CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 3 **CX/FO17/25/3Add.1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FATS AND OILS

25th Session

Kuala Lumpur, Malaysia, 27 February - 3 March 2017

INFORMATION FROM FAO AND WHO

1. At the 83rd meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA83) held in Rome, Italy, from 8 to 17 November 2016 certain contaminants in food have been evaluated.

2. Among those contaminants on the agenda of JECFA83 were two that may be of interest to the work of this committee:

- 3-MCPD esters
- Glycidyl esters

3. A summary report has been published and is available here: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/, a full report is in preparation and will be published soon and a detailed monograph is also in preparation.

4. In Appendix, the relevant excerpts from the summary report are reproduced and the committee is kindly requested to take note.

5. FAO and WHO note the request of the committee for scientific advice regarding an evaluation whether the 23 substances were suitable as previous cargoes and to provide an assessment against the four criteria as mentioned in the Code of Practice for the Storage and Transport of Edible Fats and Oils in Bulk (CAC/RCP 36-1987). FAO and WHO also note that the evaluation should at least address ease of cleaning (impact with respect to possible carry-over of residues into edible oils and fats), toxicological profile, possible allergenicity, reactivity with edible oils and fats resulting in reaction products that would result in adverse human health effects for the substances and their expected impurities; and.

6. FAO and WHO further welcome the work of the committee to cluster the 23 substances based on chemical properties and rank according to priorities (i.e. low, medium or high).

7. FAO and WHO would like to reiterate their position expressed in Appendix II of CX/CAC 15/38/16 and CX/CAC 16/39/15, Status of Requests for FAO/WHO Scientific Advice that such an evaluation will require an expert meeting (including the participation of private sector experts) to gather and evaluation the necessary information.

8. As stated in Appendix II of CX/CAC 15/38/16 and CX/CAC 16/39/15, Status of Requests for FAO/WHO Scientific Advice the costs of such a meeting are not covered through the regular programme budgets of FAO or WHO and extra-budgetary resources of approximately US$100,000 would be required to start this task. At the current workload of FAO and WHO in the scientific advice programme, the work could start in 2019, provided the respective funds are made available to both organizations.

Appendix

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Eighty-third meeting

Rome, 8–17 November 2016

SUMMARY AND CONCLUSIONS

Issued 23 November 2016

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 8 to 17 November 2016. The purpose of the meeting was to evaluate certain contaminants in food.

Dr R. Cantrill, American Oil Chemists' Society, United States of America, served as Chairperson, and Dr D. Benford, Food Standards Agency, United Kingdom, served as Vice-Chairperson.

Dr M. Lipp, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, Department of Food Safety and Zoonoses, World Health Organization, served as Joint Secretaries.

The present meeting was the eighty-third in a series of similar meetings. The tasks before the Committee were (a) to elaborate principles governing the evaluation of contaminants in food; (b) to undertake toxicological evaluations and dietary exposure assessments for six contaminants or groups of contaminants in food; and (c) to undertake toxicological evaluations and dietary exposure assessments in relation to co-exposure to two groups of contaminants in food.

The report of the meeting will be published in the WHO Technical Report Series. Its presentation will be similar to that of previous reports – namely, general considerations, comments on specific contaminants or groups of contaminants, and future work and recommendations. An annex will include a summary (similar to the summary in this report) of the main conclusions of the Committee in terms of provisional maximum tolerable daily intakes and other toxicological and safety recommendations.

The participants in the meeting are listed in Annex 1. Items of a general nature that the Committee would like to disseminate quickly are included in Annex 2. Future work and recommendations are listed in Annex 3.

Toxicological and dietary exposure monographs on the contaminants or groups of contaminants considered will be published in WHO Food Additives Series No. 74.

More information on the work of JECFA is available at:

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/

and

http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/

Evaluations of contaminants

[…]

[text deleted for brevity, full document is available here:

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/]

Glycidyl esters

Glycidyl esters are processing-induced contaminants primarily found in refined fats and oils and foods containing fats and oils. Initial research related to glycidyl esters was largely performed as part of the investigation into 3-monochloro-1,2-propanediol (3-MCPD) esters. During 3-MCPD ester analysis, variable 3-MCPD concentrations were obtained, leading to a proposal that additional compounds were present in edible oils and converted to 3-MCPD during sample analysis. The presence of additional processing-induced contaminants, glycidyl esters, in refined edible oils was later confirmed. Initially it was assumed that 3-MCPD esters and glycidyl esters were formed by similar processes, but it is now known that their mechanisms of formation are different, with glycidyl ester formation directly associated with elevated temperatures (>240 °C) and time at these elevated temperatures. Glycidyl esters are generally formed from diacylglycerols, with no requirement for the presence of chlorinated compounds. Formation of glycidyl esters occurs following intramolecular rearrangement, elimination of a fatty acid and epoxide formation.

Glycidyl esters have not been evaluated previously by the Committee. The present evaluation was conducted in response to a request from CCCF.

Experimental evidence indicates that glycidyl esters are substantially hydrolysed to glycidol in the gastrointestinal tract and elicit toxicity as glycidol. The Committee therefore based its evaluation on the conservative assumption of complete hydrolysis of glycidyl esters to glycidol. Whereas the experimental data supporting substantial hydrolysis are derived from studies with post-weaning animals, the Committee concluded that the capacity of the neonate to hydrolyse fatty acids in the gut is efficient, and therefore the same assumption of substantial hydrolysis could be extended to this age group.

The Committee concluded that glycidol is a genotoxic compound and considered its carcinogenicity as the most sensitive end-point on which to base a point of departure. The lowest $BMDL_{10}$ was 2.4 mg/kg bw per day for mesotheliomas in the tunica vaginalis/peritoneum in male rats observed in the NTP (1990)[1] carcinogenicity study (doses adjusted for non-continuous dosing; with quantal linear, gamma, Weibull and multistage 2 degree models giving the same result).

The Committee noted that there are no published collaboratively studied methods for the determination of glycidyl esters in complex foods in contrast to the situation with fats and oils; therefore, caution should be applied when interpreting analytical data from complex foods.

The Committee further noted that there was uncertainty in comparing the reported levels in the same foods from different regions because of the lack of interlaboratory comparisons and the absence of data arising from proficiency testing schemes.

As it is not appropriate to establish a health-based guidance value for substances that are both genotoxic and carcinogenic, the margin of exposure approach is chosen.

National estimates of dietary exposure were used for determining the margins of exposure. This was because they were considered to be the most representative of dietary exposure as they are based on consumption data from national dietary surveys. The majority of the surveys used include 2 or more days of data, which better estimate chronic dietary exposure.

The national dietary exposures are considered to be reliable estimates, as they are based on a range of foods in the diet and include the key foods in which glycidol contamination is known to occur – namely, fats and oils. The concentrations in specific foods in the majority of cases have been able to be matched directly with consumption data for the same foods.

[1] NTP (1990). National Toxicology Program (NTP) technical report on the toxicology and carcinogenesis studies of glycidol (CAS no. 556-52-5) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park (NC): National Toxicology Program (NTP Technical Report 374).

The Committee considered that the lower ends of the ranges of the margins of exposure for infants, children and adults (Table 1) were low for a compound that is genotoxic and carcinogenic and that they may indicate a human health concern.

Table 1

Dietary exposures and margins of exposure compared with the $BMDL_{10}$

Population group	Range of estimated dietary exposures to glycidol (µg/kg bw per day)[a]		Margins of exposure[b]	
	Mean	High percentile	Mean	High percentile
Adults	0.1–0.3	0.2–0.8	8 000–24 000	3 000–12 000
Children	0.2–1.0	0.4–2.1	2 400–12 000	1 100–6 000
Infants	0.1–3.6	0.3–4.9	670–24 000	490–8 000

[a] Includes LB and UB estimates from a range of national estimates of dietary exposure.

[b] Compared with a $BMDL_{10}$ of 2.4 mg/kg bw per day. Margins of exposure are expressed as a range; the lower end of the range relates to UB mean and high-percentile exposures, and the higher end of the range relates to LB mean and high-percentile exposures.

3-MCPD esters

3-Monochloro-1,2-propanediol (3-MCPD) esters are processing-induced contaminants found in various refined oils and fats and are formed from acylglycerols in the presence of chlorinated compounds during deodorization at high temperature. "3-MCPD esters" is a general term for 3-MCPD esterified with one (sn1- and sn2-monoesters) or two identical or different fatty acids (diesters). Depending on the fatty acid composition of the oil or fat, a variety of different 3-MCPD esters can be formed during processing. In foods that contain refined vegetable oils or fats, mainly diesters are found. Concentrations of 3-MCPD esters in refined oils increase incrementally in the following order: rapeseed oil < soya bean oil < sunflower oil < safflower oil < walnut oil < palm oil.

3-MCPD esters have not been previously evaluated by the Committee. The present evaluation was conducted in response to a request from CCCF for an evaluation of 3-MCPD esters. 3-MCPD has been evaluated at the forty-first, fifty-seventh and sixty-seventh meetings of JECFA. At the sixty-seventh meeting, the Committee reaffirmed a PMTDI for 3-MCPD of 2 µg/kg bw, based on a lowest-observed-effect level (LOEL) of 1.1 mg/kg bw per day for tubule hyperplasia in the kidney seen in a long-term carcinogenicity study in rats. An uncertainty factor of 500 was applied to allow for the absence of a clear no-observed-effect level (NOEL) and to account for the effects on male fertility and inadequacies in the studies of reproductive toxicity.

Experimental evidence indicates that 3-MCPD esters are substantially hydrolysed to 3-MCPD in the gastrointestinal tract and elicit toxicity as free 3-MCPD. The Committee therefore based its evaluation on the conservative assumption of complete hydrolysis of 3-MCPD esters to 3-MCPD. Whereas the experimental data supporting substantial hydrolysis are derived from studies with post-weaning animals, the Committee concluded that the capacity of the neonate to hydrolyse fatty acids in the gut is efficient, and therefore the same assumption of substantial hydrolysis could be extended to this age group.

The main target organs for 3-MCPD and its esters in rats and for 3-MCPD in mice are the kidneys and the male reproductive organs. 3-MCPD was carcinogenic in two rat strains, but not in mice. No genotoxic potential has been demonstrated in vivo for 3-MCPD. Two long-term carcinogenicity studies with 3-MCPD in rats[2] were identified as pivotal studies, and renal tubular hyperplasia was identified as the most sensitive end-point. The lowest $BMDL_{10}$ (restricted log-logistic model) for renal tubular hyperplasia was calculated to be 0.87 mg/kg bw per day for male rats. After application of a 200-fold uncertainty factor, the Committee established a group PMTDI of 4 µg/kg bw for 3-MCPD and 3-MCPD esters singly or in combination (expressed as 3-MCPD equivalents) (rounded to one significant figure). The overall uncertainty factor of 200 incorporates a factor of 2 related to the inadequacies in the studies of reproductive toxicity.

[2] Sunahara G, Perrin I, Marchesini M (1993). Carcinogenicity study on 3-monochloropropane-1,2-diol (3-MCPD) administered in drinking water to Fischer 344 rats. Unpublished report no. RE-SR93003 submitted to WHO by Nestec Ltd, Research & Development, Switzerland.
Cho WS, Han BS, Nam KT, Park K, Choi M, Kim SH et al. (2008). Carcinogenicity study of 3-monochloropropane-1,2-diol in Sprague-Dawley rats. Food Chem Toxicol. 46:3172–7.

The previous PMTDI of 2 µg/kg bw for 3-MCPD, established at the fifty-seventh meeting and retained at the sixty-seventh meeting, was withdrawn.

The Committee noted that there are no published collaboratively studied methods for the determination of 3-MCPD esters in complex foods in contrast to the situation with fats and oils; therefore, caution should be applied when interpreting analytical data from complex foods.

The Committee further noted that there was uncertainty in comparing the reported levels in the same foods from different regions because of the lack of interlaboratory comparisons and the absence of data arising from proficiency testing schemes.

The Committee noted that estimated dietary exposures to 3-MCPD for the general population, even for high consumers (up to 3.8 µg/kg bw per day), did not exceed the new PMTDI. Estimates of mean dietary exposure to 3-MCPD for formula-fed infants, however, could exceed the PMTDI by up to 2.5-fold for certain countries (e.g. 10 µg/kg bw per day in the first month of life).

While the current evaluation was specific to the request for an evaluation of 3-MCPD esters, the Committee was aware that 2-MCPD esters can be detected in some of the same foods as 3-MCPD esters. There are, however, currently limited food occurrence data for 2-MCPD and 2-MCPD esters available in the GEMS/Food contaminants database, and the toxicological database is currently insufficient to allow a hazard characterization.

[….]

[text deleted for brevity, full document is available here:

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/]

Annex 1

Eighty-third meeting of the

Joint FAO/WHO Expert Committee on Food Additives[3]

Rome, 8–17 November 2016

Members

Professor J. Alexander, Norwegian Institute of Public Health, Oslo, Norway

Dr S. Barlow, Brighton, East Sussex, United Kingdom

Dr D. Benford, Risk Assessment Unit, Food Standards Agency, London, United Kingdom (*Vice-Chairperson*)

Dr M. Bolger, Annapolis, MD, USA

Dr R. Cantrill, American Oil Chemists' Society, Urbana, IL, USA (*Chairperson*)

Mr P. Cressey, Institute of Environmental Science and Research Ltd (ESR), Christchurch, New Zealand

Dr M. De Nijs, RIKILT Wageningen University & Research, Wageningen, the Netherlands (*Co-Rapporteur*)

Professor S. Edwards, Harper Adams University, Newport, Shropshire, United Kingdom

Mr M. Feeley, Bureau of Chemical Safety, Food Directorate, Health Canada, Ottawa, Ontario, Canada

Dr U. Mueller, Food Standards Australia New Zealand, Canberra, ACT, Australia (*Co-Rapporteur*)

Dr G.S. Shephard, Institute of Biomedical and Microbial Biotechnology, Cape Peninsula University of Technology, Bellville, South Africa

Secretariat

Professor G.O. Adegoke, Department of Food Technology, University of Ibadan, Ibadan, Nigeria (*FAO Expert*)

Professor K.E. Aidoo, Department of Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom (*FAO Expert*)

Dr N. Arnich, French Agency for Food, Environmental and Occupational Health and Safety (Anses), Maisons-Alfort, France (*WHO Expert*)

Dr D. Bhatnagar, Agricultural Research Service, United States Department of Agriculture, New Orleans, Louisiana, USA (*FAO Expert*)

Dr P. Boon, Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands (*FAO Expert*)

Dr G. Brisco,* Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy (*Codex Secretariat*)

Dr C. Carrington, Gaithersburg, Maryland, USA (*WHO Expert*)

Dr D.R. Doerge, National Center for Toxicological Research, United States Food and Drug Administration, Jefferson, Arkansas, USA (*WHO Expert*)

Dr L. Edler, German Cancer Research Center, Heidelberg, Germany (*WHO Expert*)

Ms B. Engeli, Federal Food Safety and Veterinary Office (FSVO), Bern, Switzerland (*WHO Expert*)

Dr V. Fattori, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Secretariat*)

Ms Z. Gillespie, Bureau of Chemical Safety, Food Directorate, Health Canada, Ottawa, Ontario, Canada (*WHO Expert*)

[3] Participants marked with an asterisk (*) did not attend the entire meeting.

