An Alternative Use of *In Vitro* Cytotoxicity Test Data to Determine When Rat Acute Oral Toxicity Testing Should Start with the Limit Test

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Depending on the specific regulatory needs, acute oral toxicity test guidelines (i.e., the Up-and-Down Procedure [OECD TG 425] and the Acute Toxic Class method [OECD TG 423]) indicate that substances suspected to have LD_{50} > 2000 mg/kg or LD_{50} > 5000 mg/kg should be tested with the corresponding limit test using a small number of animals to confirm their lack of toxicity. Graphical plots of *in vitro* basal cytotoxicity IC_{50} (μg/mL) values vs. LD_{50} (mg/kg) values for the 418 Registry of Cytotoxicity chemicals with rat oral LD_{50} data were used to determine if the IC_{50} values could predict whether chemicals should be tested with the limit test instead of the main test, thereby reducing the use of animals. Chemicals with LD_{50} values less than the limit doses were categorized as positives (toxic) while those with LD_{50} values greater than the limit doses were categorized as negatives (nontoxic). Counts of chemicals above and below targeted IC_{50} cutoff values were used to calculate performance characteristics for the prediction of positive/negative. IC_{50} values ranging from 1 to 10,000 μg/mL were used to predict positive/negative at LD_{50} > 2000 mg/kg or LD_{50} > 5000 mg/kg. In each case, high false negative rates would be associated with an increase in the number of animals that die during testing, while high false positive rates would be associated with an increase in the total number of animals tested. For both limit doses, high IC_{50} values (≥ 1000 μg/mL) yielded high (≥ 79%) accuracy and sensitivity (i.e., low false negatives), but with low (< 63%) specificity (i.e., high false positives). Conversely, low IC_{50} values (≤ 60 μg/mL) yielded high (≥ 85%) specificity (i.e., low false positives), but low (≤ 62%) accuracy and sensitivity (i.e., high false negatives). These data can be used to identify the optimal IC_{50} values to indicate that testing should start with the limit test.
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