

NICEATM Poster Presentation

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The Use of Mouse Fibroblast (3T3) and Normal Human Epidermal Keratinocytes (NHK) Cytotoxicity Assays for Estimating Acute Oral Toxicity of Formulations and Mixtures

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The Registry of Cytotoxicity (RC), which consists of *in vivo* acute oral toxicity data from rats and mice and *in vitro* cytotoxicity data from multiple mammalian cell lines for 347 chemicals, was published in 1998 (Halle 1998). A regression model constructed from these data was proposed by ZEBET, the German National Center for the Documentation and Evaluation of Alternative Methods to Animal Experiments, as a method to reduce animal use by identifying the most appropriate starting doses for acute oral systemic toxicity tests (Halle 1998; Spielmann et al. 1999). The regression line, however, presents LD50 data in mmoles/kg body weight making it unsuitable for formulations and mixtures. NICEATM/ECVAM has performed a validation study to evaluate 3T3 and NHK cells in basal cytotoxicity assays with a neutral red uptake (NRU) cell viability endpoint to predict starting doses for the acute oral Up-and-Down Procedure (UDP). Linear regression models were determined using the log rat LD50 (mg/kg) versus the log IC50 (µg/mL) for the 55 RC chemicals evaluated in this study. This regression line was compared to a similarly derived regression utilizing the RC dataset for these chemicals and was found to be in agreement. A review of the NICEATM/ECVAM data and the RC data confirms that those chemicals with known mechanisms of toxicity (i.e., cholinesterase inhibitors, etc.) or those requiring metabolic activation are often discordant with the model. By removing these chemicals from the analysis, a newly derived linear regression utilizing the RC dataset of rat LD50 values (285/347 chemicals) in mg/kg body weight may be suitable for estimating the starting doses for rat LD50 determinations for formulations and mixtures using the UDP. A similar model can be derived for the mouse utilizing the RC dataset (242/347 chemicals). Supported by NIEHS contract N01-ES-35504.

SOT Itinerary Information:

ID# 1969
Location: Exhibit Hall (Convention Center)
Date/Time: March 8, 2006 / 1:30 – 4:30 pm
Category: Alternatives to Mammalian Models, (Regulatory/Policy)