In Vitro Cytotoxicity Test Methods for Estimating Rat Acute Oral Toxicity: Prediction of GHS Acute Oral Toxicity Categories

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A multi-laboratory international validation study evaluated the accuracy of Globally Harmonized System (GHS) acute oral toxicity category predictions using IC_{50} values from two *in vitro* neutral red uptake (NRU) basal cytotoxicity test methods with two IC_{50}-LD_{50} regressions developed from the 282 rat oral LD_{50} values and corresponding IC_{50} values from the Registry of Cytotoxicity (RC). One regression was based on molar units of chemicals and the other was based on weight units. Predicted LD_{50} values were used to classify up to 68 coded chemicals into GHS acute oral toxicity categories. The accuracy of the two NRU test methods and regressions for predicting GHS acute oral toxicity categories was 29-31%. Toxicity was overpredicted for 33-40% of the chemicals and underpredicted for 31-36% of the chemicals. Accuracy was highest for chemicals in the $300 < LD_{50} \leq 2000$ mg/kg range (75-81%) and lowest for chemicals with $LD_{50} \leq 5$ mg/kg (0%) or with $LD_{50} > 5000$ mg/kg (0-17%). For comparison, overall accuracy for predicting GHS categories using the RC IC_{50} values and the original RC regression was 40%. These results indicate that *in vitro* basal cytotoxicity tests are not sufficiently accurate when used alone for predicting GHS acute oral toxicity hazard classification. Supported by: NIEHS contracts N01-ES-35504, N01-ES-75408; EPA IAG DW-75-93893601-0; European Commission 19416-2002-04 F2ED ISP GB.