of solubility problems. API and Texaco also commented that the dose must be radiolabeled or large enough to enable the measurement of metabolic intermediates. EPA has modified this section to state "the intravenous dose should result in a level of commercial hexane in the blood that approximates the level from the other routes of exposure so that the data can be used to determine absorption and excretion parameters."

4. *Dosage and treatment, inhalation.* API (Ref. 1) and Texaco (Ref. 3) commented that the proposed

requirement to use nose-cone or head-only dosing during the inhalation experiments is not supported by the argument that it will prevent ingestion through grooming because the test substance is volatile and the animal is restrained during the exposure period. EPA disagrees. Since commercial hexane may contain non-volatile residues which can deposit on the fur, ingestion of nonrepresentative amounts of the residues may result from grooming. Furthermore, full-body exposure to hexane vapors is expected to result in a certain amount of dermal absorption which may alter the apparent pharmacokinetics via the inhalation route (Ref. 6).

5. Dosage and treatment, dermal absorption studies. API (Ref. 1) and Texaco (Ref. 3) commented that Susten's method is not routine, would have to be modified to deliver the large dose required to test commercial hexane, and could not be validated by two commercial laboratories (Hazleton, Wisconsin, and Bio-Research). API recommended an alternate method by T. J. Franz (Ref. 7). API questioned the purpose and practicality of trying to measure dermal absorption of a liquid when 99 percent volatilizes from the skin and most occupational exposures are to the vapor instead of the liquid. EPA's purpose for including the Susten method was misconstrued. The Susten method was included for illustrative purposes. Susten's method or an equivalent should be used for the dermal absorption studies. EPA recognizes the difficulties in performing dermal absorption studies with volatile compounds and believes that sufficient latitude is present in the final rule to overcome the difficulties (Ref. 6).

6. Dosage and treatment, washing efficacy study. API (Ref. 1) and Texaco (Ref. 3) commented that no justification was provided to require a washing efficacy study. API also commented that the study would be difficult to conduct because of the volatile nature of commercial hexane. EPA recognizes the difficulty in obtaining meaningful results from a washing efficacy study with a volatile compound such as commercial hexane. Therefore, the washing efficacy study has been deleted (Ref. 6).

7. Dosing and sampling schedule, rat dermal studies. API (Ref. 1) questioned how solubilizing a section of dosed skin will allow EPA to distinguish test material "on" the skin from that which is "in" the skin. EPA disagrees with this contention. Because the test cited will be conducted at the termination of the dermal absorption study, which could be as long as 7 days after the 6-hour

exposure period, EPA believes any commercial hexane "on" the skin would have volatilized and thus would not be detected as "in" the skin (Ref. 6).

D. Test Procedures, Rat Pharmacokinetics Studies

API (Ref. 1) and Texaco (Ref. 3) commented that the proposed § 795.232(c)(3)(i)(A) requires clarification because it implies that blood and excreta samples must be taken during the exposure phase of the dermal and inhalation studies. This, they commented, conflicts with the proposed § 795.232(c)(2)(iii)(A) which requires the collection of only excreta during the exposure period and with the proposed § 795.232(c)(4)(i)(A)(1) which implies that blood samples are collected after exposure.

Also concerning the proposed § 795.232(c)(2)(iii)(A) and (3)(i)(A), API (Ref. 1) and Texaco (Ref. 3) questioned the requirement for the inhalation and dermal studies to collect excreta during the 6 hour exposure periods prior to the placement of the animals in metabolic units. API argues that there is currently no apparatus available for separating urine and feces during this phase of the experiment and significant methods development would be required to meet the requirement. EPA agrees that technical difficulties exist with respect to obtaining excreta samples during head-only inhalation exposure. Therefore, § 795.232(c)(2)(iii), (iii)(D), and (c)(3)(i) have been revised in the final rule to require collection of excreta samples after cessation of inhalation exposure. However, these difficulties are not believed to exist for the collection of blood samples during head-only inhalation exposure and for collection of blood and excreta samples during dermal exposure. Section 795.232(c)(4)(i)(A) has been revised in the final rule to clarify this requirement. Blood and excreta samples shall be collected during and following dermal exposure and following intravenous dosing; blood samples shall be collected during and after head-only inhalation exposure (Ref. 6).

