Summary of project B10 for CEFIC website

Background and aims

In risk assessments of exposure to environmental chemicals, derivation of human exposure standards is often based 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.

As is to be expected, there was considerable variation between substances in respect of the nature and extent of data considered in setting of reference values by regulatory agencies. In part this stems from decisions en route through the regulatory process. Amongst reasons for this are 1) the type of chemical and whether there are specific data requirements; 2) the date of the assessment; 3) variations between agencies and individuals with respect to the detail in which studies are summarised; 4) variations of study design; 5) data on health endpoints not regarded as critical at an early stage being unlikely to be reported in as much detail as those on the critical endpoints; and 6) similarly, collection and reporting of human and animal data not regarded as of comparable quality and relevance to standard setting being less likely to be pursued with equal completeness and rigour.

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 revealed clear patterns of variation of the ratios of the human- and animal based RVs or any differential patterns regarding the values of UFs used, or the dependence on NOAEL or BMD as the point of departure if benchmark dose calculations were used. There is perhaps a weak suggestion that human-based values are higher than the corresponding animal-based value more often than vice versa.

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 (chlorinated by-products and adverse reproductive effects) demonstrates that, in appropriate circumstances, there is potentially an advantageous impact of joint modelling of animal and human data on standard setting compared to their separate use, and more broadly on the

design of studies and programmes of investigation to underpin such standard setting. The methods so developed yield both dose-response relationships and uncertainty estimates based on multi-species evidence which can be incorporated into standard approaches to standard or limit setting, and a transparent, quantified approach to designing future research for optimum data collection. This transparency allows the results and the procedure leading to them to be a) appropriately appraised and checked, b) reproduced by others if necessary, and c) easily updated or modified, for example to incorporate additional data as they become available. Sensitivity analyses allow direct and quantitative assessment of the impact of assumptions including a) relevance assessments, and b) omission of studies, for example on grounds of study quality. Generalisation of the approach to different dose-response models is conceptually straightforward, although of course data limitations may still be important. However, implementation of joint modelling of human and animal data in practice still requires further development and systematization.

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 currently being investigated in further examples drawn from the study.