Session: Regulatory Application of Science

Moderator: Len Levy, PhD and Nils Krueger, PhD, DVM

Presentation Summary

Title: "Acute Inhalative Toxicity Part 1: The challenge to create particulate aerosols for acute toxicity testing – a systematic approach"

Juergen Nolde, PhD

Large differences between lethal and non-lethal concentrations of different forms of the same substance have been documented through a large number of acute inhalation studies which do not conform to the results from acute oral or dermal studies which did not provide any concerns on potential toxicity for the same substance. Therefore, it is necessary to look for the cause of these contrary results in the different behavior of the particles of the substance in the inhalation equipment, up to the point when the particles are delivered to the nose of the rat

OECD test guidelines for acute inhalation studies require defined maximum particle sizes (MMAD max. 4 µm) and concentration up to 5000 mg/m^3 or, the maximum technical feasible concentration. However, this technical feasible concentration and even more importantly, its measurement, is not defined. The challenge to create particulate aerosols for acute toxicity testing using a systematic approach will be presented. The aim is to examine optimized aerosol generation and its monitoring, including detailed characterisation of the exposure atmospheres in the test equipment (stability, particle concentration, particle size distribution over time) from the point of generation to the point of release out of the system prior to performing OECD animal inalation studies. It was our intention to these perform rat studies with the highest technically feasible concentration without significant aerosol altering. Studies of aerosol generation on this scale and detail with several different particular substances e.g., silica, organic pigments, aluminium oxide, sugar, flour dust and calcium carbonate have not previously been carried out in any acute animal inhalation studies. A very detailed evaluation of the aerosol generation can help to predict the outcome of rat inhalation studies with particles and therefore, reduce the number of future animal acute inhalation tests.

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Presentation Summary

Title: "Acute Inhalative Toxicity Part 2: Non-specific particle effects now trigger classification"

Nils Krueger, PhD, DVM

Particulate substance such as titanium dioxide (TiO_2) or different forms of synthetic amorphous silica (SAS) are currently under regulatory scrutiny. Classification and labeling hazards (CLH) or use restrictions have been proposed, or already established (TiO_2). The particles of those substances all have in common a low bulk density and no systemic toxicity but either are already classified, or in the process to be classified as a hazardous or toxic substance under CLH in the EU.
High concentrations of low-density particles, such as hydrophobic SAS, can cause lethality in acute inhalation tests at a concentration up to 1000 mg/m³. Currently, no classification has been proposed by European authorities for SAS, or any other similar particle, except TiO_2, based on non-specific dust effects observed in repeated dose or short-term acute inhalation studies. The European Risk Assessment Committee (RAC) proposed for one form of a hydrophobic SAS the Acute Tox Cat 2 (fatal if inhaled) classification based on the lethality of test animals observed at 440 mg/m³. In contrast to humans, the rat is an obligatory nose breather. While restrained in a tube for 4 hours during acute inhalation studies, the rat can neither protect its nose nor carry out usual cleaning routines. In the case of lethality, the OECD guideline methods only require the count of dead animals and a rough macroscopical examination of the outer surfaces of the organs in the abdominal and thoracal cavity. A thorough pathological examination and a histopathological examination of the respiratory tract, especially the upper respiratory tract (nasal cavities), is not required. This OECD guideline protocol may be fully appropriate for most chemical substances with toxicological properties, but specific questions for poorly-soluble particles, such as mechanical blockage of the respiratory tract associated with suffocation as cause of mortality cannot be detected in most cases. Acute rat inhalation studies, focused on the clarification of the causes of mortality associated with low-density particles were performed with the highest technically-feasible concentration without significant alterations of the aerosol characteristics.