API (Ref. 4) commented that the expired air, which is required to be collected after the placement of the animals in the metabolic units, will contain not only hexane which has been exhaled but also hexane which has been outgassed from excreted feces and urine. EPA does not agree that this is a problem because methods are available for retaining volatile compounds in urine and feces in a metabolic unit while at the same time collecting exhaled volatiles (Ref. 6).

E. Measurements, Rat Pharmacokinetics Studies

1. Bioavailability. Although in agreement with the proposed total of seven sampling times in § 795.232(c)(4)(i)(A)(1), API (Ref. 1) is concerned that the animal strain and sample radioactivity make it impractical to collect the proposed number of samples from a single animal during the first 2 hours of the sampling procedures. EPA has placed no upper limit on the number of animals used in the pharmacokinetics studies; the only requirement is that at least four animals per sex per group be used. Similarly, the proposed sampling points were meant to be illustrative and not a requirement of the study. Industry may use any appropriate protocol to insure that the study objectives are met (Ref. 6), and should strive to use the minimum number of animals to fully accomplish the rule's objectives.

2. Extent of absorption. API (Ref. 1) commented that the proposed § 795.232(c)(4)(i)(A)(2), should be clarified to state that collection of excreta should be terminated after 7 days or after at least 90 percent of the radioactivity has been recovered, "whichever occurs first". EPA agrees (Ref. 6); the phrase has been added in § 795.232(c)(4)(i)(B) in the final rule.

F. Measurements, Rat Metabolism Studies

API (Ref. 1) commented that EPA did not provide justification for requiring efforts to identify any metabolite which comprises five or more percent of the dose eliminated. API recommends that a more practical objective is the identification of any metabolite comprising five or more percent of the dose administered. EPA agrees (Ref. 6); the revision has been made in § 795.232(c)(4)(ii)(A) in the final rule.

G. Data and Reporting

1. Chemical characterization. Texaco (Ref. 3) commented that the reference to chemical purity should be deleted and replaced by a specification that the percents of MCP and *n*-hexane in the test samples be reported. EPA agrees that the term "chemical purity" has no meaning for a complex mixture such as commercial hexane; this reporting requirement has been changed as follows: "the percentages of MCP and *n*-hexane in the test samples shall be reported". EPA does not agree that "chemical purity" of the synthesized radiolabeled hexane and MCP is "not clear". Industry shall report the chemical purity of the radiolabeled *n*-

hexane and MCP before they are mixed with the commercial hexane (Ref. 6).

2. *Biotransformation pathways and pharmacokinetics models.* API (Ref. 1) commented that the proposed test requirements will not provide sufficient information to adequately determine biotransformation pathways or enough data for the development of physiologically based pharmacokinetics models. EPA agrees that sufficient data may not be available to define every step in biotransformation pathways or to develop a pharmacokinetics model. These requirements were revised such that biotransformation pathways and pharmacokinetics models shall be reported to the extent that the products are known and to the extent that any pharmacokinetics models can be developed with available data (Ref. 6).

H. Pharmacokinetics Testing Requirements for Commercial Hexane

API commented that the test rule should require that the animal strain used for the pharmacokinetics test should be the same as that used in the oncogenicity study. EPA understands the benefits of requiring the same strain for the pharmacokinetics test that is used in other tests; however, EPA believes the strain used in the pharmacokinetics test should be the same as the strain used in the subchronic and chronic studies. This has been incorporated as a requirement of the test rule in § 799.2155(c)(8).

I. Availability of Test Facilities

API (Ref. 4) commented that there are only 15 to 20 laboratories that conceptually can do the study, but API has not found anybody that they believe can do this testing because the combined expertise in inhalation methods and pharmacokinetics is rare. EPA suggests that API contact the industry laboratories which have done previous inhalation pharmacokinetics studies required by section 4.

J. Storage of Test Substance

API (Ref. 4) commented on the magnitude of the storage and disposal problems associated with testing a chemical that is not acutely toxic at 75 percent of the lower explosive limit, i.e. 9,000 ppm. API commented that 300 55-gallon drums of commercial hexane must be stored during the course of the 2 to 3 years of testing, as well as retained until the end of the studies as required by the Good Laboratory Practice Standards. API is having difficulty locating a single storage facility that meets local fire codes which limit the amount of volatile material in a single facility.

On June 23, 1989, API formally requested an exemption from the GLP requirement (Ref. 9), which EPA granted on July 13, 1989 (Ref. 10). This exemption allows disposal of the drums during the course of the testing provided that a full and accurate accounting is maintained of the location of test material and drums between initial receipt at the warehouse and final disposition.

K. Disposal of Test Substance

API (Ref. 4) commented on the cost of disposing of the commercial hexane which is removed from laboratory air by pollution control devices. API commented that they must dispose of the 300 drums of commercial hexane absorbed on charcoal in the air pollution control devices, as well as pay for the charcoal.

EPA agrees that these additional costs are part of the cost of testing and should be shared by those subject to the rule. They are not high enough, however, to alter the final economic analysis (Ref. 12).

III. Pharmacokinetics Test Standard

The purpose and need for pharmacokinetics testing of commercial hexane is stated in the proposed rule published November 9, 1988 (53 FR 45289). At this time, EPA is requiring that the pharmacokinetics testing of commercial hexane be conducted according to the test standard and requirements described in this rule.

The test standard requires investigators to use 7- to 9-week old rats for these studies, because rats have been used extensively for pharmacokinetics and metabolism studies. The test substance shall be administered by the dermal and inhalation routes of exposure. Two doses will be required in these studies, a "low" dose and a "high" dose. The "high" dose should induce minimal toxicity, but shall not exceed the lower explosive limit. The "low" dose should correspond to 1/10 of the high dose.

Both radiolabeled and unlabeled test substance shall be used to perform the tests. Each test described in this document, except for the bioavailability measurements, shall be performed separately with each of the two radiolabeled test substances. One radiolabeled test substance shall contain ¹⁴C-methylcyclopentane (MCP) and the other shall contain ¹⁴C-n-hexane. The bioavailability measurements need only be conducted with the test substance containing ¹⁴C-n-hexane or, if it can be demonstrated that the analytical sensitivity is equal or greater, unlabeled test substance may be used. Intravenous tests are also

required to obtain baseline information on the metabolism and excretion of the test substances when they are completely absorbed.

The studies will measure blood concentrations, urinary and fecal excretion, and metabolites of the test substances. These data will permit comparisons of absorption and metabolic processes operating via dermal and inhalation routes of exposure by monitoring excretion (urine feces, expired air) of test substances during the study and tissue distribution of test substances at the end of the study.

EPA believes that this test methodology will provide the basis for a valid and scientifically acceptable test. EPA is adopting the test guideline described in this document as the test standard for the pharmacokinetics studies of commercial hexane. All persons conducting tests shall submit plans and conduct tests in compliance with the TSCA Good Laboratory Practice Standards found in 40 CFR part 792.

IV. Reporting Requirements

All data developed under this final rule shall be reported in accordance with TSCA GLP Standards.

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. EPA is requiring that the test sponsors complete the pharmacokinetics testing and submit the final report to EPA within 18 months of the effective date of this final test rule establishing pharmacokinetics test standards and reporting requirements. Interim progress reports shall be provided to EPA at 6-month intervals, beginning 6 months after the effective date of this final rule establishing test standards and reporting requirements for the required pharmacokinetics testing, until the final report has been submitted to EPA.

V. Economic Analysis

To assess the potential economic impact of the final test rule for commercial hexane published in the Federal Register of February 5, 1988 (53 FR 3382), EPA has estimated the cost of the testing regimen. Total test costs for the final test rule were estimated to range from \$2.2 to \$2.9 million. As a result of these costs, EPA determined that the likelihood of significant adverse economic impact was low for the manufacturers of commercial hexane.

