

The Dermal Up-and-Down Procedure: An Alternative Test Method for Acute Dermal Systemic Toxicity Testing

W Stokes^{1,4}, J Strickland², R Morris³, L Ho³, J Wilkerson³, F Stack², M Paris², L Rinckel², W Casey¹

¹NICEATM/NTP/HHS, RTP, NC, USA; ²ILS, Inc., RTP, NC, USA; ³SRA International, RTP, NC, USA; ⁴Current affiliation: Kelly Services, Inc., NIEHS, RTP, NC, USA

Acute dermal systemic toxicity testing is required to identify chemicals and products that have the potential to cause life-threatening or fatal toxicity following skin exposures. Such testing is one of the five most commonly conducted safety tests and requires up to 20 or more animals per test. A dermal up-and-down procedure (UDP) was developed to estimate acute dermal toxicity hazard classification categories with fewer animals. The UDP incorporates an efficient experimental design using sequential testing to estimate LD₅₀ rather than the simultaneous testing of multiple groups of animals at multiple doses, as specified by current regulatory test guidelines. In the dermal UDP, individual animals are dosed sequentially, and the response of each animal after 48 hours is used to determine the dose applied to the next animal. If a dose produces significant toxicity, the next animal is tested at a lower dose. Conversely, if no significant toxicity is observed, the next animal is tested at a higher dose, with the highest dose not to exceed a pre-specified limit dose. Unless there is a basis for a lower starting dose, the initial dermal UDP starting dose is the appropriate limit test dose (2000 or 5000 mg/kg). The default dose-progression factor for subsequent doses is 4.2. If the expected LD₅₀ is less than the default starting dose, testing is started at one dose below the closest default dose. Using a starting dose of 5000 mg/kg, default doses are 5000, 1200, 300, 70, 15, and 4 mg/kg, while the default doses for a starting dose of 2000 mg/kg are 2000, 500, 100, 25, and 5 mg/kg. The dermal UDP provides LD₅₀ point estimates and confidence limits for dermal hazard classifications while using up to 85% fewer animals. The proposed dermal UDP can support accurate hazard identification while significantly reducing animal use. Supported by ILS staff under NIEHS Contract N01-ES-35504 and SRA staff supported by NIEHS Contract GS-23F-9806H.