

## **A Reference Database for the Evaluation of Alternative Tests for Acute Dermal Systemic Toxicity**

J Strickland<sup>1</sup>, F Stack<sup>1</sup>, M Paris<sup>1</sup>, L Rinckel<sup>1</sup>, W Stokes<sup>2,3</sup>, W Casey<sup>2</sup>

<sup>1</sup>NICEATM/NTP/HHS, RTP, NC, USA; <sup>2</sup>ILS, Inc., RTP, NC, USA; <sup>3</sup>Current affiliation: Kelly Services, Inc., NIEHS, RTP, NC, USA

Alternatives for acute systemic toxicity testing are one of the highest priorities of ICCVAM and NICEATM. These are the most commonly performed product safety tests worldwide and are required by multiple U.S. Federal agencies. Acute toxicity testing can involve large numbers of animals and result in significant unrelieved pain and distress to test animals. High quality reference data are needed to evaluate alternative toxicity tests that may reduce, refine (enhance animal well-being and lessen or avoid pain and distress), and replace the use of animals for acute dermal systemic toxicity testing. To identify appropriate reference data for the acute dermal systemic toxicity test, NICEATM collected and analyzed data for 1897 substances. Rabbits were used for 28% (526) of the studies, and rats were used for 72% (1371). Of the 1897 substances, 84% (1598/1897) had data for both male and female animals, and 98% (1561/1598) of those substances were in the same GHS dermal hazard category. For the 37 substances that showed a different dermal hazard category between the sexes, female values were more often in a higher hazard category (21 for females vs. 16 for males). Two hundred forty six studies reported day of death. Approximately two thirds of the deaths (67% of male deaths [513/761]; 63% of female deaths [463/733]) occurred by Day 2 after a 24-hour dermal treatment on Day 0. Eighty-five substances had sufficient data to calculate dermal dose–mortality slopes. Dose–mortality slopes did not vary by species, sex, or GHS hazard category. As expected, the dermal dose–mortality slopes were lower than acute oral dose–mortality slopes. These data were used to design a proposed sequential test for acute dermal systemic toxicity, the dermal up-and-down procedure, to reduce the number of animals tested for acute dermal hazard classification. Supported by ILS staff under NIEHS Contract N01-ES-35504.