

40 C.F.R. § 799.9420

TSCA carcinogenicity.

(a) *Scope.* This section is intended to meet the testing requirements under section 4 of TSCA. The objective of a long-term carcinogenicity study is to observe test animals for a major portion of their life span for development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration.

(b) *Source.* The source material used in developing this TSCA test guideline is the OPPTS harmonized test guideline 870.4200 (June 1996 Public Draft). This source is available at the address in paragraph (g) of this section.

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

Carcinogenicity is the development of neoplastic lesions as a result of the repeated daily exposure of experimental animals to a chemical by the oral, dermal, or inhalation routes of exposure.

Cumulative toxicity is the adverse effects of repeated dose occurring as a result of prolonged action on, or increased concentration of, the administered test substance or its metabolites in susceptible tissues.

Dose in a carcinogenicity study is the amount of test substance administered via the oral, dermal or inhalation routes for a period of up to 24 months. Dose is expressed as weight of the test substance (grams, milligrams) per unit body weight of test animal (milligram per kilogram), or as weight of the test substance in parts per million (ppm) in food or drinking water. When exposed via inhalation, dose is expressed as weight of the test substance per unit volume of air (milligrams per liter) or as parts per million.

Target organ is any organ of a test animal showing evidence of an effect induced by a test substance.

(d) *Test procedures—(1) Animal selection—(i) Species and strain.* Testing shall be performed on two mammalian species. Rats and mice are the species of choice because of their relatively short life spans, limited cost of maintenance, widespread use in pharmacological and toxicological studies, susceptibility to tumor induction, and the availability of inbred or sufficiently characterized strains. Commonly used laboratory strains shall be used. If other mammalian species are used, the tester shall provide justification/reasoning for their selection.

(ii) *Age/weight.* (A) Testing shall be started with young healthy animals as soon as possible after weaning and acclimatization.

(B) Dosing should generally begin no later than 8 weeks of age.

(C) At commencement of the study, the weight variation of animals used shall not exceed $\pm 20\%$ of the mean weight for each sex.

(D) Studies using prenatal or neonatal animals may be recommended under special conditions.

- (iii) *Sex.* (A) Equal numbers of animals of each sex shall be used at each dose level.
- (B) Females shall be nulliparous and nonpregnant.
- (iv) *Numbers.* (A) At least 100 rodents (50 males and 50 females) shall be used at each dose level and concurrent control group.
- (B) If interim sacrifices are planned, the number shall be increased by the number of animals scheduled to be sacrificed during the course of the study.
- (C) For a meaningful and valid statistical evaluation of long term exposure and for a valid interpretation of negative results, the number of animals in any group should not fall below 50% at 15 months in mice and 18 months in rats. Survival in any group should not fall below 25% at 18 months in mice and 24 months in rats.
- (D) The use of adequate randomization procedures for the proper allocation of animals to test and control groups is required to avoid bias.
- (E) Each animal shall be assigned a unique identification number. Dead animals, their preserved organs and tissues, and microscopic slides shall be identified by reference to the unique numbers assigned.
- (v) *Husbandry.* (A) Animals may be group-caged by sex, but the number of animals per cage must not interfere with clear observation of each animal. The biological properties of the test substance or toxic effects (e.g., morbidity, excitability) may indicate a need for individual caging. Animals should be housed individually in dermal studies and during exposure in inhalation studies.
- (B) The temperature of the experimental animal rooms should be at 22 ± 3 °C.
- (C) The relative humidity of the experimental animal rooms should be 30 to 70%.
- (D) Where lighting is artificial, the sequence should be 12 h light/12 h dark.
- (E) Control and test animals should be fed from the same batch and lot. The feed should be analyzed to assure uniform distribution and adequacy of nutritional requirements of the species tested and for impurities that might influence the outcome of the test. Animals should be fed and watered ad libitum with food replaced at least weekly.
- (F) The study should not be initiated until animals have been allowed a period of acclimatization/quarantine to environmental conditions, nor should animals from outside sources be placed on test without an adequate period of quarantine.
- (2) *Control and test substances.* (i) Where necessary, the test substance is dissolved or suspended in a suitable vehicle. If a vehicle or diluent is needed, it should not elicit toxic effects itself. It is recommended that wherever possible the use of an aqueous solution be considered first, followed by consideration of solution in oil, and finally solution in other vehicles.
- (ii) One lot of the test substance should be used, if possible, throughout the duration of the study, and the research sample should be stored under conditions that maintain its purity and stability. Prior to the initiation of the study, there should be a characterization of the test substance, including the purity of the test compound, and, if possible, the name and quantities of contaminants and impurities.

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