
Executive summary

This advisory report is concerned with scientific developments that are important in relation to the use of so-called ‘uncertainty factors’ for the determination of health-based recommended exposure limits and for toxicological risk assessment. Such factors are used to make allowance for differences between laboratory animal species and humans, for inter-personal sensitivity variations and for shortcomings in the research data (chapters 1 and 2).

The report covers various scientific disciplines and methodologies. Toxicological insight into substance kinetics and dynamics is increasing all the time: the absorption, dispersion, metabolism and excretion of substances are increasingly well understood, as are the mechanisms by which substances can be toxic to organisms that are exposed to them. Various molecular analysis techniques, cell culture techniques and computer modelling methods are proving valuable in this context. In more and more cases, such methodologies make it possible to specify the qualitative and quantitative differences between laboratory animals and humans (chapter 3).

Chapter 4 reviews current scientific thinking with regard to appropriate numeric values for the various uncertainty factors. The basic principle advocated is that case-specific values should be assigned where possible, and default values used otherwise.

Epidemiologists are also looking for new ways of enhancing research quality and increasing the evidential value of research data. Important developments include the emergence of validated methods for the estimation of past exposure,

the use of biomarkers (early effects known to serve as predictors of subsequent health deterioration) and statistical analysis techniques for the combination of data from various studies (chapter 5). An uncertainty factor for shortcomings in the data can then become smaller or can even become superfluous.

In parallel with the developments outlined above, probabilistic methodologies are entering increasingly widespread use. The problem with default uncertainty factors is that it is unclear how conservative the assigned values are. This issue can be addressed by combining probability distributions, rather than absolute estimates, and then calculating a health-based recommended exposure limit on the basis of an acceptably low degree of probability that adverse effects will occur. Good communication with regulatory bodies is very important in this context, because such methodologies have yet to gain formal approval (chapter 6).

It is sometimes the case that little is known about the toxicity of a substance. Chapter 7 of the report accordingly outlines a number of methods by which it can sometimes nevertheless be possible to calculate recommended exposure limits (albeit provisional or indicative limits) under such circumstances.

The final chapter of the report (chapter 8) summarises the main recommendations of the committee responsible for the report:

- Allometric scaling factors should be used wherever possible.
- The definition of chemical-specific adjustment factors (CSAFs) is preferable whenever enough is known about the toxic activity of a substance. International cooperation in the definition of CSAFs should be encouraged.
- Understanding of toxic activity can be advanced by the application of new toxicological analysis techniques, such as (Q)SARs and *in vitro* methodologies, as well as modelling techniques, such as physiologically based kinetic modelling.
- At the same time, more widespread use and further development of probabilistic methodologies is desirable. These methodologies promise a major improvement on the 'classic' approach, based on the use of default values for uncertainty factors.
- In recent years, there has been increasing interest in methods for the health-based assessment of substances in the absence of ample toxicity data. It is important to encourage and facilitate initiatives in this field.