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40 C.F.R. § 799.9748

TSCA metabolism and pharmacokinetics

(a) *Scope.* (1) This section is intended to meet the testing requirements under section 4 of the Toxic Substances Control Act (TSCA). (1) Testing of the disposition of a test substance is designed to obtain adequate information on its absorption, distribution, biotransformation, and excretion and to aid in understanding the mechanism of toxicity. Basic pharmacokinetic parameters determined from these studies will also provide information on the potential for accumulation of the test substance in tissues and/or organs and the potential for induction of biotransformation as a result of exposure to the test substance. These data can be used to assess the adequacy and relevance of the extrapolation of animal toxicity data (particularly chronic toxicity and/or carcinogenicity data) to human risk assessment.

(2) Metabolism data can also be used to assist in determining whether animal toxicity studies have adequately addressed any toxicity concerns arising from exposure to plant metabolites, and in the setting of tolerances, if any, for those metabolites in raw agricultural commodities.

(b) *Source.* The source material used in developing this TSCA test guideline is the Office of Prevention, Pesticides and Toxic Substances (OPPTS) harmonized test guideline 870.7485 (August 1998, final guideline). This source is available at the address in paragraph (h) of this section.

(c) *Definitions.* The following definitions apply to this section.

Metabolism (biotransformation) is the sum of the processes by which a foreign chemical is subjected to chemical change by living organisms.

LOEL is the lowest observable effects level.

NOEL is the no observable effects level.

Pharmacokinetics is the quantitation and determination of the time course and dose dependency of the absorption, distribution, biotransformation, and excretion of chemicals.

(d) *Good laboratory practice standards.* The pharmacokinetics and metabolism tests outlined in this guideline must conform to the laboratory practices stipulated in 40 CFR Part 792—Good Laboratory Practice Standards.

(e) *Test Procedures.* Test procedures presented below utilize a tier system to minimize the use of resources and to allow flexibility in the conduct of metabolism studies. The proposed tier system consists of a basic data set (Tier 1) and additional studies (Tier 2). These additional studies may be requested based upon the existing toxicology data base and/or the results of Tier 1 testing which are found to impact upon the risk assessment process. For Tier 1 testing, the oral route will typically be required; however, if the use pattern results in other types of exposure, other routes (dermal and/or inhalation) may be required for initial testing of the disposition of a chemical substance. The registrant should justify the route of exposure to the

Agency. Complete descriptions of the test procedures for these other routes of exposure can be found in paragraph (i) of this section. Except in unusual circumstances, the tiered approach to metabolism testing should apply to all listed routes of exposure.

(1) *Pilot studies.* The use of pilot studies is recommended and encouraged for the selection of experimental conditions for the pharmacokinetics and metabolism studies (mass balance, analytical procedures, dose-finding, excretion of CO_2, etc.).

(2) *Animal selection*—(i) *Species.* The rat must normally be used for testing because it has been used extensively for metabolic and toxicological studies. The use of other or additional species may be required if critical toxicology studies demonstrate evidence of significant toxicity in these species or if metabolism is shown to be more relevant to humans in the test species.

(ii) *Strain.* Adult animals of the strain used or proposed to be used for the determination of adverse health effects associated with the test substance.

(3) *Material to be tested*—(i) *Test substance.* (A) A radiolabeled test substance using C should be used for all material balance and metabolite identification aspects of the study. Other radioactive and stable isotopes may be used, particularly if the element is responsible for or is a part of the toxic portion of the compound. If it can be demonstrated that the material balance and metabolite identification requirements can be met using unlabeled test substance, then radiolabeled compound need not be used. If possible, the radiolabel should be located in a core portion of the molecule which is metabolically stable (it is not exchangeable, is not removed metabolically as CO_2, and does not become part of the one-carbon pool of the organism). Labeling of multiple sites of the molecule may be necessary to follow the metabolic fate of the compound.

(B) The label should follow the test compound and/or its major metabolites until excreted. The radiopurity of the radioactive test substance shall be the highest attainable for a particular test substance (ideally it should be greater than 95%) and reasonable effort should be made to identify impurities present at or above 2%. The purity, along with the identity of major impurities which have been identified, shall be reported. For other segments of the study, nonradioactive test substance may be used if it can be demonstrated that the analytical specificity and sensitivity of the method used with nonradioactive test substance is equal to or greater than that which could be obtained with the radiolabeled test substance. The radioactive and nonradioactive test substances shall be analyzed using an appropriate method to establish purity and identity. Additional guidance will be provided in chemical specific test rules to assist in the definition and specifications of test substances composed of mixtures and methods for determination of purity.

(ii) *Administration of test substance.* Test substance should be dissolved or suspended homogeneously in a vehicle usually employed for acute administration. A rationale for the choice of vehicle should be provided. The customary method of administration will be by oral gavage; however, administration by gelatin capsule or as a dietary mixture may be advantageous in specific situations. Verification of the actual dose administered to each animal should be provided.