
40 C.F.R. § 799.9346

TSCA 90-day inhalation toxicity.

(a) *Scope.* This section is intended to meet the testing requirements under section 4 of TSCA. In the assessment and evaluation of the toxic characteristics of a gas, volatile substance, or aerosol/particulate, determination of subchronic inhalation toxicity may be carried out after initial information on toxicity has been obtained by acute testing. The subchronic inhalation study has been designed to permit the determination of the no-observed-effect-level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. This study is not capable of determining those effects that have a long latency period for development (e.g., carcinogenicity and life shortening). Extrapolation from the results of this study to humans is valid only to a limited degree. It can, however, provide useful information on health hazards likely to arise from repeated exposures by the inhalation route over a limited period of time. It will provide information on target organs and the possibilities of accumulation, and can be of use in selecting concentration levels for chronic studies and establishing safety criteria for human exposure. Hazards of inhaled substances are influenced by the inherent toxicity and by physical factors such as volatility and particle size.

(b) *Source.* The source material used in developing this TSCA test guideline is the OPPTS harmonized test guideline 870.3465 (June 1996 Public Draft). This source is available at the address in paragraph (h) of this section.

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

Aerodynamic equivalent diameter is defined as the diameter of a unit density sphere having the same terminal settling velocity as the particle in question, whatever its size, shape, and density. It is used to predict where in the respiratory tract such particles may be deposited.

Concentration in a subchronic inhalation study is the amount of test substance administered via inhalation for a period of 90-days. Concentration is expressed as weight of the test substance per unit volume of air (milligrams per liter or parts per million).

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

Inhalable diameter refers to that aerodynamic diameter of a particle which is considered to be inhalable for the organism. It is used to refer to particles which are capable of being inhaled and may be deposited anywhere within the respiratory tract

Mass median aerodynamic diameter (MMAD) is the median aerodynamic diameter and along with the geometric standard deviation (GSD) is used to describe the particle size distribution of any aerosol statistically based on the weight and size of the particles. Fifty percent of the particles by weight will be smaller than the median diameter and 50% of the particles will be larger.

No-observed-effect-level (NOEL) is the maximum concentration used in a study which produces no adverse effects.

Subchronic inhalation toxicity is the adverse effects occurring as a result of the repeated daily exposure of experimental animals to a chemical by inhalation for part (approximately 10%) of a life span.

(d) *Limit test*. If exposure at a concentration of 1 mg/L (expected human exposure may indicate the need for a higher concentration), or where this is not possible due to physical or chemical properties of the test substance, the maximum attainable concentration produces no observable toxic effects, then a full study using three concentrations might not be necessary.

(e) *Test procedures*—(1) *Animal selection*—(i) *Species and strain*. A mammalian species shall be used for testing. A variety of rodent species may be used, although the rat is the preferred species. Commonly used laboratory strains should be employed. If another mammalian species is used, the tester shall provide justification/reasoning for its selection.

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

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

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

(iii) *Sex*. (A) Equal numbers of animals of each sex shall be used at each concentration.

(B) Females shall be nulliparous and nonpregnant.

(iv) *Numbers*. (A) At least 20 animals (10 females and 10 males) should be used for each test group.

(B) If interim sacrifices are planned, the number of animals shall be increased by the number of animals scheduled to be sacrificed before the completion of the study.

(C) To avoid bias, the use of adequate randomization procedures for the proper allocation of animals to test and control groups is required.

(D) 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 animal's unique number.

(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 must be housed individually in inhalation chambers during exposure to aerosols.

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