Ms T. Hambridge, Food Data Analysis Section, Food Standards Australia New Zealand, Barton, ACT, Australia (*FAO Expert*)

Dr J.C. Leblanc, Food Safety and Quality Unit, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Secretariat*)

Professor P. Li, Oil Crops Research Institute, Chinese Academy of Agricultural Sciences, Wuchang, Wuhan, Hubei Province, China (*FAO Expert*)

Dr M. Lipp, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Joint Secretary*)

Professor H.A. Makun, Federal University of Technology, Minna, Nigeria (*FAO Expert*)

Dr D. Miller,* Department of Chemistry, Carleton University, Ottawa, Ontario, Canada (*WHO Expert*)

Dr N.J. Mitchell, Department of Food Science and Human Nutrition, Michigan State University, East Lansing, Michigan, USA (*WHO Expert*)

Dr T. Rawn, Food Research Division, Health Canada, Ottawa, Ontario, Canada (*FAO Expert*)

Dr R.T. Riley, Athens, Georgia, USA (*WHO Expert*)

Dr A.-C. Roudot, Université de Bretagne Occidentale, Brest, France (*WHO Expert*)

Ms M. Sheffer, Orleans, Ontario, Canada (*WHO Technical Editor*)

Ms J.H. Spungen, Office of Analytics and Outreach, Center for Food Safety and Applied Nutrition, United States Food and Drug Administration, College Park, Maryland, USA (*FAO Expert*)

Dr A. Tritscher, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland (*WHO Joint Secretary*)

Dr T. Umemura, Division of Pathology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan (*WHO Expert*)

Dr M. Wheeler, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA (*WHO Expert*)

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Annex 2

General considerations

An edited version of this section will appear in the report of the eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information can be disseminated quickly.

Considerations for dose–response modelling

Introduction

The present meeting used dose–response modelling to evaluate exposure-related effects and to derive a point of departure to establish a health-based guidance value or a margin of exposure for risk assessment, referring to previous guidance and practices of JECFA (e.g. Environmental Health Criteria [EHC] 239 and EHC 240 as well as the report of the seventy-second meeting of JECFA). During the meeting, the Committee recognized several issues concerning the selection of models to be included in the set of models fitted to the dose–response data identified as pivotal for risk assessment.

Theoretical considerations

Dose–response models are mathematical models that approximate a biological process in a range of observed data. When extrapolating below the lowest dose of the experimental data, it should not be assumed that any one model is an accurate representation of the true underlying dose–response. There are often several different models that describe the data adequately, and there is often considerable uncertainty in the form of the approximation of the dose–response relationship.

Benchmark dose methodology ideally avoids this problem by confining the modelling process to doses at which the relationship between dose and response is highly constrained by empirical data, so that the differences between the estimates generated by alternative models are slight. For example, when considering quantal data, a dose that results in a 10% increase in excess risk is typically used, because this is a size of effect that is typically bracketed by standard testing methodologies using experimental animals. However, the data often do not conform to that ideal. Laboratory studies may be limited by the number of animals per dose or employ doses that are far apart from the dose at which the critical adverse health effects become evident for risk assessment. Epidemiological studies have a different set of theoretical problems (e.g. dose misclassification).

Therefore, the Committee concluded that model estimates cannot rely solely on empirical guidance on performing dose–response analyses and stressed the need to use toxicological knowledge, weight of evidence and other information. Curve fitting, such as benchmark dose modelling, fulfils one key aspect of such an evaluation – it ensures that the dose is “associated” with an effect. As all models are approximations, fitting the data does not necessarily make the model’s estimate plausible. The curve-fitting process must be scrutinized with other criteria based upon biological considerations. These considerations come under the headings of plausibility and analogy:

- *Plausibility*. Quantitative dose–response analysis is rooted in biochemistry. Although absorption, distribution, metabolism and excretion make toxicological interactions more complicated than biochemical interactions in vitro, the combination of such interactions in a living organism should still bear some resemblance to the first- and second-order kinetics suggested by biochemistry. As first-order interactions are approximately linear at low doses and second-order interactions are sublinear at low doses, it is reasonable to suppose that toxicological effects may exhibit dose–response relationships that are linear, highly sublinear (i.e. threshold-like) or anywhere in between. Mathematical models that demonstrate supralinearity at low doses are not toxicologically plausible and should be used with caution.
- *Analogy*. Even if the shape of a dose–response relationship is not well characterized, experience should inform the modelling decisions. In particular, a reasonable approach would assume that it would be rare to observe a completely different dose–response relationship than previously observed, and caution should be taken when extrapolating risk from such models. This reasoning is by analogy. One uses past experience analogically to guide the decisions in a similar situation.

Supralinearity in benchmark dose estimation

When dose–response curves are fitted to data, the benchmark dose (BMD) as well as the corresponding lower bound (BMDL) are computed from these curves, which are based upon a prespecified excess risk value – the benchmark response (BMR). In many situations, the dose–response curve appears supralinear at the doses tested, and models that support supralinearity may describe the data better than models that do not support supralinear dose–response data. One reason is that the set of models available on modelling software allows for both sublinearity and supralinearity. The Committee agrees that these models should not be dismissed for statistical reasons but should be evaluated based upon biological plausibility, and, in many situations, these models can be used to estimate the BMD. For illustrative purposes, Fig. 1 describes such a situation. The fitted dose–response curve (solid line) and corresponding BMD appear reasonable; however, the dose–response curve that is used to calculate the BMDL (dashed line) is clearly unreasonable, as it is essentially vertical at doses corresponding to risk around the BMR (i.e. the slope is infinite at zero). In such a situation, the model should not be used.