In accordance with the specifics of the new proposed protocol, EPA reevaluated the cost of conducting

pharmacokinetics testing on commercial hexane. This estimated cost was \$208,000 to \$262,000, and is discussed in more detail in a memorandum in the rulemaking record (Ref. 8). As a result of the comments EPA received in response to the proposed pharmacokinetics test, several of the proposed requirements have been deleted in this final rule; therefore, the estimated cost of the test has been reduced to \$177,000 to \$234,000 (Ref. 13). The total test costs with the new protocol for pharmacokinetics range from \$2.4 million to \$3.1 million (Ref. 12).

On the basis of the costs estimated in the economic analysis for the final commercial hexane test rule, and the incremental cost of this pharmacokinetics test standard, the additional testing cost will not result in any change from the conclusions of the prior economic analysis. Refer to the economic impact analysis of the final test rule for commercial hexane for a complete discussion of potential economic impact.

API has commented that the cost of purchasing, storing, and disposing of the test material is an additional economic burden of approximately \$492,000. If this cost were added to the test costs, the total costs associated with testing would range from \$2.9 million to \$3.6 million, which would require an increase in price of commercial hexane estimated to range from 0.33 percent to 0.41 percent. This increase is not sufficient to change the conclusions of the prior economic analysis (Ref. 12).

VI. 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, EPA believes that there will be test facilities and personnel available to perform the testing required by this final rule.

VII. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42064H). This record includes the basic information considered by EPA in

developing this rule and appropriate Federal Register notices.

This record includes the following information:

A. Supporting Documentation

(1) Federal Register notices pertaining to this proposed test standard consisting of:

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

(b) Notice of proposed test rule on methylcyclopentane and commercial hexane (51 FR 17854; May 15, 1986).

(c) Notice of final test rule for commercial hexane and methylcyclopentane (53 FR 3382; February 5, 1988).

(d) Notice of final rule on new definition of test substance and effective date (53 FR 38952; October 4, 1988).

(e) Notice of proposed pharmacokinetics test requirements and revision of proposed test guideline (53 FR 45289; November 9, 1988).

(2) Communications consisting of:

(a) Written public comments and letters.

(b) Contact reports of telephone conversations.

B. References

(1) API American Petroleum Industry, Washington, DC. Comments on EPA's proposed pharmacokinetics test requirements and test guidelines for commercial hexane (December 27, 1988).

(2) HSI. Halogenated Solvents Industry Alliance, Washington, DC. Comments on EPA's proposed pharmacokinetics test requirements and test guideline for commercial hexane (December 22, 1988).

(3) Texaco, Inc. Comments on EPA's proposed pharmacokinetics test requirements and test guideline for commercial hexane (December 22, 1988).

(4) Transcript of public meeting on the proposed pharmacokinetics test requirements and test guideline for commercial hexane (January 12, 1989).

(5) OECD. Organization for Economic Cooperation and Development. OECD Guideline for Testing of Chemicals, #417, Toxicokinetics (Adopted April 4, 1984).

(6) USEPA. U.S. Environmental Protection Agency. "Response to comments on proposed test standard for commercial hexane." Intraagency memorandum from Leonard Keifer, Toxic Effects Branch, Office of Toxic Substances, to Richard Troast, Test Rules Development Branch, Office of Toxic Substances, USEPA, Washington, DC (February 8, 1989).

(7) Franz, T. J. "Percutaneous absorption of benzene." In: "Advances in Modern Environmental Toxicology", Volume VI: Applied Toxicology of Petroleum Hydrocarbons (1984).

(8) USEPA. Intraagency memorandum from Mark Dreyfus, Regulatory Impacts Branch, to Catherine Roman, Test Rules Development

Branch, discussing the cost of the new pharmacokinetics testing protocol for commercial hexane (August 2, 1988).

(9) API. Letter from Dr. Robert T. Drew, Director, Health and Environmental Sciences Dept., API, to Dr. Michael Shapiro, Acting Deputy Asst. Administrator, Office of Pesticides and Toxic Substances, USEPA. (June 23, 1989).

(10) USEPA. Letter from Michael Shapiro, Acting Deputy Asst. Administrator, Office of Pesticides and Toxic Substances, USEPA, to Dr. Robert T. Drew, Director, Health and Environmental Sciences Dept., API. (July 13, 1989).

(11) Guidelines for the Care and Use of Laboratory Animals. DHHS/PHS NIH Publication No. 86-23 (1985).

(12) USEPA. Intraagency memorandum from Michael Shapiro, Economics and Technology Division, to Joseph Merenda, Existing Chemicals Assessment Division (March 29, 1989).

(13) USEPA. Intraagency memorandum from Dan Axelrad, Economics and Technology Division, to Catherine Roman, Existing Chemicals Assessment Division (September 1, 1989).

A record of this rulemaking is available for inspection in the TSCA Public Docket Office, NE-G004, 401 M St., SW., Washington, DC, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

VIII. Other Regulatory Requirements

A. Executive Order 12291

EPA has judged that the final test rule for commercial hexane was not subject to the requirement of a Regulatory Impact Analysis under Executive Order 12291. EPA has determined that this final test rule for pharmacokinetics testing does not alter this determination.

This final rule was submitted to 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 certified that the final test rule for commercial hexane would not have a significant impact on a substantial number of small businesses. The final pharmacokinetics test standard and reporting requirements do not change this determination.

C. Paperwork Reduction Act

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

Public reporting burden for this collection of information is estimated to average 159 hours per response, the estimates include time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (2070-0033), Washington, DC 20503.

List of Subjects in 40 CFR Parts 795 and 799

Chemicals, Environmental protection, Hazardous substances, Laboratories Recordkeeping and reporting requirements, Testing.

Dated: November 17, 1989.

Linda J. Fisher,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, 40 CFR Chapter I, Subchapter R, is amended as follows:

PART 795—[AMENDED]

1. In part 795:

a. The authority citation continues to read as follows:

Authority: 15 U.S.C. 2603.

b. By adding § 795.232 to read as follows:

§ 795.232 Inhalation and dermal pharmacokinetics of commercial hexane.

(a) *Purposes.* The purposes of these studies are to:

(1) Determine the bioavailability of the test substances after dermal and inhalation administration.

(2) Compare the pharmacokinetics and metabolism of the test substances after intravenous, dermal, and inhalation administration.

(3) Examine the effects of repeated doses on the pharmacokinetics and metabolism of the test substances.

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

(2) "Metabolism" means the sum of the enzymatic and nonenzymatic processes by which a particular substance is handled in the body.

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

(4) "Low dose" should correspond to 1/10 of the high dose.

(5) "High dose" shall not exceed the lower explosive limit (LEL) and ideally should induce minimal toxicity.

(6) "Test substance" refers to the unlabeled and both radiolabeled mixtures (^{14}C -*n*-hexane and ^{14}C -methylcyclopentane) of commercial hexane used in the testing.

(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.* Adult male and female rats shall be used for testing. The rats shall be 7 to 9 weeks old and their weight range should be comparable from group to group. The animals shall be purchased from a reputable dealer and shall be permanently identified upon arrival. The animals shall be selected at random for the testing groups, and any animal showing signs of ill health shall not be used.

(iii) *Animal care.* (A) Animal care and housing shall be in accordance with DHHS/PHS NIH Publication No. 80-23, 1985, "Guidelines for the Care and Use of Laboratory Animals."

(B) The animals shall be housed in environmentally controlled rooms with at least 10 air changes per hour. The rooms shall be maintained at a temperature of 18 to 28 degrees centigrade and humidity of 40 to 70 percent with a 12-hour light/dark cycle per day. The animal subjects 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 minimum of 48 hours prior to treatment.

(C) During the acclimatization period, the rats shall 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 substances.* The study will require the use of both radiolabeled and unlabeled test substances. All unlabeled commercial hexane shall be from the same lot number. Two kinds of radiolabeled test substances will be tested. ^{14}C -*n*-hexane shall be the only radiolabeled component of one, and ^{14}C -MCP shall be the only radiolabeled component of the other test substance. The use of both radiolabeled test substances is required for all pharmacokinetics and metabolism studies described in this rule, except for the bioavailability measurements required in (c)(4)(i)(A). The bioavailability measurements need only be conducted with the test substance containing ^{14}C -*n*-hexane or an

unlabeled test substance may be used if it can be demonstrated that the analytical sensitivity of the method used with the unlabeled test substance is equal to or greater than the sensitivity which could be obtained with the radiolabeled test substance. If an unlabeled test substance is used for bioavailability measurements, these measurements shall be extended to include relevant metabolites of *n*-hexane. These test substances shall contain at least 40 liquid volume percent but no more than 55 liquid volume percent *n*-hexane and no less than 10 liquid volume percent methylcyclopentane (MCP) and otherwise conform to the specifications prescribed in the American Society for Testing and Materials Designation D 1836-83 (ASTM D 1836), "Standard Specification for Commercial Hexanes", published in the 1988 *Annual Book of ASTM Standards: Petroleum Products and Lubricants*, ASTM D 1836-83, pp. 966-967, 1988, which is incorporated by reference in accordance with 5 U.S.C. 552(a). ASTM D 1836-83 is available for public inspection at the Office of the Federal Register, Rm. 8301, 11th and L St., NW., Washington, DC 20408, and copies may be obtained from the EPA, TSCA Public Docket Office, Rm. NE G-004, 401 M St., SW., Washington, DC 20460. This incorporation by reference was approved by the Director of the Office of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. This material is incorporated as it exists on the date of approval, and a notice of any change in this material will be published in the Federal Register.

(ii) *Dosage and treatment*—(A) *Intravenous.* An appropriate dose of the test substance shall be administered intravenously. The intravenous data obtained in this portion of the study shall be suitable for the determination of absorption, distribution, and excretion parameters of the test substance. Factors that should be considered in the selection of the intravenous doses are: The acute toxicity of the test substance, the availability of a suitable vehicle (if saline is unsuitable) and the solubility of the test substance in the vehicle.

(B) *Inhalation.* Two concentrations of each test substance shall be used in this portion of the study, a low concentration and a high concentration. The high concentration should induce minimal toxicity, but shall not exceed the lower explosive limit (LEL). The low concentration shall correspond to 1/10 of the high concentration. Inhalation treatment shall be conducted using a "nose-cone" or "head only" apparatus to

reduce ingestion of the test substance through "grooming" or dermal absorption.

(C) *Dermal*. Dermal absorption studies should be conducted by the methodology of Susten, A.S., Dames, B.L. and Niemeier, R.W., "In vivo percutaneous absorption studies of volatile solvents in hairless mice. I. Description of a skin depot", in: *Journal of Applied Toxicology* 6:43-46, (1986), or by some other suitable method because the test-substances have significant volatility. The high and low doses shall be tested in rats.

(iii) *Dosing and sampling schedule*. Each experimental group shall contain at least four animals of each sex. After administration of the test substance, each rat shall be placed in an individual metabolic unit for collection of urine, feces, and expired air. For the dermal studies, excreta from the rats shall also be collected during the exposure periods. At the end of each collection period, the metabolic units shall be cleaned to recover any excreta that might adhere to the units. All studies, except the repeated dose studies, shall be terminated at 7 days, or after at least 90 percent of the administered radioactivity has been recovered in the excreta, whichever occurs first. All studies described below shall be conducted separately with each radiolabeled test substance.

(A) *Intravenous study*. Group A shall be given a single intravenous dose of the radiolabeled test substance to result in a level of commercial hexane in the blood that approximates the level from the other routes of exposure so that the data can be used to determine absorption and excretion parameters.

