TOX/2020/01

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

WHO public consultation on the JECFA/JMPR update of Chapter 5 (EHC 240) (Deadline: 31 Jan 2020)

Introduction

1. The World Health Organisation (WHO) have launched a public consultation on the Joint FAO/WHO Expert Committee on Food Additives/ Joint FAO/WHO Meeting on Pesticide Residues (JECFA/JMPR) update of Chapter 5 of the "Principles and methods for the risk assessment of chemicals in food, Environmental Health Criteria 240" (EHC 240). The update to Chapter 5: dose-response assessment and derivation of health-based guidance values reflects new scientific developments and contributes to international harmonization in the application of dose-response modelling and derivation of acute and chronic health-based guidance values taking into account toxicological as well as microbiological and pharmacological effects.

2. The deadline for submission of comments is Friday 31st January 2020.

3. Members are invited to submit their comments on the draft update to Chapter 5 (attached in Annex 1). These comments will then be submitted to the WHO by the secretariat. The key areas of the chapter are summarised below:

Dose–response assessment and derivation of health-based guidance values

4. The introductory paragraph of this chapter defines a health-based guidance value (HBGV) and point of departure (POD).

Dose-response assessment

Basic concepts of dose-response assessment

5. Dose-response assessment (DRA) is described as a key step in hazard characterisation, that establishes relationships between exposure and adverse health outcomes. DRA is used to derive PODs from which MOEs or HBGVs such as the acceptable daily intake (ADI), tolerable daily intake (TDI) or acute reference dose (ARfD) can be established.

6. Different approaches in dose-response assessment are reported, such as historical approaches that involve deriving the POD using the NOAEL or LOAEL of dose-response data. Whereas more recent modelling approaches include the benchmark dose (BMD) approach, which is now the preference in determining PODs.

7. The document also addresses the origins of dose-response data as being from *in vivo* studies (in animals or humans) and *in vitro* studies; which are also used for mode of action investigations and comparative biological potency assessment. Further to this the challenges of BMD modelling and desires to reduce animal testing were also raised.

8. Concepts of “dose” and “response” in risk assessments are discussed, it is acknowledged that the three types of dose include: external, internal, or tissue. The external dose is the amount of chemical administered to an animal or human in an experimental setting, occupational setting or epidemiological study. The internal dose is the amount of the external dose that is systemically available. It is affected by absorption, distribution, metabolism and excretion (ADME). Biomarkers from epidemiological studies such as plasma concentration or concentrations excreted urine can be used as the internal dose for DRA. Finally, the tissue dose is the amount present in a specific tissue of interest, it can be used to identify a critical effect or response at the target tissue of interest.

9. Additional concepts of dose discussed are the determinants of dose which include dosing duration and dose frequency as well as selection of study type (e.g. acute, chronic and sub-chronic) in establishing a HBGV.

10. Other concepts of dose mentioned regarded chemical-specific adjustment factors (CSAFs) and its incorporation with chemical-specific toxicokinetic data and information on the relationship between external and internal dose. CASF can also be considered to be an adjustment to dose based on relative internal doses. Ultimately, the use of physiologically- based pharmacokinetic (PBPK) and biologically-based-dose-response (BBDR) models in risk assessment was addressed.

11. With regards to the concept of response, a response was recognised as an observation or effect seen following exposure in vivo or in vitro and can fall into any of the 6 categories: continuous, quantal, counts, ordinal categorical, hierarchically nested and multivariate. Additionally, adverse responses were defined as a change in morphology, physiology, growth, development, reproduction or lifespan of an organism or subsystem that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences. It was determined that PODs should be based on effects linked to adverse responses.

12. The preferred approach of dose-response assessment to develop risk assessment advice expressed by JECFA and JMPR is presented in Figure 1. It is preferred because the BMD takes into account all of the dose-response data, uncertainty in the data and uncertainty can be modelled. Dose response modelling (DRM) involves a suite of mathematical models that are fitted to define the dose-response relationship between zero dose and the maximum tested/observed dose. DRM is used to determine the benchmark response (BMR) and the dose associated with the BMR, known as the BMD can be estimated and used to establish a HBGV or to calculate an MOE. Further to this, pairwise comparisons of the data at different dose levels can allow identification of the NOAEL or LOAEL which can be used as a POD.

