6.0   GLOSSARY

Note: These definitions are based on (1) definitions used by one or more Breakout Groups at the *In vitro* Workshop or (2) a commonly used interpretation or definition.

Acute Toxic Class Method (ATC): An *in vivo* approach to assessing acute toxicity that tests animals in a step-wise fashion. Based on mortality and/or morbidity (or absence thereof), testing continues at the next highest (or lowest) fixed dose until an adequate assessment can be made. The method usually entails testing at two to four step-wise doses.

Acute Toxicity: The adverse effects occurring within a relatively short time after administration of a single dose of a substance or multiple doses within a 24-hour period. BG3 added: *"toxicity occurring within 14 days of a single exposure or multiple exposures within 24 hours"*.

Acute Systemic Toxicity: Acute effects that require absorption and distribution of the toxic agent from its entry point to a distant site at which adverse effects are produced vs. acute local toxicity.

ADAPT: (Automated Data Analysis by Pattern recognition Techniques); commercially available QSAR system for the evaluation of LD50s and MTDs; available from the laboratory of Peter Jurs, Penn State University.

ADME: biokinetic information on Absorption, Distribution, Metabolism, and Excretion.

Biotransformation: the series of chemical reactions of a compound in a biological system occurring within the body usually due to enzymatic metabolic reactions.

CASE: (Computer Automated Structure Evaluation); commercially available QSAR software

Cytotoxicity: The adverse effects of interference with structures and/or processes essential for cell survival, proliferation, and/or function. These effects may involve the integrity of membranes and the cytoskeleton, metabolism, the synthesis and degradation or release of cellular constituents or products, ion regulation, and cell division.

  Basal cytotoxicity: Involves one or more of the above mentioned structures or processes that would be expected to be intrinsic to all cell types.   Sometimes called general cytotoxicity.

  Selective cytotoxicity: Occurs when some types of differentiated cells are more sensitive to the effects of a particular toxicant than others, potentially as a result of, for example, biotransformation, binding to specific receptors, or uptake by a cell type specific mechanism.

  Cell specific function cytotoxicity: Occurs when the toxicant affects structures or processes that may not be critical for the affected cells themselves, but which are critical for the organism as a whole. For example, such toxicity can involve effects on cell to cell communication, via the synthesis, release, binding and degradation of cytokines, hormones and transmitters.

DEREK: (Deduction of Risk from Existing Knowledge); commercially available knowledge-based QSAR expert system.

EUCLID: (Electronically Useful Chemistry Laboratory Instructional Database); database of industrial chemicals tested in Europe maintained by the European Union.

Fixed Dose Procedure (FDP): An *in vivo* approach to assessing acute toxicity that avoids using death of animals as an endpoint, but instead uses the observation of clear signs of toxicity at one of a series of fixed dose levels. Instead of providing an LD50 value, this method estimates a range in which the LD50 of the test substance is estimated to occur.

Galileo: A publicly available database of chemicals that have been tested for toxicity (from alternative studies, mostly related to cosmetics testing).

Globally Harmonized System (GHS): Co-ordinating Group for the Harmonization of Chemical Classification Systems (CG/HCCS) was

established to promote and oversee the work to develop a GHS. The group would integrate the harmonized classification scheme with a harmonized hazard communication system to give an overall Globally Harmonized Classification and labeling System (GHS): OECD-sponsored.

IC50: (Inhibitory Concentration 50); the concentration of a material estimated to inhibit the biological endpoint of interest (e.g., cell growth, ATP levels) by 50%.

LD50: (Median Lethal Dose); a statistically derived single dose of a substance that can be expected to cause death in 50% of animals. This value is expressed in terms of the weight of the test substance per unit weight of the test animal.

LD50 Test, Conventional: An *in vivo* approach to assessing acute toxicity that tests several dose levels using groups of animals. Doses selected are often determined from a range-finding study. Observations of mortality and morbidity, as well as effects, are made for each dose group, and the LD50 is derived based on those observations.

MCASE: (Model-based Computer Automated Structure Evaluation); commercially available QSAR system for the evaluation of LD50s and MTDs available from Multicase, Inc.

Moribund: A clinical condition of a test animal that is indicative of impending death. Animals in the moribund state are humanely killed and are considered for acute toxicity testing purposes in the same way as animals that died.

MEIC: Multicenter Evaluation of In Vitro Cytotoxicity. Established by the Scandinavian Society for Cell Toxicology in 1989 to investigate the relevance of *in vitro* test results for predicting the acute toxic action of chemicals in humans directly rather than in rodents.

MEIC approach: The MEIC team collected case reports from human poisonings with the 50 reference chemicals to provide LC data with known times between ingestion and sampling/death. Constructed time-related LC curves for comparison with the IC50 values for different incubation times *in vitro (see.* 50 MEIC

Monographs [MEMO]). Analyses of test results were based on *in vitro* cytotoxicity data presented as IC50 values. The predictability of *in vivo* acute toxicity from the *in vitro* IC50 data was assessed against human lethal blood concentrations compiled from three different data sets: clinically measured acute lethal serum concentrations, acute lethal blood concentrations measured post-mortem, and peak lethal concentrations derived from approximate LC50 curves over time. The analysis showed that *in vitro* assays that were among the most predictive generally used human cell lines. Human-derived cells appeared to be the most predictive for human acute toxicity. The most predictive and cost-effective test battery consisted of four endpoints/two exposure times (protein content/24 hours; ATP content/24 hours; inhibition of elongation of cells/24 hours; pH change/7 days) in three human cell line tests. The test battery was found to be highly predictive of the peak human lethal blood concentrations of all 50 chemicals when incorporated into an algorithm developed by the team.

Mortality: Death of the test animals presumably due to the toxicity of the test material.

Predictive range: Range for various chemical properties over which the *in vitro* assay might be expected to provide reasonable LD50 estimates.

Quantitative Structure Activity Relationships (QSAR): The measurable biological activity of a series of similar compounds based on one or more physicochemical or structural properties of the compounds.

Registry of Cytotoxicity (RC): ZEBET database of acute oral LD50 data from rats and mice (taken from the NIOSH Registry of Toxic Effects of Chemical Substances [RTECS]) and IC50x values of chemicals and drugs from *in vitro* cytotoxicity assays. Currently contains data on 347 chemicals.

TOPKAT: (The Open Practical Knowledge Acquisition Toolkit); commercially available QSAR software.

Toxicokinetics: kinetics or biokinetics (BG2 definition).

Up-and-Down Procedure (UDP): An *in vivo* approach to assessing acute toxicity. Animals are dosed, one at a time, at 48-hour intervals. The first animal receives a dose at the investigator's best estimate of the LD50, and subsequent animals are given a higher or lower dose depending on the survival of the previous animal. After reaching the point where an increasing (or decreasing) dose pattern is reversed by giving a small (or higher dose), four additional animals are dosed following the same method, and the LD_{50} is calculated using the method of maximum likelihood.

ZEBET approach: Strategy to reduce the number of animals required for acute oral toxicity testing; Strategy involves using *in vitro* cytotoxicity data to determine the starting dose for *in vivo* testing. Researchers report the findings of an initial study conducted to assess the feasibility of applying the standard regression between mean IC50 values (i.e., IC50*x*, the mean concentration estimated to affect the endpoint in question by 50%) and acute oral LD50 data included in the Register of Cytotoxicity (RC) to estimate the LD50 value which can then be used to determine the *in vivo* starting dose.

ZEBET: Zentralstelle zur Erfassung und Bewertungvon Ersatz- und Ergänzungsmethoden zum Tierversuch (Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments)