

## **Background and aims**

In risk assessments of exposure to environmental chemicals, derivation of human exposure standards is often based partly on animal data. The overall aim of project B10 is to provide a systematic and quantifiable comparison of NOAELs and Reference Values (RVs) identified from animal studies with those from human studies for a range of chemicals, and to develop robust evidence synthesis (meta-analytical) methodology combining all available information for identification of an integrated NOAEL or RV.

## **Comparison of human- and animal-based limits**

About 170 substances for which substantial human and animal data are available were identified using systematic literature review approaches. A purposive sample of 20 was chosen from them to include substances in several categories (metals, solvents, pesticides, other) for which appropriate human (and animal) data were likely to be available, and to cover a range of adverse health effects. In this subsample, where data were of sufficient quality, comparison of the RVs identified from human data with those from animal data, and investigation of factors affecting the relationship between animal- and human- based RVs were undertaken.

Although for some substances the human-based and animal-based RVs are very similar, some differ by factors of order 10 (and in isolated cases, more than this). Exploratory analyses do not reveal clear patterns of variation of the ratios of the human- and animal based RVs.

## **Combination of human and animal data**

Building on available cross-design evidence synthesis methods, development of (meta-analysis) techniques for combining human and animal data in derivation of RVs is explored. A proof-of-principle example demonstrates the potential impact of joint modelling of animal and human data on standard setting, and more broadly on the design of studies and programmes of investigation to underpin such standard setting. However, implementation of joint modelling of human and animal data in practice is much more problematical, with further development and systematization of the approach being needed.

## **Recommendations for risk assessment practice and research include:**

- The increasing use and documentation of systematic review approaches in compiling human and animal data underpinning RV calculations should be adopted as universal practice.
- Similarly, reasons for final preference being given to use of human or animal data, particular endpoints, and particular studies\data sets should be explicitly stated.
- Approaches (beyond use of 'uncertainty factors') to acknowledging and quantitative reporting of uncertainty in estimated RVs and other critical values should be adopted

- Further comparison of RVs based on human data with those based on animal data should be explored in a larger set of potentially comparable human- and animal-based RVs. Similarly, critical appraisal and comparison of synthesis of evidence from both animals and humans, in key examples, with synthesis of evidence from animals alone, or from humans alone will be needed.

### **Conclusions**

From the comparisons of animal- and human-based RVs undertaken here it cannot be safely concluded that RVs based on human data are generally higher or lower than those based on animal data. Evidence supporting reliable substitution of animal-based and human-based RVs for each other is lacking. The added value of combining both epidemiological and toxicological data in calculating RVs is being investigated in further examples drawn from the study.