

Kinetic considerations for the interpretation of *in vitro* toxicity data in risk assessment

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Toxicity data derived from *in vitro* experiments are normally expressed as the concentrations giving a certain degree of effect, e.g. the concentration resulting in 50% of the maximal effect (EC₅₀). This type of data is of relevance for the assessment of the mechanism of toxicity and the toxic hazard of the compound under study.

The interpretation of these results in terms of risk, however, requires the “translation” of the data towards the expected exposure in an intact organism. Thus, the relevance of the EC₅₀s, expressed as molar concentrations will need to be converted to the amount (i.e. the dose) to which the organism is exposed.

Issues to be considered are:

1. what is the actual (free) concentration to which the cells in an *in vitro* system are exposed to;
2. are there relevant differences in the conditions of exposure at a cellular level between the *in vitro* systems and the situation *in vivo*, e.g. with regard to protein binding, evaporation, etc.;
3. what factors are involved in the distribution of the compound in an intact organism;
4. to what extent is the absorption of the compound (e.g. after oral exposure) a limiting factor for systemic exposure of target cells?

Issues mentioned under 1) and 2) – the biokinetics *in vitro* – are considerations that should be taken into account in designing and interpreting *in vitro* toxicity systems in general.

Regarding 3) and 4), an evaluation was made of the most important parameters determining the distribution of compounds, making use of physiologically based biokinetic (PBBK) modelling. The models showed that determining factors are the lipophilicity, the intrinsic clearance, plasma protein binding and the absorption rate in the gastro-intestinal tract. These parameters can either be estimated from physico-chemical properties of the test compound under study, or by determining them in *in vitro* systems.

Making use of these modelling parameters, a conversion was calculated of the EC₅₀ values for cytotoxicity determined in the A-Cute-Tox programme to toxic doses (LD₅₀s). It was shown that the correlations with the experimentally determined LD₅₀ in rodents considerably improved.