Introduction and Background

In this guide

23. Annex A - References

Discussion paper on benchmark dose modelling in a UK chemical risk assessment framework

TOX/2024/03 discussed in COT February Meeting 2024.

Introduction

1. In 2021 (TOX/2021/1) as part of a horizon scanning exercise, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) identified the UK in future may need benchmark dose (BMD) modelling guidance. It was stated that in order that there is consistency in the implementation and in the interpretation of the BMD outputs, it is essential that there is guidance from a UK perspective. A COT (or wider UK) guidance document should be put together which would detail, amongst other things, a description of BMD modelling, including when it should be used; the software available and its respective limitations; and interpretation of the outputs. It should also list relevant resources with links. Discussions with experts in-the-field would likely be necessary to ensure that the guidance is accurate, reliable and future-proof for the Food Standards agency (FSA), COT and other relevant government departments (OGD).

2. Whilst carrying out its normal functions the COT is likely to come across instances where it will be essential that there is a good understanding of BMD modelling. The secretariat, in addition may also need to know how to carry out the modelling.

3. In 2022 (TOX/2022/07), as part of a horizon scanning exercise, the possibility of a workshop on BMD modelling was considered but it was agreed that a discussion paper would be most appropriate in the first instance.

4. Furthermore, in 2022 Members from COT, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) and the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) reviewed and discussed the recently published draft updated EFSA guidance on the BMD Approach; the most notable change being a move to use a Bayesian rather than frequentist approach in the modelling. In the discussion it was noted that the BMD was considered by EFSA to

be scientifically more advanced than the NOAEL/LOAEL approach.

5. The Food Standards Agency (FSA) and COT are considering the use and practice of BMD as part of its ongoing evaluation of New Approach Methodologies (NAMs) in chemical risk assessment, within a UK food safety context for the safety of UK consumers.

6. This discussion paper provides information on the theory and practice of the BMD approach. The paper draws on previous evaluations by regulatory bodies and authorities (e.g. EFSA and US EPA). Furthermore, it includes a discussion of the areas of consensus and divergence between organisations and expert groups. It also highlights the work of the FSA Computational Fellow and describes a case study, that has used BMD modelling to derive a HBGV, as a proof of concept.

Background

7. The benchmark dose (BMD) approach was introduced almost 40 years ago as a more quantitative and informative estimate of the reference point (RP) from dose-response experiments. It was proposed as an alternative to the traditionally used No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) (Crump, 1984).

8. The first established “safe dose” based on a BMD approach was for methylmercury, loaded onto the U.S. Environmental Protection Agency’s (EPA) Integrated Risk Information System (IRIS) in 1995 (Haber et al., 2018). In 2005, EFSA first recommended the BMD approach for deriving RPs for substances that are both genotoxic and carcinogenic (EFSA, 2005). In 2005, the World Health Organisation’s (WHO) International Programme on Chemical Safety (IPCS) published their “Principles for modelling dose-response for the risk assessment of chemicals” (FAO/WHO, 2005) and in 2006, the Joint Expert Committee on Food Additives (JECFA) began applying this approach for the safety evaluation of certain genotoxic and carcinogenic contaminants in food (FAO/WHO, 2006). Both the EPA and EFSA now recommend using the BMD approach, where appropriate, as the preferred methods to identify a RP for both genotoxic and non-genotoxic compounds (EFSA, 2017; US EPA, 2012).

9. Guidance on the BMD approach, including the statistical basis of the approach as well as technical guidance on its use and implementation have been provided by multiple authorities or committees (EFSA, 2022, 2017, 2009; FAO/WHO, 2020; US EPA, 2012) as well as many other reviews and discussions on

the topic (Crump, 1984; Gephart et al., 2001; Haber et al., 2018; Slob, 2002).