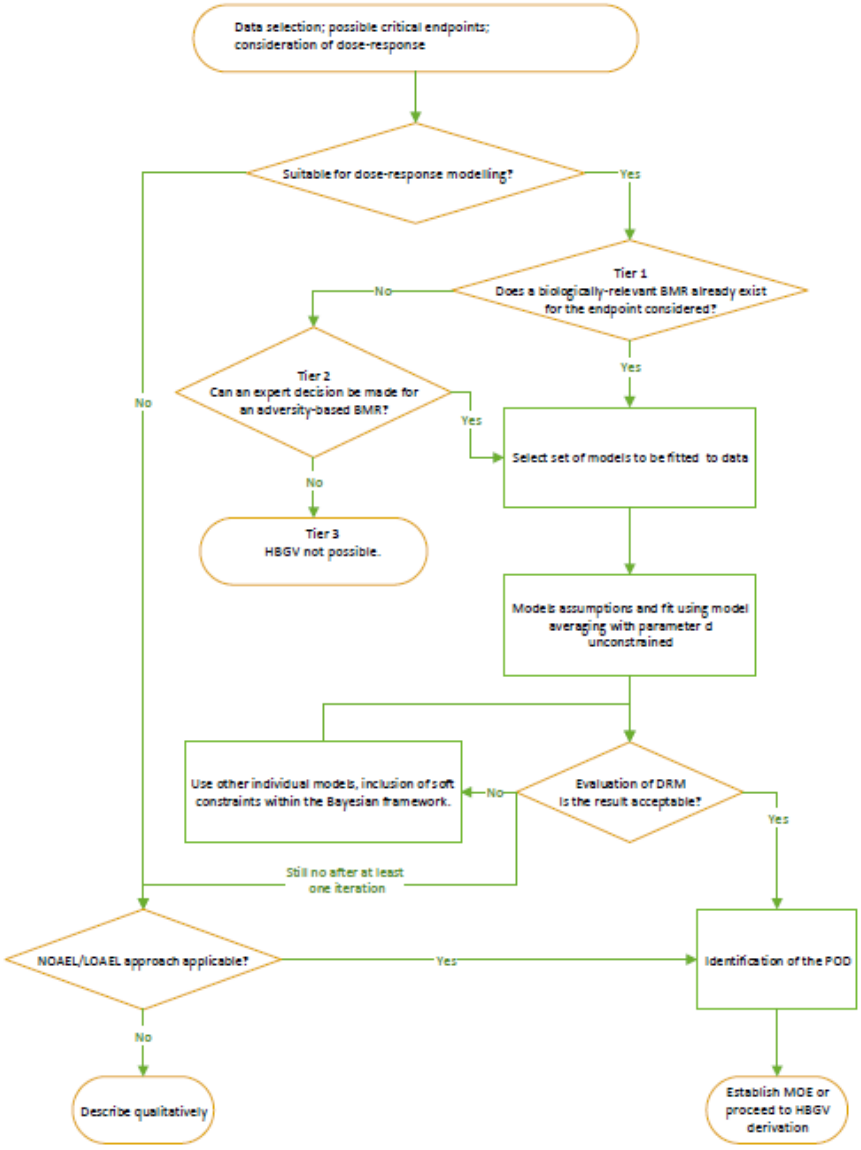

Figure 1 Flow chart for the dose-response assessment processes used to develop risk assessment advice.

Dose-response modelling (DRM)

13. Figure 1 outlines DRM process as a step by step process for a single data set. When the POD is based on more than one data set, the process needs to be reiterated for each relevant dataset and results need to be summarised to identify the POD.

14. The first step in DRM regards the suitability of the dataset, data should be evaluated for biological and statistical significance, human relevance and the existence of dose-response relationship. In the next step an appropriate degree of change (the BMR) is chosen, this will determine the BMD. The third step involves fitting a set of models to the dataset, which is dependent on the nature of the data. For animal datasets the POD used is the benchmark dose level (BMDL) whereas for

human datasets the POD used is the BMD. The outcome of the DRM is used to characterise uncertainty around the POD. Ultimately, once all possible critical endpoints have been determined, it will be possible to identity the most sensitive relevant effect and select the POD that will establish the HBGV.

