

## WP1: Generation of a database with toxicity data from animal tests and human accidents (in vivo data)

WP1 has been responsible for generation of an *in vivo* acute toxicity database for the 97 selected ACuteTox reference chemicals. The main purpose of this database is to enable evaluation and calibration of the data generated by *in vitro* toxicity testing in other WPs and in particular to allow validation of the ensuing *in vitro* test strategy. The *in vivo* compilation covered mammalian acute toxicity studies (LD50 experiments) derived from published literature, and human acute poisoning cases (blood concentration measurements, including victim observations) available from clinical/forensic medical reports. Over 2200 LD50 values have been compiled from rodent (rat, mouse) and other studies, including various administration routes (oral, intravenous, etc.). Nearly 2800 human cases have been compiled, comprising three categories of single dose (exposure) acute poisoning, each with/without time information, *viz*: sub-lethal, lethal, and post-mortem (Table 1). WP1 has also contributed to compilation of physical-chemical properties for the reference chemicals and summary descriptions, including toxicokinetic and pharmacokinetic data. All information about the chemicals has been entered into AcuBase (see WP3).

**Table 1. Totals of animals studies and human cases compiled for the 97 reference chemicals**

Animal acute toxicity			Human acute poisoning: (a) time related, (b) without time					
Rat	Mouse	Other	Sublethal (a)	Sublethal (b)	Lethal (a)	Lethal (b)	Postmortem (a)	Postmortem (b)
921	906	376	908	377	436	372	215	472

The distribution of animal studies and human cases was variable among the reference chemicals. In particular, availability of human poisoning data was frequently limited by improbable occurrence of acute exposure (i.e., accidental ingestion, suicidal overdose, etc.) and/or unknown clinical/forensic monitoring of a patient/victim with reported blood concentration measurements. Twelve reference chemicals remain without any reported acute poisoning cases.

A statistical evaluation of the animal data indicates good reproducibility. Furthermore, rat and mouse mean LD50 were highly correlated with two exceptions: warfarin and cycloheximide were much more toxic in the rat. Regression of human acute lethal doses with rat oral LD50 data for 30 reference chemicals resulted in a coherent correlation with slope 0.955, intercept -0.615, and coefficient of determination 0.571, which was similar to results obtained in the MEIC study (Ekwall et al 1998). For 62 reference chemicals, EU/GHS toxicity classifications/categories were allocated, corresponding to respective maximum and minimum LD50 values. Fifty seven (92%) and 53 (85%) of the chemicals (EU and GHS, respectively) display individual ranges of LD50 limited to two adjacent classification categories. For 4 (6%) and 7 (11%) of the chemicals (EU and GHS, respectively) LD50 values span three different classifications. For 1 (1.6%) and 2 (3%) of the chemicals (EU and GHS, respectively) cited LD50 values allow scope for more than three different classifications.

### References:

Ekwall, B. et al (1998) MEIC evaluation of acute systemic toxicity: Part VI. The prediction of human toxicity by rodent LD50 values and results from 61 *in-vitro* methods. *ATLA* 26: 617-658.