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

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

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

(C) *Dermal studies*. The test substance shall be applied and kept on the skin for a minimum of 6 hours. The covering apparatus components shall be assayed to recover residual radioactivity. At the termination of the studies, each animal shall be sacrificed and the exposed skin area removed. An appropriate section of the skin shall be solubilized and assayed for radioactivity to ascertain whether the skin acts as a reservoir for the test substance.

(1) Group D shall be given one dermal, low dose of the radiolabeled test substance.

(2) Group E shall be given one dermal, high dose of the radiolabeled test substance.

(D) *Repeated dosing study*. Group F shall receive a series of single daily 6-hour inhalation exposures to unlabeled test substance at the low dose over a period of at least 7 days. A single 6-hour inhalation exposure to the radiolabeled test substance at the low dose shall be administered 24 hours after the last unlabeled exposure. Following administration of the radiolabeled substance, the rats shall be placed in individual metabolic units and excreta collected. The study shall be terminated 7 days after the last exposure, 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 animal subjects administered the test substance intravenously (i.e., Group A), the concentration of test substance in blood and excreta shall be measured following administration. In animal subjects administered the test substance by the inhalation and dermal routes (i.e., Groups B through F), the concentration of test substance in blood shall be measured at selected time intervals during and following the exposure period. In animal subjects administered the test substance by the inhalation route (i.e., Groups B, C, and F) the concentration of test substance in excreta shall be measured following exposure. In animal subjects administered the test substance by the dermal route (i.e., Groups D and E) the concentration of test substance in excreta shall be measured during and following exposure. These measurements allow calculation of uptake, half lives, and clearance. In addition, in the groups administered the test substance by inhalation (i.e., Groups B, C, and F), the concentration of test substance in the exposure chamber 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 measurement of the quantities of test substance and metabolites.

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

(A) *Bioavailability*. The levels of test substance and relevant metabolites, as appropriate, shall be determined in whole blood, blood plasma or blood serum at appropriate intervals after initiation of intravenous, dermal, and inhalation exposure. The sampling intervals should be compatible with the exposure route under study. The determinations need only be done on animals administered the test substance containing ¹⁴C-*n*-hexane or, if the analytical sensitivity is equal or greater, unlabeled test substance may be used.

(B) *Extent of absorption*. The total quantities of radioactivity shall be determined for excreta collected daily for 7 days, or until at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(C) *Excretion*. The quantities of radioactivity eliminated in the urine, feces, and expired air shall be determined separately at time intervals that provide accurate measurement of clearance and excretory rates. The collection of 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 shall be determined in blood and in various tissues, including bone, brain, fat, gastrointestinal tract, gonads, heart, kidney, liver, lungs, muscle, skin, spleen, thymus, and residual carcass of each animal.

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

(ii) *Metabolism*. At least four animals from each group shall be used for these purposes.

(A) *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 administered.

(B) *Changes in biotransformation*. Appropriate qualitative and quantitative assay methods shall be used to compare the composition of radioactive compounds in excreta from rats receiving a single inhalation exposure (Groups B and C) with that from rats

receiving repeated inhalation exposures (Group F).

(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 data shall be evaluated by appropriate statistical methods.

(3) *Reporting results.* In addition to the reporting requirements as specified in 40 CFR part 792, the following information shall be reported.

(i) Strain of laboratory animals.

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

(A) For the radiolabeled test substances, information on the sites and degree of radiolabeling, including type of label, specific activity, chemical purity prior to mixing with the unlabeled hexane mixture, and radiochemical purity

(B) For the unlabeled test substance, information on lot number and the percentage of MCP and *n*-hexane.

(C) Results of chromatography.

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

(iv) Percent and rate of absorption of the test substance after inhalation and dermal exposures.

(v) Quantity and percent recovery of radioactivity in feces, urine, expired air, and blood. For dermal studies, include recovery data for skin and residual radioactivity in the covering apparatus.

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

(vii) Biotransformation pathways, to the extent possible, and quantities of the test substances and metabolites in excreta collected after administering single high and low doses.

