NICEATM Poster Presentation

Society of Toxicology
45th Annual Meeting
March 5 - 9, 2005
San Diego, CA

Reducing Animal Use in Acute Systemic Toxicity Testing by Using *In Vitro* Cytotoxicity Assays for Estimating Starting Doses

J.A. Strickland[1,2]; M.W. Paris[1,2]; S. Casati[3]; R.R. Tice[2]; W.S. Stokes[2]; R. Lee[4]; E. Harvey[4]; J. Haseman[5]; H. Raabe[6]; C. Cao[7]; R. Clothier[8]; G. Mun[4]; A. Sizemore[6]; G. Moyer[6]; J. Madren-Whalley[6]; C. Krishna[7]; M. Owen[8]; N. Bourne[9]; M. Wenk[9]; M. Vallant[10]

1. Integrated Laboratory Systems, Inc., RTP, NC, USA.
2. NICEATM, NIEHS/NIH/DHHS, Research Triangle Park, NC, USA.
3. ECVAM, JRC, Ispra, Italy.
4. Constella Group, Durham, NC, USA.
5. Consultant, Raleigh, NC, USA.
6. IIVS, Gaithersburg, MD, USA.
7. US Army ECBC, Aberdeen Proving Ground, MD, USA.
8. Univ. of Nottingham, Nottingham, United Kingdom.
9. BioReliance Corp., Rockville, MD, USA.
10. NIEHS, NIEHS/NIH/DHHS, Research Triangle Park, NC, USA.

NICEATM and ECVAM organized a multi-laboratory validation study to evaluate the use of two neutral red uptake (NRU) *in vitro* basal cytotoxicity test methods for predicting starting doses for acute oral systemic toxicity assays such as the Up-and-Down Procedure (UDP). IC_{50} values from 72 coded chemicals tested in the mouse fibroblast BALB/c (3T3) and normal human keratinocyte (NHK) NRU assays were used with IC_{50}-oral LD_{50} regressions to predict LD_{50} values, which were then used as starting doses for computer simulated UDP testing. Simulated UDP testing of each chemical was employed to determine animal use and animal deaths using the default starting dose or the starting dose determined by each NRU method. UDP testing was simulated 2000 times for each starting dose for each chemical. Using the Registry of Cytotoxicity IC_{50}-LD_{50} regression, average animal savings (compared to the default starting dose of 175 mg/kg) for the test chemicals was 7% for both 3T3 and NHK NRU methods. For chemicals with low *in vivo* toxicity, average animal savings were much higher: 23% for 3T3 and 21% for NHK for chemicals with LD_{50} = 2000-5000 mg/kg; and 21% for 3T3 and 18% for NHK for chemicals with LD_{50} > 5000 mg/kg. For chemicals with LD_{50} values near the default starting dose, 50-300 mg/kg, there were no animal savings. Animal savings using other regressions were also evaluated. 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#	1968
Location:	Exhibit Hall (Convention Center)
Date/Time:	March 8, 2006 / 1:30 – 4:30 pm
Category:	Alternatives to Mammalian Models, (Safety Evaluation), (Biological Modeling)