15. The document explains the use of mathematical models for dose-response data and how suites of models are commonly used. Models for the following data types were discussed: dichotomous and continuous, continuous, quantal, counts, ordinal categorical, nested and multivariate responses.

Model fitting and estimation of parameters

16. The purpose of model fitting is to best describe the dose-response data, and the credibility for interpolating and extrapolating a data set derives mainly from their fit to the data. Model fitting makes statistical assumptions about the data, two methods include frequentist and Bayesian approaches.

17. It was highlighted that model averaging is recommended as a method to address uncertainty in DRM, it allows estimation of the BMD. It is also considered advantageous due to its use of unconstrained models. Although, single models can be used where model averaging results are deemed inappropriate.

18. Other areas highlighted include model parameter constraints, the following parameters maybe constrained: background response, potency of the substance, maximum response and steepness (i.e. influences the slope). A constraint on the steepness parameter can substantially impact on estimates of BMD and strategies to minimise this effect are listed. All other parameters previously described were determined to rarely be of importance.

19. The WHO also suggested PROAST or BMDS as specialised software that meet the requirements able to fit dose-response models.

Modelling observational data from epidemiological studies

20. The document indicates that information from observational/epidemiological studies can be used in DRM, although as exposure assignment is not under control of the investigator in observational studies, this poses challenges of exchangeability, positivity and consistency.

21. In BMD analysis, adjustments for covariates are required for observational settings. It was noted that some BMD software are not designed to deal with multivariable modelling requirements, but statistical packages can be used for this purpose. Confounder-adjusted summary statistics can be generated to reflect dose response curves of aggregated or/quantile data and used to analyse epidemiological data.

22. For observational studies, the equivalent of a control group or “zero dose” would be the lowest quantile of the dataset. Additionally, the exposure range is often

narrower and sampling sizes can be larger than those found in experimental settings.

Determining the point of departure (POD) – NOAEL and BMDL

23. The POD is used to define the dose associated with a risk that can be estimated from a dose-response model and the methodology of defining a POD was discussed in the draft update.

Data selection

24. Advice is given on what experimental and human observational data to select for risk assessment. The initial step is to exclude studies with NOAELs that are greater than those from other studies on end-points that are not markedly different in severity. Also, end-points not showing a dose response relationship on visual and statistical inspection of the data can be omitted. Next steps include selecting potentially relevant end-points for DRM.

25. If a BMD approach is used, three or four different doses (including controls) alongside different levels of effect are recommended for DRM. Two or more similar studies can be combined for analysis in a BMD approach. The NOAEL approach serves as an alternative to the BMD approach when DRM is considered inappropriate. However, neither of the approaches are considered appropriate when animal numbers per dose group are small. Advantages and disadvantages of these approaches and caveats of the BMD approach were recognised.

NOAEL approach for deriving a POD

26. When using a NOAEL approach to determine a POD, sensitivity of the test method is important, statistical significance needs to be established using an appropriate statistical test. Given that the minimum effect size that can be detected by statistical test may be larger than 10%, therefore the NOAEL should be regarded as a dose where the effect is between 0 and 10% or more. Furthermore, the selection of the NOAEL identifies the highest dose level that does not produce a statistically significant effect compared with the control. Ultimately, various study design characteristics that can limit the NOAEL were discussed.

The benchmark dose approach for deriving a POD

27. The BMD approach determines a POD by defining a level of exposure producing a pre-specified response, using DRM. The BMDL (the lower confidence bound of the BMD) is used as the POD to account for experimental variation.

28. The BMR must be selected, it defines an adverse change in response. Its value needs to be within and towards the lower end of the observed range of the experimental response.

29. When continuous data is used to determine a BMDL, a tiered approach should be followed. In tier 1 biologically-relevant adverse effect size or cut point for the respective endpoint is used. In tier 2 experts collaborate to define the quantitative

definition of adverse. In the final tier if no definite BMR can be established the assessment should be considered to be outside the scope of BMD framework, but does not necessarily prevent assessment via DRM.

30. Other areas with the BMD approach discussed include model selection based on data type (e.g. quantal, continuous, count, multivariate). Model assumptions and model fitting, particularly how the distribution of the response must be assumed before a model is fitted. Further to this it is indicated that dose response models must be evaluated for adequate description and fit of data, and results from BMD must be reported, for which guidance is provided in the document.