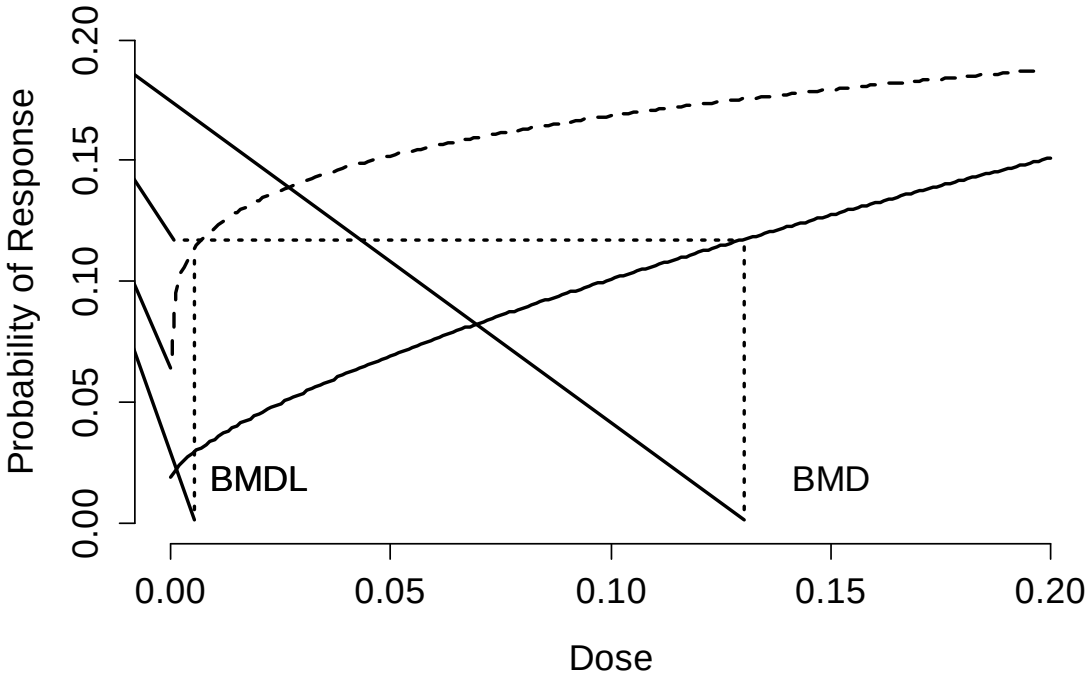

Fig. 1: Plot of a hypothetical dose–response curve (solid line) and its corresponding 95% UB, dashed line. The vertical lines represent the BMD and BMDL. Here, the fitted dose–response curve appears reasonable, but the UB curve, which defines the BMDL, is biologically unreasonable.

It is sometimes the case that the estimate of the BMDL is unreasonable given other considerations; for example, the BMDL may imply that exposure to only a few molecules of a chemical could increase risk by 10%. A check for supralinearity is to estimate the BMD and the BMDL at BMRs above and below the BMR chosen a priori. If the resultant BMDs and BMDLs are approximately located in the linear or sublinear range along the levels tested, the values can be used without objection. If there is a strong pattern of supralinearity, the model may be dismissed as not biologically appropriate. Fig. 2 shows such a plot, where the left pane describes three BMDLs computed at BMRs of 5%, 10% and 20%, and the estimates appear to be on a line. The right pane describes the same circumstance, but there is a large deviation above the line, which indicates supralinearity. In this case, toxicological evidence for that estimate should be investigated, and it should be dismissed if it is found to be biologically implausible.

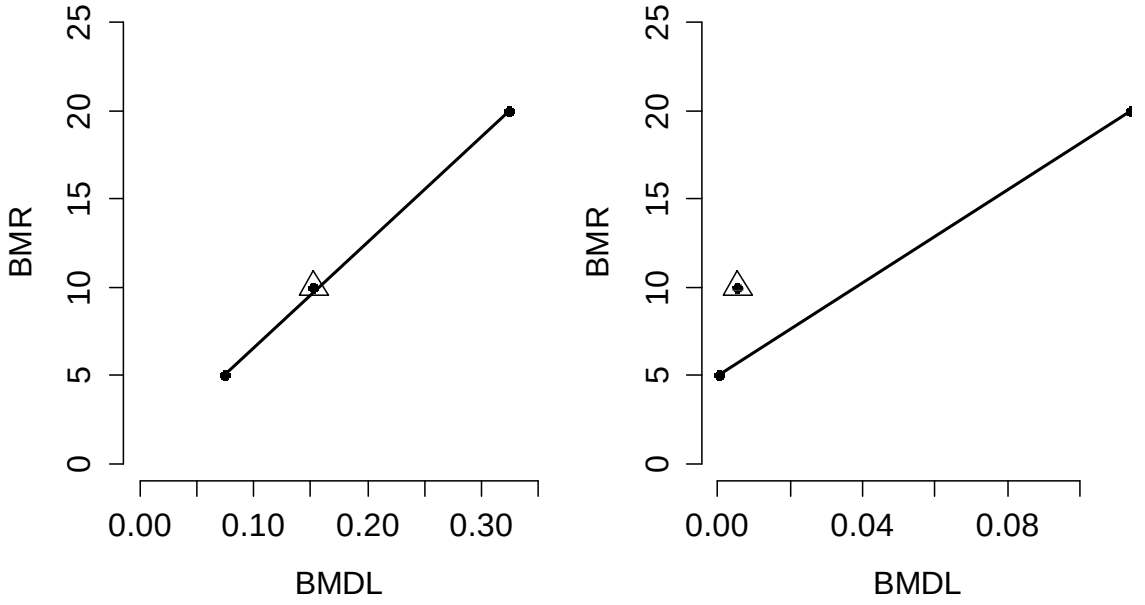

Fig. 2: Comparison of the BMDL computed across different BMRs for a model that is linear (left pane) and supralinear (right pane).

