An analysis of the limitations and uncertainties of animal based toxicity assessments to identify the potential for non-animal approaches in regulatory toxicology

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INTRODUCTION

Change towards regulatory reliance on non-animal-methods (NAMs) appears essential in the light of the current green policy advocating challenging goals like safe and sustainable chemicals and a comprehensive (eco)toxicological knowledge base on chemicals allowing to work towards a zero-pollution goal . A critical challenge for the greater reliance on NAMs is the difficulty of deciding on acceptable uncertainty from their use. Transparency on the limitations and uncertainties of current animal testing based approaches may provide a useful, objective benchmark that may support such decision making.

METHODOLOGY

For a set of different regulatory endpoints, i.e. developmental neurotoxicity, carcinogenicity and acute aquatic toxicity, a systematic description of the limitations and uncertainties of animal testing based approaches was carried out in qualitative and quantitative terms [1-3]. This was accomplished by re-purposing an OECD format originally developed to characterize NAMs [4]. The tabulated information was compared with the conceptual uncertainties of the respective NAM based approaches. Similarities between the three different endpoints are discussed.

RESULTS

The following conclusions appear valid for the three analysed regulatory fields and may therefore be equally relevant for all fields of regulatory toxicology:

- The relative practical advantages of NAM based approaches are the abolishment of the 3Rs conflict, the higher throughput, the lower costs and the deeper mechanistic information.
- Relative to animal tests, NAMs are usually standardised to a higher degree and validated for experimental variability. Moreover, for NAMs the basic study design is much easier to improve in terms of replicates, number of concentrations, and

inclusion of study-internal positive controls and the development of a larger historical negative and positive control database.

- The extrapolation from experimental animal data to real life, be it human or multi-species environments, is necessarily uncertain. Pragmatism and data-based extrapolation models are needed for the regulatory use of experimental animal data. Mode of action coverage is limited and uncertain. Similar considerations apply to the use of NAMs.

DISCUSSION

NAMs allow (eco)toxicological data to be generated for many more chemicals, providing mechanistic information for extrapolation needs and providing lower uncertainty for data variability. This can increase the availability, reliability and chemical-to-chemical comparability of (eco)toxicological data for globally effective safety regulation. Assessing the significant uncertainties for extrapolation from animal test data to real human or multi-species environments, it appears realistic that with the use of NAMs at least similar protection levels can be achieved than with animal test data. This work on systematic uncertainty analysis of animal tests was already carried out for eye irritation [5, 6] , skin sensitisation [7, 8], acute rodent toxicity [9], in vivo point of departure derivation [10] and is currently being followed up more broadly by the US National Academy of Science . This information shall be used for the development of NAM based IATAs for developmental neurotoxicity, non-genotoxic carcinogenicity and acute aquatic toxicity which is ongoing at OECD level [11-14]. However, ultimately out of the box thinking will be necessary to fully rely on NAMs in regulatory toxicology.