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40 C.F.R. § 799.9365

TSCA combined repeated dose toxicity study with the reproduction/developmental toxicity screening test.

(a) *Scope*—(1) *Applicability.* This section is intended to meet testing requirements of the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601).

(2) *Source.* The source material used in developing this TSCA test guideline is the Office of Prevention, Pesticides and Toxic Substances (OPPTS) harmonized test guideline 870.3650 (July 2000, final guidelines). This source is available at the address in paragraph (h) of this section.

(b) *Purpose.* (1) This screening test provides limited information on systemic toxicity, neurotoxicity, and/or immunotoxicity following repeated exposure over a limited time period. In addition, it can be used to provide initial information on possible effects on male and female reproductive performance such as gonadal function, mating behavior, conception, development of the conceptus, and parturition. It is not an alternative to, nor does it replace, the existing test guidelines in §§ 799.9370, 799.9380, 799.9620, and 799.9780 of this part.

(2) This test does not provide complete information on all aspects of reproduction and development. In particular, it offers only limited means of detecting postnatal manifestations of prenatal exposure, or effects that may be induced during postnatal exposure. Due (amongst other reasons) to the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/developmental effects.

(3) This test can be used to provide initial information either at an early stage of assessing the toxicological properties of chemicals, or chemicals of high concern. It can also be used as part of a set of initial screening tests for existing chemicals for which little or no toxicological information is available or when otherwise considered relevant. It also can serve as an alternative to conducting two separate screening tests for repeated dose toxicity as described in § 799.9305 of this part and reproductive/developmental toxicity as described in § 799.9355 of this part.

(c) *Definitions.* The definitions in section 3 of TSCA and in 40 CFR Part 792—Good Laboratory Practice Standards apply to this section. The following definitions also apply to this section.

Dosage is a general term comprising dose, its frequency and the duration of dosing.

Dose is the amount of test substance administered. Dose is expressed as weight (g, gm) or as weight of test substance per unit weight of test animal (e.g., mg/kg), or as constant dietary concentration (parts per million (ppm)).

No-observed-effects level (NOEL) is the maximum dose used in a study which produces no adverse effects. The NOEL is expressed in terms of the weight of a test substance given daily per unit weight of test animal (milligrams per kilogram per day).

(d) *Principle of the test.* (1) The test substance must be administered in graduated doses to several groups of males and females. Males should be dosed for a minimum of 4 weeks, up to and including the day before scheduled sacrifice (this includes a minimum of 2 weeks prior to mating, during the mating period and, approximately, 2 weeks post mating). In view of the limited pre-mating dosing period in males, fertility may not be a particularly sensitive indicator of testicular toxicity. Therefore, a detailed histological examination of the testes is essential. The combination of a pre-mating dosing period of 2 weeks and subsequent mating/fertility observations with an overall dosing period of at least 4 weeks, followed by detailed histopathology of the male gonads, is considered sufficient to enable detection of the majority of effects on male fertility and spermatogenesis.

(2) Females should be dosed throughout the study. This includes 2 weeks prior to mating (with the objective of covering at least two complete oestrous cycles), the variable time to conception, the duration of pregnancy and at least 4 days after delivery, up to and including the day before scheduled sacrifice.

(3) Duration of study, following acclimatization, is dependent on the female performance and is approximately 54 days, (at least 14 days pre-mating, (up to) 14 days mating, 22 days gestation, 4 days lactation).

(4) During the period of administration, the animals are observed closely each day for signs of toxicity. Animals which die or are sacrificed during the test are necropsied and, at the conclusion of the test, surviving animals are sacrificed and necropsied.

(e) *Description of the method*—(1) *Selection of animal species.* This test guideline is designed for use with the rat. If other species are used, appropriate modifications will be necessary. Strains with low fecundity or well-known high incidence of developmental defects should not be used. Healthy virgin animals, not subjected to previous experimental procedures, should be used. The test animals should be characterised as to species, strain, sex, weight and/or age. At the commencement of the study the weight variation of animals used should be minimal and not exceed ±20% of the mean weight of each sex. Where the study is conducted as a preliminary study to a long-term or a full-generation study, preferably animals from the same strain and source should be used in both studies.

(2) *Housing and feeding conditions.* (i) The temperature in the experimental animal room should be 22 °C (±3°). The relative humidity should be at least 30% and preferably not exceed 70% other than during room cleaning. Lighting should be artificial, the sequence being 12 hours light, 12 hours dark. For feeding, conventional laboratory diets may be used with an unlimited supply of drinking water. The choice of diet may be influenced by the need to ensure a suitable admixture of a test substance when administered by this method.

(ii) Animals may be housed individually or be caged in small groups of the same sex; for group caging, no more than five animals should be housed per cage. Mating procedures should be carried out in cages suitable for the purpose. Pregnant females should be caged individually and provided with nesting materials.

(3) *Preparation of the animals.* Healthy young adult animals must be randomised and assigned to the treatment groups and cages. Cages should be arranged in such a way that possible effects due to cage placements are minimized. The animals must be uniquely identified and kept in their cages for at least 5 days prior to the start of the study to allow for acclimatisation to the laboratory conditions.

(4) *Preparation of doses.* (i) It is recommended that the test substance be administered orally unless other routes of administration are considered more appropriate. When the oral route is selected, the test compound is usually administered by gavage; however, alternatively, test compounds may also be administered via the diet or drinking water.