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# 40 C.F.R. § 798.4700

## Reproduction and fertility effects.

(a) *Purpose.* This guideline for two-generation reproduction testing is designed to provide general information concerning the effects of a test substance on gonadal function, conception, parturition, and the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, and preliminary data on teratogenesis and serve as a guide for subsequent tests.

(b) *Principle of the test method.* The test substance is administered to parental (P) animals prior to their mating, during the resultant pregnancies, and through the weaning of their $F_1$ offspring. The substance is then administered to selected $F_1$ offspring during their growth into adulthood, mating, and production of an $F_2$ generation, up until the $F_2$ generation is weaned.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species and strain.* The rat is the preferred species. If another mammalian species is used, the tester shall provide justification/reasoning for its selection. Strains with low fecundity shall not be used.

(ii) *Age.* Parental (P) animals shall be about 5 to 8 weeks old at the start of dosing.

(iii) *Sex.* (A) For an adequate assessment of fertility, both males and females shall be studied.

(B) The females shall be nulliparous and non-pregnant.

(iv) *Number of animals.* Each test and control group shall contain at least 20 males and a sufficient number of females to yield at least 20 pregnant females at or near term.

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

(ii) If a vehicle is used in administering the test substance, the control group shall receive the vehicle in the highest volume used.

(iii) If a vehicle or other additive is used to facilitate dosing, it shall not interfere significantly with absorption of the test substance or produce toxic effects.

(3) *Dose levels and dose selection.* (i) At least three dose levels and a concurrent control shall be used.

(ii) The highest dose level should induce toxicity but not high levels of mortality in the parental (P) animals.

(iii) The lowest dose level should not produce any grossly observable evidence of toxicity.

(iv) Ideally the intermediate dose level(s) should produce minimal observable toxic effects. If more than one intermediate dose is used, dose levels should be spaced to produce a gradation of toxic effects.