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40 C.F.R. § 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 (C-*n*-hexane and 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. 86-23, 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 26 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 he 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. C-*n*-hexane shall be the only radiolabeled component of one, and 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) of this section.The bioavailability measurements need only be conducted with the test substance containing 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 *1986 Annual Book of ASTM Standards: Petroleum Products and Lubricants,* ASTM D 1836-83, pp. 966-967, 1986, which is incorporated by reference in accordance with 5 U.S.C. 552(a).ASTM D 1863-83 is available for public inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.* Copies are available at the addresses in § 700.17(b)(1) and (2) of this chapter. 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.