The use of benchmark dose modelling in chemical risk assessment

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The benchmark dose (BMD) approach has gained increasing recognition among international regulatory authorities as a scientifically robust and data-driven method for deriving reference points (RPs) for use in chemical risk assessment. While there is general consensus on the value of BMD modelling, differences remain in the specifics of its application, including model selection, statistical paradigms, and software tools.

EFSA has been a leading proponent of BMD modelling in Europe, issuing a series of guidance documents that have progressively refined the approach. In 2005, EFSA first recommended BMD modelling for genotoxic and carcinogenic substances, advocating for the use of the 95% lower confidence level for a 10% increase in tumour incidence compared to the background response, as a benchmark response (BMR), i.e. BMDL10, as a pragmatic estimate of the reference point (RP). This was then used to calculate a margin of exposure, where a conservatively high value was considered to be of low concern. By 2009, EFSA had expanded its support for BMD modelling as a general tool in chemical risk assessment for determining RPs, recommending default BMRs of 10% for quantal data and 5% for continuous data. EFSA's 2017 update introduced model averaging as the preferred method for estimating BMD confidence intervals, arguing that this approach better reflects the uncertainty inherent in model selection. Their most recent 2022 guidance marked a significant shift by recommending the use of a Bayesian framework over the traditional frequentist approach. EFSA argues that Bayesian methods allow for the incorporation of prior knowledge, provide more intuitive credible intervals, and support a learning-based model of risk assessment. They also updated their suite of default models, unifying the approach for both continuous and quantal data, and emphasized the importance of model flexibility and the use of goodness-of-fit criteria such as the Akaike Information Criterion (AIC).

The United States Environment Protection Agency (US EPA) has played a pivotal role in advancing BMD modelling and use in regulatory assessment (Document Display | NEPIS | US EPA, 1995), particularly through the development of the BMDS software and the release of definitive technical guidance for BMD modelling in 2012. While the EPA agrees with EFSA on the scientific superiority of BMD over

NOAEL/LOAEL, their guidance to implementation differs in key respects. The EPA prefers a case-by-case model selection strategy rather than model averaging, arguing that selecting a single well-fitting model provides clearer interpretability and avoids the statistical complexities of averaging. They recommend using a BMR of 10% for quantal data and suggest defining BMRs for continuous data based on the standard deviations rather than percentage changes. The EPA also supports the use of constraints in model fitting to avoid biologically implausible results, such as steep supralinear curves, and they provide detailed decision trees and workflows to guide users through the modelling process. Although the EPA acknowledges the potential of Bayesian methods and continue to develop their own models and software in this respect, they have not yet adopted them as the default approach, citing concerns about complexity and interpretability. However, this is a rapidly changing area, with software availability and recommendations still evolving.

The FAO/WHO JECFA have also supported the use of the BMD approach as a more informative alternative to the traditional NOAEL/LOAEL methods. FAO/WHO guidance, particularly in Environmental Health Criteria (EHC) 240 (2009, updated 2020), emphasizes the importance of using all available dose-response data to derive a point of departure. This guidance highlights the need for transparency and reproducibility in BMD modelling, recommending that any software used should have publicly available source code and be thoroughly tested. They endorse the use of both the US EPA’s BMDS and EFSA’s PROAST software, noting that while no single software package is preferred, clarity in reporting and justification of model choices is essential. The guidance also stresses the importance of selecting a biologically meaningful BMR, and they support the use of model averaging and Bayesian methods to better capture uncertainty, especially in complex or data-limited scenarios.