BENCHMARK DOSE MODELLING FOR THE SAFETY ASSESSMENT OF NOVEL FOOD: OVERVIEW OF USES AND CHALLENGES

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INTRODUCTION

Safety assessments of novel foods (NFs) usually rely on the establishment of a reference point (RP) allowing the determination of a safe maximum daily intake by humans. Traditionally, when experimental animal data have been used for risk assessment of substances in foods which are not genotoxic or carcinogenic, the RP has been derived from the No-Observed-Adverse-Effect-Level (NOAEL) and/or the Lowest-Observed-Adverse-Effect-Level (LOAEL). However, such approaches do not make extensive use of the data available in a quantitative manner. To overcome this issue, as of 2009, the European Food Safety Authority (EFSA) has been recommending the use of the benchmark dose (BMD) approach, which estimates the shape of the overall dose-response relationship for a particular endpoint. The BMD is a dose level derived from the estimated dose-response curve associated with a specified change in response, the Benchmark Response (BMR). The aim of this study is to monitor the use of BMD and to assess the challenges associated with its implementation at the level of NF applications, by creating a database of published opinions with information from outputs where this approach was used.

METHODOLOGY

An overview of how the BMD modelling approach is employed in the safety assessment of NFs was carried out. The currently available Guidance documents from EFSA and the literature were consulted as sources of theoretical background. All opinions published by EFSA under Regulation (EC) No 258/97 and those pursuant to Article 10 of Regulation (EU) 2015/2283 since the Guidance of the Scientific Committee on Use of the benchmark dose approach in risk assessment (2009) was published were reviewed in order to define the proportion of opinions that used the BMD approach for deriving the RP. In each case, the BMR values, their associated endpoints and the reasoning for their use were listed and compared to default values, values proposed in the literature or values established by other Scientific Panels. Furthermore, when the information was available, the BMDU/BMDL ratios were calculated in order to evaluate the uncertainty of the analysis, as stated in the corresponding Guidance document.

RESULTS

Among the 104 NF opinions that had been published since the adoption of the Guidance, seven assessments mention the use of the BMD approach, but only five used it as an RP. The remaining opinions deriving the RP from a dose-effect relationship from a toxicological endpoint used the NOAEL (33 opinions) or the LOAEL (one opinion). Beyond that, other reasonings, such as the history of use or the nature of the food, were used to derive the RP. When BMD modelling was used, risk assessors used the default BMR values in four cases. For phenylcapsaicin, a BMR of 20 % was used for increased plasma alanine aminotransferase levels based on a recommendation by the EFSA Scientific Committee in 2017 for liver enzymes. The other custom BMR value found (suggested by the applicant) was 25 % for urine volume, but it was ultimately not considered for the definition of the RP in favour of body weight changes (BMR = 5 %), for the safety of dried aerial parts of Hoodia parviflora. Regarding the uncertainty quantification, 5 of the 7 opinions included the BMDU/BMDL ratio. The two opinions that did not provide this data were published before the 2017 Guidance update, where this requirement was indicated for the first time.

DISCUSSION

The rare use of the BMD approach in NF risk assessment is evidence of the challenges associated with its implementation. Among potential causes, the fact that toxicity studies are currently designed based on OECD guidelines, which favour the use of the LOAEL or NOAEL, often leads to BMD values being derived that fall far outside the tested dose range. More importantly, the stringency/inadequateness of the current BMR default values of 5 % for continuous data and 10 % for quantal data proposed by the Guidance appear to hinder the use of BMD among risk assessors. While the updated Guidance from 2017 on the use of the benchmark dose approach in risk assessment provides more insights on BMD application, further guidance is needed to achieve homogeneity and consistency among all NFs, and ultimately all substances assessed by EFSA. With this database, we aim to provide a simple and transitory tool to help risk assessors in the NF area navigate and visualise previous uses of the BMD approach.