E4: The Use of *In Vitro* Data to Estimate Starting Doses for Acute Oral *In Vivo* Studies

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The Register of Cytotoxicity (RC) currently contains *in vitro* cytotoxicity data (IC50) and *in vivo* oral toxicity data (LD50) for 500 chemicals. A linear regression of the RC data was used to develop a prediction model (PM) that we propose for prediction of starting doses for *in vivo* studies in order to further reduce animal use. The total number of animals used in the 3 oral toxicity-testing methods, Fixed Dose Procedure (FDP), Acute Toxicity Class Method (ATC), and Up-and-Down Procedure (UDP), is dependent on the distance between the starting dose and true LD50. For the UDP, for example, if no information is available, a starting dose of 175 mg/kg is recommended. Applying the PM will, in many instances, estimate a starting dose that is closer to the actual LD50 than the 175 mg/kg figure. This typically will result in fewer animals that need to be used before achieving the first reversal in the UDP test. The greatest reduction in animal use occurs for those chemicals that have an LD50 above the limit dose, especially 5g/kg. Thus, if the *in vitro* test predicts an LD50 above 5g/kg, 3 animals would be used, rather than 6 animals, if dosing were started at 175 mg/kg. In this example a 50% reduction in animal use would be achieved, as well as a timesaving of 6 days. The procedure to check suitability of a cytotoxicity test protocol and the potential reduction in animal use for the FDP, ATC, and UDP will be presented.