
40 C.F.R. § 799.9135

TSCA acute inhalation toxicity with histopathology.

(a) *Scope.* This section is intended to meet the testing requirements under section 4 of the Toxic Substances Control Act (TSCA). In the assessment and evaluation of the potential human health effects of chemical substances, it is appropriate to test for acute inhalation toxic effects. The goals of this test are to characterize the exposure-response relationship for sensitive endpoints following acute exposure and to characterize toxicologic response following acute high exposures. The latter is of particular concern in relation to spills and other accidental releases. This testing is designed to determine the gross pathology and histopathology resulting from acute inhalation exposure to a substance. Because toxic effects on the respiratory tract are of particular concern following inhalation exposure, several indicators of respiratory toxicity consisting of histopathology on fixed tissue and evaluation of cellular and biochemical parameters in bronchoalveolar lavage fluid should be employed. The respiratory histopathology consists of specialized techniques to preserve tissues of the respiratory tract in order to allow detailed microscopic examination to identify adverse effects of chemical substances on this organ system. The bronchoalveolar lavage is designed to be a rapid screening test to provide an early indicator of pulmonary toxicity by examining biochemical and cytologic endpoints of material from the lungs of animals exposed to potentially toxic chemical substances. These acute tests are designed to assess the relationship, if any, between the animals' exposure to the test substance and to demonstrate relationship between the animals' exposure and the incidence and severity of observed abnormalities, including gross or histopathologic lesions, body weight changes, effects on mortality, and any other toxic effects. These acute tests are not intended to provide a complete evaluation of the toxicologic effects of a substance, and additional functional and morphological evaluations may be necessary to assess completely the potential effects produced by a chemical substance. Additional tests may include longer-term exposures, or more in-depth evaluation of specific organ systems as indicated by signs of toxicity following acute exposure.

(b) *Source.* This a new section developed by the United States Environmental Protection Agency.

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

Aerodynamic diameter (d_{ae}) refers to the size of particles. It is the diameter of a sphere of unit density that behaves aerodynamically (has the same settling velocity in air) as the particle of the test substance. It is used to compare particles of different size, shape, and density, and to predict where in the respiratory tract such particles may be primarily deposited.

Exposure response is the relationship between the exposure concentration and the measured toxic response, whether expressed as a group mean \pm standard deviation) in the case of a continuous variable or as incidence in the case of a quantal variable. This definition should not preclude the exploration of other dose metrics in establishing this relationship.

Geometric standard deviation (GSD) is a dimensionless number equal to the ratio between the mass median aerodynamic diameter (MMAD) and either 84% or 16% of the diameter size distribution (e.g., MMAD = 2 μ m;

84% = 4 μm ; GSD = $4/2 = 2.0$.) The MMAD, together with the GSD, describe the particle size distribution of an aerosol. Use of the GSD may not be valid for non-lognormally distributed aerosols. (If the size distribution deviates from the lognormal, it shall be noted).

Inhalability is the ratio of the number concentration of particles of a certain aerodynamic diameter, d_{ae} , that are inspired through the nose or mouth to the number concentration of the same d_{ae} present in the inspired volume of ambient air. In humans, inhalability can exceed 15 μm d_{ae} , whereas inhalability dramatically decreases for particles above 4 μm d_{ae} in small laboratory animals.

Lower respiratory tract consists of those structures of the respiratory tract below the larynx.

Mass geometric mean aerodynamic diameter or the mass median aerodynamic diameter (MMAD) is the calculated aerodynamic diameter that divides the particles of an aerosol (a gaseous suspension of fine liquid or solid particles) in half, based on the weight of the particles. By weight, 50% of the particles will be larger than the MMAD and 50% of the particles will be smaller than the MMAD.

Particle regional deposition is the fraction of inhaled particles that deposits in the specific region of the respiratory tract. The major mechanisms of particle deposition in the respiratory tract include impaction, sedimentation, diffusion, interception, and electrostatic precipitation. The deposition mechanism that is dominant for a given region depends on the respiratory tract architecture and ventilation rate of the species and the aerosol particle size and distribution. The respiratory tract in both humans and various experimental mammals can be divided into three regions on the basis of structure, size, and function:

- (1) The extrathoracic region or upper respiratory tract that includes the nose, mouth, nasopharynx, oropharynx, laryngopharynx, and larynx.
- (2) The tracheobronchial region that includes the trachea, bronchi, and bronchioles (including the terminal bronchioles).
- (3) The alveolar region that includes the respiratory bronchioles (if present in the species), alveolar ducts, alveolar sacs, and alveoli.

Respiratory effects are any adverse effects on the structure or functions of the respiratory system related to exposure to a chemical substance.

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