
40 C.F.R. § 799.9380

TSCA reproduction and fertility effects.

- (a) *Scope.* This section is intended to meet the testing requirements under section 4 of the TSCA. This section is for two-generation reproduction testing and is designed to provide general information concerning the effects of a test substance on the integrity and performance of the male and female reproductive systems, including gonadal function, the estrous cycle, mating behavior, conception, gestation, parturition, lactation, and weaning, and on the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, target organs in the offspring, and preliminary data on prenatal and postnatal developmental toxicity and serve as a guide for subsequent tests. Additionally, since the study design includes *in utero* as well as postnatal exposure, this study provides the opportunity to examine the susceptibility of the immature/neonatal animal.
- (b) *Source.* The source material used in developing this TSCA test guideline is the OPPTS harmonized test guideline 870.3800 (February 1996 Public Draft). This source is available at the address in paragraph (g) of this section.
- (c) *Good laboratory practice standards.* The study shall be conducted in compliance with 40 CFR part 792—Good Laboratory Practice Standards.
- (d) *Principle of the test method.* The test substance is administered to parental (P) animals prior to and during their mating, during the resultant pregnancies, and through the weaning of their F1 offspring. The substance is then administered to selected F1 offspring during their growth into adulthood, mating, and production of an F2 generation, until the F2 generation is weaned.
- (e) *Test procedures—(1) Animal selection—(i) Species and strain.* The rat is the most commonly used species for testing. If another mammalian species is used, the tester shall provide justification/reasoning for its selection, and appropriate modifications will be necessary. Healthy parental animals, which have been acclimated to laboratory conditions for at least 5 days and have not been subjected to previous experimental procedures, should be used. Strains of low fecundity shall not be used.
- (ii) *Age.* Parental (P) animals shall be 5 to 9 weeks old at the start of dosing. The animals of all test groups should be of uniform weight, age, and parity as nearly as practicable, and should be representative of the species and strain under study.
- (iii) *Sex.* (A) For an adequate assessment of fertility, both males and females shall be studied.
- (B) The females shall be nulliparous and nonpregnant.
- (iv) *Number of animals.* Each control group shall contain a sufficient number of mating pairs to yield approximately 20 pregnant females. Each test group shall contain a similar number of mating pairs.
- (v) *Identification of animals.* Each animal shall be assigned a unique identification number. For the P generation,
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this should be done before dosing starts. For the F1 generation, this should be done for animals selected for mating; in addition, records indicating the litter of origin shall be maintained for all selected F1 animals.

(2) *Administration of test and control substances* — (i) *Dose levels and dose selection*. (A) At least three-dose levels and a concurrent control shall be used. Healthy animals should be randomly assigned to the control and treatment groups, in a manner which results in comparable mean body weight values among all groups. The dose levels should be spaced to produce a gradation of toxic effects. Unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some reproductive and/or systemic toxicity but not death or severe suffering. In the case of parental mortality, this should not be more than approximately 10%. The intermediate dose levels should produce minimal observable toxic effects. The lowest dose level should not produce any evidence of either systemic or reproductive toxicity (i.e., the no-observed-adverse-effect level, NOAEL) or should be at or near the limit of detection for the most sensitive endpoint. Two- or four-fold intervals are frequently optimal for spacing the dose levels, and the addition of a fourth test group is often preferable to using very large intervals (e.g., more than a factor of 10) between dosages.

(B) It is desirable that additional information on metabolism and pharmacokinetics of the test substance be available to demonstrate the adequacy of the dosing regimen. This information should be available prior to testing.

(C) The highest dose tested should not exceed 1,000 mg/kg/day (or 20,000 ppm in the diet), unless potential human exposure data indicate the need for higher doses. If a test performed at the limit dose level, using the procedures described for this study, produces no observable toxicity and if an effect would not be expected based upon data from structurally related compounds, then a full study using three dose levels may not be considered necessary.

(ii) *Control group*. (A) A concurrent control group shall be used. This group shall be an untreated or sham treated group or a vehicle-control group if a vehicle is used in administering the test substance.

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