In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Rat Acute Oral Toxicity Tests: Impact on Animal Savings

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A multi-laboratory international validation study evaluated the reduction in animal use and deaths when two *in vitro* neutral red uptake (NRU) basal cytotoxicity test methods were used to predict starting doses for two *in vivo* acute oral toxicity test methods. NRU IC_{50} values for up to 68 coded chemicals were used with regression models developed from the rat oral LD_{50} values and corresponding IC_{50} values from the Registry of Cytotoxicity to determine starting doses for computer simulated *in vivo* tests. For each chemical, the number of animals used and that died using either the default starting dose or the IC_{50}-based starting dose was computed. Using the NRU methods produced animal savings of up to 28% (average savings 5-10%). Compared with the default starting dose, the IC_{50}-based starting doses produced fewer deaths in one *in vivo* test method but not for the other. A weight unit IC_{50}-LD_{50} regression, developed to evaluate mixtures, produced similar animal savings but has not been tested with mixtures. These data demonstrate that *in vitro* cytotoxicity methods can be used to reduce the number of animals required for acute oral toxicity testing. Supported by: NIEHS contracts N01-ES-35504, N01-ES-75408; EPA IAG DW-75-93893601-0; European Commission 19416-2002-04 F2ED ISP GB.