1711 Globally Harmonized Guidance for Dose-Response Analysis and Derivation of Health-Based Guidance Values for Chemicals in Food. Part I—What's New

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The World Health Organization (WHO) recently coordinated an international effort to update its guidance document on dose-response assessment for chemicals in foods, including additives, contaminants, natural toxicants, and residues of pesticides and veterinary drugs. This guidance also provides practical recommendations in deriving health-based guidance values, such as acceptable daily intake and acute reference dose, as the basis of establishing food safety regulations and safety standards in international food trade. Although the purpose of the guidance is related to the WHO food safety programs, the guidance reflects the latest expert thinking on dose-response assessment and benchmark dose (BMD) modeling, including some key areas of consensus among international experts, and so will be broadly applicable to areas beyond chemicals in food. Key motivators for the update were newly available modeling technology and the need for harmonization of the BMD approaches used by the US Environmental Protection Agency (US EPA) and the European Food Safety Authority (EFSA). This two-part Workshop includes presentations and demonstrations given by scientists who played essential roles in an international working group charged with drafting this harmonized guidance. Part I of the Workshop will focus on the basic elements and key updates in the new guidance, while Part II is designed as a practical demonstration session that builds on presentations in Part I. Part I will begin with an introduction that provides an overview of this guidance, the objectives of the working group, and a summary of notable updates. The second presentation will address the need for global harmonization with some food-related case studies and will present the new consensus decision tree scheme for dose-response analysis designed to aid in harmonizing approaches. The decision tree scheme, embracing a new tiered approach for the benchmark response for continuous endpoints, provides a practical guide to risk assessors and managers by illustrating how key decision points are affected by a variety of practical scenarios. The third presenter, who played a leading role in the incorporation of model averaging into the US EPA BMD software, will focus on the harmonization of BMD methodology by specifically outlining important considerations in the practice of BMD, explaining recommendations of modeling strategies for different types of data, and presenting challenges and solutions in harmonizing different methods. The session will conclude with an interactive panel discussion with all speakers, Chairs, and a moderator who collectively represent end users of this guidance from different sectors.

1712 Bring Together Multidisciplinary Expertise: Highlights of Updates in the New Dose-Response Analysis Guidance for Chemicals in Food

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For chemicals in food, health-based guidance values (HBGVs), such as acceptable or tolerable daily intakes and acute reference doses, represent a range of oral exposures that are expected to be without appreciable health risk. The WHO original guidance, "Principles and Methods for the Risk Assessment of Chemicals in Food" (i.e., Environmental Health Criteria [EHC] 240), had limited context related to benchmark dose modeling, a field that has since rapidly evolved into different perspectives and approaches. By convening toxicologists, epidemiologists, mathematical modelers, risk assessors, and regulators, a multidisciplinary approach was used to update the guidance to provide a practical and harmonized recommendation to perform dose-response assessment (DRA) and establish HBGVs. Notable updates to the contents include dose-response modeling methodology (e.g., software, statistical issues, model evaluation criteria), a tiered approach to determining a benchmark response (BMR); a decision tree diagram for DRA leading to the establishment of HBGV or margin of exposure, new sections on dealing with epidemiological and *in vitro* data, incorporating new methods to derive chemical-specific adjustment factors, and revised terminology to improve consistency, clarity, and accuracy. The update also includes an appendix of examples based on dichotomous, continuous, and epidemiological data and additional information and references detailing model components, statistical fitting methods, and uncertainty. This overview will set the stage for the subsequent speakers to illustrate important technical applications of the new guidance, including choice of BMR and how model averaging and Bayesian approaches minimize issues related to model choice.

1713 Step by Step: Decision Tree for Dose-Response Analysis and Choice of the Benchmark Response

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Key challenges in dose-response assessment have been disagreement on when it is appropriate and necessary to conduct dose-response modeling and differences in the specifics of the modeling guidance from different organizations, particularly the US EPA and European Food Safety Authority (EFSA). The importance of these differences and the need for harmonization are illustrated using case studies of two chemical food contaminants: 3-monochloropropane-1,2-diol, a contaminant in (3-MCPD) (impact of restricting models) and 5-hydroxymethylfurfural (HMF) (implications of considering visual fit, the Akaike information criterion [AIC], and scaled residuals in choosing models). An important aspect of the new guidance is a decision tree designed to aid risk assessors and managers and lead to a harmonized approach. The decision tree, agreed upon with full consensus at a meeting of international experts convened by WHO in March 2019, lays out the key steps in the dose-response assessment. Steps for conducting benchmark dose modeling and non-modeling approaches are addressed. The decision tree introduces a tiered approach for choosing the BMR for continuous endpoints, including (1) using a biologically meaningful adverse effect size; (2) expert judgment on the quantitative definition of adverse; and (3) using dose-response data to calculate a margin of exposure. Examples of application of the tiering will be provided.

1714 Bring Harmonization into Dose-Response and Benchmark Dose Modeling Guidance

M. Wheeler. *CDC, Cincinnati, OH.* Sponsor: Y. Zang

To establish a point of departure, some form of dose-response analysis (DRA) must be employed. Benchmark dose (BMD) modeling is the preferred approach over the NOAEL/LOAEL approach for a number of reasons, as identified by the WHO risk assessment guidance EHC 240. However, there are myriad choices available to the modeler, which range from the form of the dose-response curve to the type of analysis (e.g., frequentist versus Bayesian versus model average), and the question becomes, How does one make reproducible, scientifically valid decisions with all of these options? To bring harmonization and transparency into BMD modeling, the new guidance addresses these discrepancies by emphasizing the use of multi-model inference using model averaging, with a reliance on Bayesian models to implement "soft-constraints" on model parameters. The speaker will focus on how the newly developed guidance leverages new methodologies (e.g., model averaging and Bayesian dose-response modeling) while producing scientifically sound and robust results. Emphasis is made on the selection of different model suite and Bayesian priors for proper analyses of the BMD. This talk is geared toward toxicologists and BMD software users. It focuses on the practical choices when performing a dose-response analysis and is not intended to be technical in nature.

1715 Impacts on Human Health of Sunscreen Active Ingredients Used to Filter UV Light

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There are several known adverse health effects in the skin following overexposure to ultraviolet (UV) light from the sun. Acute effects from UV light overexposure include erythema, immunosuppression, and burns; chronic effects include photoaging and cancer. Occurrence of skin cancer from overexposure to sunlight is on the rise, alarming many health agencies. Total avoidance of sunlight and the wearing of protective clothing are the best ways to evade the harmful effects of sunlight. However, these two practices are not always the most practical way to avoid sunlight. In addition, excessive avoidance of sunlight may result in vitamin D deficiency, which has its own adverse effects, such as risk for cardiovascular disease and cancer. A more convenient means of protection from UV light from the sun is the application of sunscreen onto exposed skin. Sunscreens are basically inorganic (physical) and organic (chemical) filters of UV light. The main types of inorganic sunscreens or UV filters are zinc oxide and titanium dioxide, while several chemical classes are used as ingredients of organic sunscreens. Examples include the benzophenones, cinnamates, and others. These organic UV filters are not in sunscreens alone but also are found in other personal care products such as cosmetics and hair sprays, and clothing. Human exposure to the UV filters is primarily topical but can occur via the lungs after using spray applicators or by the gastrointestinal tract after use of lip balms containing these chemicals. Concerns have been raised about the potential adverse health and environmental effects of the UV filters. For example, the benzophenone derivative, 2-hydroxy-4-methoxybenzophenone (i.e., oxybenzone, benzophenone-3), is

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and Scientific Sessions of the 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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