Conclusions

In this guide

23. Annex A - References

129. Traditionally, the NOAEL approach has been used for developing toxicological “safe dose” estimates such as reference doses (RfDs), acceptable daily intake (ADIs) values, or other values that can be used as HBGVs for chemical risk assessments. However, BMD modelling is now considered the preferred approach for deriving RPs for developing these “safe dose” estimates. BMD modelling allows a more quantitative and informative estimate of these RPs than the NOAEL approach.

130. Ideally, the BMD model used would be one that mimics the behaviour of the underlying biological system. However, in practice, most of the time the BMD modelling approach is an attempt to find the “best” mathematical model that describes the data, from a range of potential mathematical models.

131. The choice of model or models is determined by the nature of the data making up the endpoint of interest, the experimental design, dose selection etc. Similarly, the BMR can be selected based on toxicological and statistical consideration. However, in the absence of information about what biological response may be considered “adverse”, EFSA recommend either a BMR of 5% (continuous) or 10% (quantal) be set as a default depending on the data type. In contrast, the EPA recommend the BMR for continuous data be set in terms of a change relative to the standard deviation of the data, rather than % response, but agree that a BMR of 10% for quantal data is appropriate.

132. Historically, BMD software for DRMs used frequentist methodologies. However, developments in BMD software have made possible the use of Bayesian methods for the same approach. EFSA now recommend the Bayesian approach as the preferred approach to BMD modelling.

133. The BMD approach can be applied to all chemicals in food, independent of the nature or source. The BMD approach can be applied to a range of data types in including classical in vitro toxicological data, but also gene expression data, and even epidemiological data.

Advantages

134. Both EFSA and the US EPA consider the BMD approach to be the more quantitative and more scientifically advanced approach to deriving the RP from dose response data, compared to the NOAEL approach.

135. The BMD approach uses all the available dose-response information within a given dataset. The NOAEL approach, in contrast, effectively uses only the data that make up the control group and one other dose group.

136. The BMD approach provides important information regarding the uncertainties in the data. The output of the BMD approach provides a quantitative assessment of data quality, as described by the confidence (or credible) intervals.

137. BMD software can be developed and tailored to the needs of researchers. For example, specialist BMD modelling software, such as BMDExpress3 have been developed to meet the specifics of dose-response gene expression data.

138. BMD software is publicly available and accessible, along with guidance documents, user manuals tutorial videos and workshop recordings.

Challenges

139. BMD modelling software may require some training to use. Different software packages would require separate training to provide competence.

140. There are notable areas of divergence in the guidance provided by organisations such as the US EPA and EFSA with regards to BMD use and its best practices.

141. There are still significant differences in the operation and statistical basis for the various BMD modelling software. This means, in practice, that two different software analysing the same data, may generate potentially different BMD and BMDL values, and consequently will generate two different RPs and HBGVs.

Recommendations.

142. Training and competency workshops would be valuable to provide practical training for anyone on the COT or in the FSA interested in using BMD modelling approaches and BMD software.

143. Considering the areas of divergence in the current guidance around BMD, greater clarity on the accepted best practices would be appropriate. Further attempts to harmonise the approach to BMD modelling across agencies, governments and regulators would also be desirable.

144. Communication with industry, regulators and expert groups should also be encouraged to ensure that BMD modelling is adopted and integrated appropriately within the broader regulatory chemical safety environment. Development of an OECD (Organisation for Economic Co-operation and Development) guideline, as well as government and regulatory guidance around BMD implementation and experimental design, as well as clarity on requirements, reporting templates etc., should be considered.

145. A review of BMD modelling in chemical risk assessment, within an appropriate timeframe in the future, is recommended, particularly considering the rapidly changing computational and technological landscape.