Guidelines for Application of Data-Derived Uncertainty Factors in Risk Assessment

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Since the early 1980s several scientists have published improvements to methods by which the risks are assessed from the noncancer toxicity. The work described here not only builds on these previous efforts, but can be viewed as only a small contribution to the overall effort. The reader is directed to the bibliographies of the full text references enclosed at the end of this text for additional work.

The purpose of this report is to describe a brief meeting of investigators of the data-derived uncertainty factor approach for estimating tolerable intakes, acceptable daily intakes or reference doses/concentrations. This meeting was designed to move beyond the default uncertainty factors of the IPCS (1994) scheme, by providing an initial description of criteria for the sufficiency of data for use as the basis of data-derived uncertainty factors. The results of this brief meeting are intended to be reviewed and enhanced by other interested scientists and governing bodies.

Animal and human data must be compared on the basis of the measurement of similar endpoints that are relevant to the critical effect. This comparison should consider all available toxicity studies, including all available studies on potential mechanisms of toxicity, modes of action, and biological plausibility. One should recognize that *in vivo* toxicity studies can often give results that reflect both kinetic and dynamic differences, and that some information on either, or both, can be wrought from such studies.

Specifically, for consideration of adequacy of data to replace the default value for the toxicokinetic component of data within humans, or between humans and animals, a number of points should be considered. These include:

- Was it the same chemical species?
- Same active chemical species?
- Was it the correct animal species?
- Is delivery of active substances via the blood?
- Is the effect local or systemic following absorption and distribution?
- Are the numbers of animals and humans studied for interspecies comparisons adequate?

- Are the numbers and range of human studies for inter-individual comparisons adequate?

An essential element of such comparisons is quantification of key kinetic parameters for the particular chemical, based on delivery to the target organ (e.g., C_{max} or the AUC in plasma or target organ). These parameters should be influenced by a chemical's absorption, distribution, metabolism and elimination (ADME). Comparison between humans and experimental animals, would be helpful to generate a general sense of how species might compare. A good PBPK model was considered the best basis for a quantitative interspecies comparison, followed by a good kinetic study in both experimental animals and humans where issues of chemical species, route of administration, amount of dose or concentration, and length of exposure are all carefully evaluated.

Ideally, the most relevant kinetic data are those in humans at environmental exposures, or from doses or concentrations that are anticipated to be near the human ADI, RfD, RfC or TI. The collection of such data must follow strict protocols as laid out by the Helsinki agreement or others as appropriate. A comparison is then made of such human information with kinetics data from animals. Kinetic information from experimental animals should be from doses or concentrations that are near the NOAEL or benchmark dose (BMD) range. For animal to human comparisons of kinetic parameters, the appropriate ratios of the mean kinetic values should be used. The ratio should be set up so that greater sensitivity in humans is seen as a number greater than 1, and less sensitivity in humans is seen as a number less than 1. This is because either value will be used as a data-derived factor in the denominator of the equation used to calculate the RfD/TI.

Specifically, for dynamics comparison of animal to human or within human data, a number of points should also be considered. These include:

- Did *in vitro* studies use the active chemical delivered via the blood?
- Did *in vitro* studies allow local activation and cyto-protection processes?
- Were the animal and human tissues processed in such a way as to ensure comparable stability and activity (e.g., of enzyme systems)?
- Were relevant *in vitro* concentrations used?
- Is the endpoint measured critical for the adverse effect giving the NOAEL?
- Are the numbers of animals and humans studied for interspecies comparisons adequate?
- Are the numbers and range of human studies for inter-individual comparisons adequate?

Furthermore, the critical endpoint, or a related process, must be maintained in the cell lines, or other *in vitro* systems, in order for comparisons to be meaningful. In addition, dynamic comparisons should focus on concentrations giving the same response. If humans are unresponsive, then the choice of endpoint in animals should be questioned. This use of the data would not be "data-derived," but it could be used to inform other judgments or to modify default positions.

The basis of dynamic comparison must be relevant to the critical endpoint used as a basis of the RfD or TI. The quantitative determination of human toxicodynamic (and perhaps toxicokinetic) data-derived factors should compare mean values to 2 or 3 standard deviations away (as appropriate for endpoint). Comparison with sensitive subgroups should compare mean values in general population with 2 or 3 standard deviations away from the sensitive population mean value. Means values between these populations should not be used as the data-derived factor.

Acknowledgments: