NICEATM Poster Presentation

Society of Toxicology
44th Annual Meeting
March 6 - 10, 2005
New Orleans, LA

Evaluation of a Solubility Protocol for *In Vitro* Cytotoxicity Testing

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A standardized solubility protocol was tested as part of a NICEATM and ECVAM multi-laboratory validation study to evaluate the usefulness of two *in vitro* basal cytotoxicity assays for estimating rodent and human acute systemic toxicity. The intent of the protocol was to guide the selection of solvent for 72 coded chemicals and to evaluate the interlaboratory variation in solvent selection. Chemicals were tested in each of four labs for solubility in culture medium, dimethyl sulfoxide (DMSO), and ethanol (ETOH) in a hierarchical solubility protocol that favored the order listed. Solubility in DMSO and ETOH was tested at concentrations 100X greater than medium to adjust the solubility test concentrations of all solvents to equivalent concentrations to be used in the cytotoxicity assays. Chemicals were tested at successively lower concentrations that differed by fixed intervals. The criterion for solubility was a clear solution with no evidence of precipitate after vortexing, sonicating, and mild heating, as necessary. All four labs agreed on the solvent for 52 (72%) chemicals, and on both solvent and maximum concentration for 42 (58%) chemicals. For 7 of the remaining 20 chemicals, three of four labs agreed on the solvent and maximum concentration. For the remaining 13 chemicals, at least two labs agreed on the solvent, but not necessarily the highest concentration. The final solvents selected were media for 37 chemicals, DMSO for 35 chemicals, and ETOH for 0 chemicals. These data show that the protocol provided good interlaboratory reproducibility for most chemicals, but that differences in solvent selection may occur that could affect the maximum tested concentration and study outcome.
Supported by: N01-ES-35504, N01-ES-75408; EPA IAG DW-75-93893601-0; European Commission 19416-2002-04 F2ED ISP GB.

SOT Itinerary Information:

ID#	484
Location:	Exhibit Hall
Date/Time:	March 7, 2005 / 1:30 - 4:30 PM
Category:	Safety Evaluation-Evaluation of Methods In *Vitro/In Vivo*