COT’s discussion

In this guide

In this guide

1. Benchmark dose modelling in a UK chemical risk assessment framework - cover
2. Benchmark Dose Modelling in a UK Chemical Risk Assessment Framework - Executive Summary
3. Benchmark dose modelling in a UK chemical risk assessment framework - Recommendations
4. Benchmark dose modelling in a UK chemical risk assessment framework - Use
5. Benchmark dose modelling in a UK chemical risk assessment framework - Advantages of BMD modelling
6. Current challenges to the use of benchmark dose modelling in regulatory toxicology
7. Benchmark dose modelling in a UK chemical risk assessment framework - COT’s discussion
8. Benchmark dose modelling in a UK chemical risk assessment framework - Conclusions
9. Annex A - Introduction and Background
10. Annex A- Benchmark dose modelling
11. Annex A - Selected Previous Publications
12. Annex A - COT previous discussions
13. Annex A - NOAEL approach vs BMD approach
14. Annex A - Modelling the data
15. Annex A - Fitting the model to the data
16. Annex A - Bayesian vs frequentist approach
17. Annex A Case Study (FSA Computational Fellow)
18. Annex A - User experience
19. Annex A - Conclusions
20. Annex A - Questions on which the views of the Committee are sought
21. Annex A - List of Abbreviations
22. Annex A - Technical terms

23. Annex A - References

The COT discussed the paper presented in Annex A. Members of the Committee considered the current state and future direction of BMD modelling in chemical risk assessment. While the committee acknowledged the scientific rigor and potential advantages of BMD, they also highlighted significant challenges related to transparency, subjectivity, dataset suitability, and practical implementation. The consensus was that BMD modelling can serve as a valuable tool in certain circumstances, particularly for potency comparisons and for determining reference points when NOAELs cannot be identified, but there are yet many outstanding challenges preventing universal application and adoption.

Members felt there may be a growing polarisation within the toxicological community. On one side are proponents who believe BMD modelling is the only scientifically valid approach in determining RPs; on the other are sceptics who argue that its subjectivity undermines its reliability. Members emphasised that the NOAEL approach, while less statistically sophisticated, remains a valid and widely used method, and may be the only viable approach in some circumstances e.g. when effects are observed only at the highest dose. The importance of presenting BMD modelling as a legitimate, complementary approach to NOAEL identification, rather than a replacement was emphasised. It was noted that the risk assessment community has long understood the limitations of NOAEL and built frameworks around its use. Perhaps this needs to be made clearer in risk communication. For example, there is no assumption that the NOAEL represents a dose without any effects. It was noted that these discussions should inform future updates to COT guidance documents and the goal should be to equip regulatory toxicologists with a range of tools, each suited to different types of data and risk assessment scenarios.

Members highlighted that the field is currently experiencing a proliferation of software tools and modelling approaches, and it is yet unclear if, and how much, these various models and software packages diverge. This divergence, it was agreed, complicates efforts to standardize BMD modelling (e.g. for regulatory use). Some software tools have undergone more rigorous validation, particularly those endorsed by regulatory agencies such as EPA and EFSA, than others. It was also pointed out that the increasing complexity of these tools demands a higher level of statistical and computational expertise, potentially limiting their accessibility to non-specialists.

Members stressed the importance of understanding the algorithms behind BMD software, not just interpreting the output. One member drew a comparison with the early development of QSAR modelling, where there was a similar proliferation of new software and models. Members warned against the “black box” nature of some BMD tools where outputs can be generated without any true understanding of how they were arrived at. Members suggested a series of case studies to evaluate the reliability and comparability of different models before they are widely adopted. Similarly, it was also suggested reviewing past cases where BMD values were used to establish HBGVs to better understand the assumptions and limitations involved. This retrospective analysis could help build expertise and inform future updates to COT guidance documents.

Members further expressed concerns around the suitability of many datasets for BMD modelling. Members questioned how many OECD guideline studies are amenable to BMD analysis. The point was raised that, while the computational aspect might be straightforward, significant pre-selection of data occurs. The concern raised by members was that this pre-selection — choosing only datasets that are amenable to BMD modelling — can introduce bias, by ignoring more informative, albeit less well behaved, datasets. If only the most “model-friendly” datasets are used, the resulting risk assessments may not be representative of the broader toxicological evidence base. Further risk of bias may be present if practitioners select endpoints or models based on the most conservative outcomes, rather than biological relevance. This practice, while perhaps well-intentioned, further risks distorting the scientific basis of risk assessments.

Members had trepidations about the limitations of traditional toxicology study designs in the context of BMD modelling, particularly studies that had been based on OECD guidelines now superseded, or with dose spacing designed to maximise statistical sensitivity at the highest dose. Members encouraged redesigning toxicology studies to generate biologically relevant data, not just statistically significant results at the highest dose. It was suggested that this redesign should be informed by NAMs, which offer more flexible and informative experimental frameworks. Members agreed that NAMs often produce more detailed dose-response data, with many more dose levels, making them better suited for modelling. It was emphasized that BMD is particularly useful when applied to well-designed studies with multiple dose points, with a gradient in response over several dose levels, and clear biological endpoints.

The committee also emphasised the need for broader engagement with other scientific advisory committees, such as the Committee on Carcinogenicity (COC)

and the Committee on Mutagenicity (COM) and the UK Expert Committee on Pesticides (ECP), who already use BMD modelling in their assessments. Harmonizing approaches across these groups would help ensure consistency in the application of BMD modelling.

Finally, the committee broadly agreed that BMD modelling should be viewed as a transitional tool rather than an end goal. A member envisioned a future where toxicokinetic/dynamic systems models, based on *in silico* and *in vitro* data would replace both NOAEL and BMD approaches. These models would simulate the relationship between internal concentrations at target sites and biological responses, offering a more realistic and mechanistically-based understanding of toxicity.

Until such models are fully developed and validated, BMD modelling provides a valuable, if imperfect, method for quantifying and informing risk. It allows for more nuanced interpretations of dose-response data and can support the development of reference points in the absence of clear NOAELs. Moving forward, the committee recommended further training, case studies, and inter-committee collaboration to support the thoughtful integration of BMD modelling into UK chemical risk assessment. As toxicology continues to evolve toward more mechanistic and systems-based approaches, BMD modelling will play an important transitional role in bridging traditional and modern methodologies.