General approaches for identifying a BMDL

Restricted models only. This technique uses models with the default parameter constraints provided with the United States Environmental Protection Agency's (USEPA) benchmark dose modelling software (BMDS). The lowest resulting BMDL is then typically selected as the point of departure. This is the methodology used for past JECFA evaluations for acrylamide, arsenic, fumonisins and cyanogenic glycosides. This method avoids supralinearity, but can result in significantly poorer model fits for some data sets. Additionally, the statistical coverage of this method may be anti-conservative – that is, the BMDL is higher than the true BMD at a rate greater than the confidence limit specified (type I error).

Unrestricted models only. This technique uses models without constraints and also selects the lowest resulting BMDL for identifying a point of departure. This methodology was recently used by JECFA for deoxynivalenol and by the European Food Safety Authority in 2016 for 3-MCPD and other compounds. Although this methodology may avoid the statistical pitfalls of constrained models, as it allows supralinear models, implausible BMDLs may result from using this method.

Model averaging. Model averaging is a method that averages constituent dose–response models. As shown by various authors, it often avoids all of the problems listed above. Such estimates are often less sensitive to supralinear effects and result in estimates that are more reliable statistically. Although there is no current JECFA guidance to using model averaging, it is a useful adjunct to the other methods when computing the BMDL.

Approach taken at current meeting. The Committee used the restricted models to identify the point of departure and also applied the other two methods for comparative purposes.

The current Committee recommends that the JECFA Secretariat establish an expert working group to develop detailed guidance for the application of the methods most suitable to the work of the Committee.

Handling non-detected or non-quantified analytical results for food chemicals

At the current meeting, the Committee discussed two general issues in relation to non-detected or non-quantified analytical results: 1) the handling of a high percentage of left-censored occurrence data (i.e. those analytical results less than the limit of detection [LOD] or LOQ), and 2) dealing with different LODs or LOQs in the same data set for individual chemicals or for a group of chemicals (e.g. aflatoxins or fumonisins). The number of uncensored contaminant data points also needs to be considered. Combination of these parameters can lead to very different results, both in the mean occurrence values derived and in the estimates of dietary exposure. These results will then affect the assessment of risk in relation to the health-based guidance value (e.g. PMTDI) or point of departure (e.g. BMDL). Therefore, how to deal with all of these issues needs careful consideration and consistent approaches for risk assessment purposes, and updating of EHC 240 as needed.

The issue of a high proportion of left-censored data was discussed at the meeting during the evaluations of two mycotoxins, 4,15-DAS and sterigmatocystin, for which the percentages of left-censored data were over 90%. These discussions raised the need to review the current practices used by the Committee on handling left-censored data and to provide the Committee with clear recommendations on how to deal with such situations in its evaluations.

The Committee discussed a proposal but, due to the importance of this topic, decided that further considerations were required. These discussions will be continued after the meeting through a working group.

Annex 3

Future work and recommendations

Considerations for dose–response modelling

Reiterating the recommendations of the seventy-second meeting of JECFA, the current Committee recommends that the JECFA Secretariat establish an expert working group to develop detailed guidance for the application of the methods most suitable to the work of the Committee. The working group should, inter alia, address the following aspects:

- the use of constraints when fitting models that allow for restrictions on the slope and/or power parameters modelling (i.e. the use of restricted versus unrestricted models);
- models to be used from the standard BMDS suite;
- the use of model averaging, including selection of weights;
- the use of non-parametric methods as an alternative for dose–response risk assessment;
- the use of biological information for the selection and specification of models for dose–response;
- transparent presentation of modelling outcomes in JECFA publications;
- review of developments in the USEPA BMDS software.

Handling non-detected or non-quantified analytical results for food chemicals

The Committee discussed a proposal regarding guidance on how to handle left-censored data in its evaluations. However, due to the importance of this topic, the Committee decided that further considerations were required. These discussions will be continued after the meeting through a working group.