
40 C.F.R. § 799.9630

TSCA developmental neurotoxicity.

- (a) *Scope—(1) Applicability.* This section is intended to meet the testing requirements *under* section 4 of the Toxic Substances Control Act (TSCA).
- (2) *Source.* The source material used in developing this TSCA test guideline is the OPPTS harmonized test guideline 870.6300 (August 1998).
- (b) *Purpose.* In the assessment and evaluation of the toxic characteristics of a chemical substance or mixture (test substance), determination of the potential for developmental neurotoxicity is important. This study is designed to develop data on the potential functional and morphological hazards to the nervous system which may arise in the offspring from exposure of the mother during pregnancy and lactation.
- (c) *Principle of the test method.* The test substance is administered to several groups of pregnant animals during gestation and early lactation, one dose level being used per group. Offspring are randomly selected from within litters for neurotoxicity evaluation. The evaluation includes observations to detect gross neurologic and behavioral abnormalities, determination of motor activity, response to auditory startle, assessment of learning, neuropathological evaluation, and brain weights. This protocol may be used as a separate study, as a followup to a standard developmental toxicity and/or adult neurotoxicity study, or as part of a two-generation reproduction study, with assessment of the offspring conducted on the second (F2) generation.
- (d) *Test procedure—(1) Animal selection—(i) Species and strain.* Testing must be performed in the rat. Because of its differences in timing of developmental events compared to strains that are more commonly tested in other developmental and reproductive toxicity studies, it is preferred that the Fischer 344 strain not be used. If a sponsor wishes to use the Fischer 344 rat or a mammalian species other than the rat, ample justification/reasoning for this selection must be provided.
- (ii) *Age.* Young adult (nulliparous females) animals must be used.
- (iii) *Sex.* Pregnant female animals must be used at each dose level.
- (iv) *Number of animals.* (A) The objective is for a sufficient number of pregnant rats to be exposed to the test substance to ensure that an adequate number of offspring are produced for neurotoxicity evaluation. At least 20 litters are recommended at each dose level.
- (B) On postnatal day 4, the size of each litter should be adjusted by eliminating extra pups by random selection to yield, as nearly as possible, four male and four females per litter. Whenever the number of pups of either sex prevents having four of each sex per litter, partial adjustment (for example, five males and three females) is permitted. Testing is not appropriate for litters of less than seven pups. Elimination of runts only is not appropriate. Individual pups should be identified uniquely after standardization of litters. A method that may be used for identification can be found under paragraph (f)(1) of this section.
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(v) *Assignment of animals for behavioral tests, brain weights, and neuropathological evaluations.* After standardization of litters, one male or one female from each litter (total of 10 males and 10 females per dose group) must be randomly assigned to one of the following tests: Motor activity, auditory startle, and learning and memory, in weanling and adult animals. On postnatal day 11, either 1 male or 1 female pup from each litter (total of 10 males and 10 females per dose group) must be sacrificed. Brain weights must be measured in all of these pups and, of these pups, six per sex per dose must be selected for neuropathological evaluation. At the termination of the study, either 1 male or 1 female from each litter (total of 10 males and 10 females per dose group) must be sacrificed and brain weights must be measured. An additional group of six animals per sex per dose group (one male or one female per litter) must be sacrificed at the termination of the study for neuropathological evaluation.

(2) *Control group.* A concurrent control group is required. This group must be a sham-treated group or, if a vehicle is used in administering the test substance, a vehicle control group. The vehicle must neither be developmentally toxic nor have effects on reproduction. Animals in the control group must be handled in an identical manner to test group animals.

(3) *Dose levels and dose selection.* (i) At least three dose levels of the test substance plus a control group (vehicle control, if a vehicle is used) must be used.

(ii) If the test substance has been shown to be developmentally toxic either in a standard developmental toxicity study or in a pilot study, the highest dose level must be the maximum dose which will not induce in utero or neonatal death or malformations sufficient to preclude a meaningful evaluation of neurotoxicity.

(iii) If a standard developmental toxicity study has not been conducted, the highest dose level, unless limited by the physicochemical nature or biological properties of the substance, must induce some overt maternal toxicity, but must not result in a reduction in weight gain exceeding 20 percent during gestation and lactation.

(iv) The lowest dose should not produce any grossly observable evidence of either maternal or developmental neurotoxicity.

(v) The intermediate doses must be equally spaced between the highest and lowest doses used.

(4) *Dosing period.* Day 0 of gestation is the day on which a vaginal plug and/or sperm are observed. The dosing period must cover the period from day 6 of gestation through day 10 postnatally. Dosing should not occur on the day of parturition in those animals who have not completely delivered their offspring.

(5) *Administration of the test substance.* The test substance or vehicle must be administered orally. Other routes of administration may be acceptable, on a case-by-case basis, with ample justification/reasoning for this selection. The test substance or vehicle must be administered based on the most recent weight determination.

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