(viii) Biotransformation pathways, to the extent possible, and quantities of test substances and metabolites in excreta collected after administering repeated low doses.

(ix) Pharmacokinetics models to the extent they can be developed from the experimental data.

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

PART 799—[AMENDED]

2. In part 799:

a. The authority citation continues to read as follows:

Authority: 15 U.S.C. 2083, 2611, 2625.

b. In § 799.2155 by adding paragraph (c)(8) and by revising paragraph (d) to read as follows:

§ 799.2155 Commercial hexane.

(c) * * *

(8) *Pharmacokinetics*—(i) *Required testing.* Pharmacokinetics testing shall be conducted in rats in accordance with § 795.232 of this chapter. In addition, the rat strain used shall be the same as the strain used in the subchronic and chronic tests required under this section.

(ii) *Reporting requirements.* (A) The inhalation and dermal pharmacokinetics tests shall be completed and the final report submitted to EPA within 18 months after the effective date specified in paragraph (d)(1) of this section.

(B) Interim progress reports shall be submitted to EPA for the inhalation and dermal pharmacokinetics tests at 6-month intervals, beginning 6 months after the effective date specified in paragraph (d)(1) of this section, until the final report is submitted to EPA.

(d) *Effective date* (1) Section 799.2155 is effective on November 17, 1988, except for paragraph (c)(8) which is effective February 21, 1990.

(2) The guidelines and other test methods cited in this section are referenced as they exist on November 17, 1988, except for § 795.232 of this chapter cited in this rule which is referenced as it exists on February 21, 1990.

[FR Doc. 90-272 Filed 1-5-90; 8:45 am]
BILLING CODE 6560-60-D

DEPARTMENT OF TRANSPORTATION

Coast Guard

46 CFR Part 16

[CGD 88-067c]

RIN 2115-AC45

Programs for Chemical Drug and Alcohol Testing of Commercial Vessel Personnel; Pre-Employment Testing

AGENCY: Coast Guard, DOT.

ACTION: Final rule.

SUMMARY: This final rule revises the pre-employment drug testing requirement for marine employers having more than 50 employees. This change will minimize the need for additional pre-employment testing by large employers and consortiums until June, 1990, and relieve them of an unintended economic burden caused by implementation of pre-

employment testing six months before the implementation of random testing.

EFFECTIVE DATE: This rule is effective January 8, 1990.

FOR FURTHER INFORMATION CONTACT: Lieutenant Commander T. A. Murphy, Project Manager, Marine Investigation Division (G-MMI), Office of Marine Safety, Security and Environmental Protection, U.S. Coast Guard Headquarters, 2100 Second Street, SW., Washington, DC, 20593-0001, (202) 267-2215.

SUPPLEMENTARY INFORMATION: When deciding on appropriate exceptions to pre-employment testing requirements, the Department of Transportation was reviewing drug program rules for six different operating modes. The Department's rules generally provided, for all modes, an exception to pre-employment testing for employees who had been covered for a full year by a random testing program conducted by their previous employer. It was the Department's intent that after passing a pre-employment test, employees covered by an employer's random testing program would not need additional pre-employment testing when they changed jobs. However, the Coast Guard implementation schedule required implementation of pre-employment testing six months before implementation of random testing for large employers of maritime personnel. This is compounded by the relatively large and frequent turnover of covered personnel in the maritime industry. As a result, many people already tested under the Coast Guard pre-employment requirement will have to be retested if they change jobs during the next six months.

The language in § 16.210(b)(2) of title 46, Code of Federal Regulations, provides an exception to the need for pre-employment testing of new hires for individuals who had been covered under a random testing program conducted by their previous employer. This exception allows industry personnel to move from one employer's random testing program to another employer's random testing program without an intervening pre-employment test. The published implementation date for pre-employment testing by marine employers having more than 50 employees is July 21, 1989. The implementation date for random testing by these employers, however, is December 21, 1989.

In a spirit of cooperation many marine employers began pre-employment testing as early as May 1, 1989. As published, however, the regulations