Establishing health based guidance values (HBGVs)

31. HBGV are described as a quantitative expression of the range of oral exposure that is expected to be without appreciable health risk. They are not established for substances that produce effects that may have no biological threshold and is recommended that a margin of exposure approach (MOE) should be used.

32. HBGV are termed as ADIs and ARfDs when the substances being assessed are added to food (e.g. food additives, pesticides, veterinary drugs). For food contaminants HBGVs are termed as a TDI or a provisional maximum tolerable daily intake (PMTDI), provisional tolerable weekly intake (PTWI) and provisional tolerable monthly intake (PTMI). The document specifies that JECFA and JMPR establish HBGVs based on the most appropriate BMDL or NOAEL in the most sensitive species. A HBGV can be calculated as follows: where the BMDL, NOAEL or LOAEL can be used as a POD:

$$HBGV = POD/UF$$

33. Where UF is the uncertainty factor/safety factor and the BMDL, NOAEL or LOAEL can be used as a POD.

Uncertainty/safety factors

34. The draft update informs that uncertainty factor (UFs) /safety factors (SFs) are used for extrapolation of the POD to a human equivalent exposure. Chemical-specific adjustment factors (CSAFs) are used in the overall UF, CSAF are derived from chemical specific adjustment data such as inter-species and/or intra-species differences in toxicokinetics and or toxicodynamics. CSAFs cannot always be derived if data is unsuitable, in this case default factors are used to establish a HBGV. UF and SF can be used interchangeably for default factors.

35. Traditionally, an overall default UF of 100 has been used to convert a POD into a HBGV. The 100-fold UF accounts for two separate 10-fold factors; one for species differences between experimental animals and humans and two, for variability within the human population. Exceptions to use of the 100-fold SF is if the POD is derived from a human study, therefore only one of the 10-fold SFs discussed above are required.

36. Basic principles for applying appropriate UFs and numerical values for HBGV derivation were outlined.

Acceptable daily intake (ADI)

37. The ADI is used in risk assessment and determines the amount of substance to which humans can be exposed daily for up to a lifetime, without adverse health effects.

38. To establish an ADI, information on metabolism and toxicokinetics of the substance is required and the chemical nature (chemical changes/metabolic activity) of the substance in diet. Other information required is the toxicity and/or pharmacology of the substance that might occur in the diet and effects of chemical forms that consumers are exposed to in the diet.

39. The WHO highlights that metabolism should be considered when establishing an ADI, as effects of concern for a compound can be due entirely to a metabolite rather than the parent compound. For a veterinary drug the ADI established by JECFA is based on the toxicity of the parent drug, assuming all metabolites have similar or lower potency. Although, sometimes an ADI for individual metabolites needs to be calculated, there are also cases where group ADIs have been established.

40. Reference is also made to microbiological ADIs that are established on a microbiological endpoint and a decision tree approach developed by JECFA. Microbiological ADI (mADI) are calculated as follows:

$$\text{mADI} = \frac{\text{MICcalc} \times \text{Mass of colon content}}{\text{Fraction of oral dose available to microorganisms} \times \text{UF} \times 60\ \text{kg}}$$

41. Where the minimum inhibitory concentration calculation (MICcalc) represents the lower 90% confidence limit for the mean MIC50 (the minimum inhibitory concentration for 50% of strains of the most sensitive relevant organism) of relevant genera for which substance is active.

42. The mass of colon content is assumed to be 500g/day.

43. The fraction of an oral dose available to microorganisms is based on *in vivo* measurements for the substance administered orally.

44. UF is the uncertainty factor; which is used to account for uncertainty about the amount and relevance of the MIC data available for review. 60 kg is the standard human body weight.

45. There are also instances where ADIs are not specified, this occurs when the total daily intake levels of a substance required to achieve a desired technical effect does not represent a hazard to health. Therefore, establishment of an ADI in quantitative form is not necessary.

46. ADIs can also be considered temporary by two circumstances. The first is when data for a new substance are deemed adequate to set an ADI but some non-toxicological information (e.g. chemical specification) is missing. The second situation is where there are adequate key safety data to establish an ADI, yet there are minor deficiencies in toxicological information. When a temporary ADI is established a higher than normal uncertainty factor is used, usually higher by a factor of 2.

Tolerable intakes (TIs)

47. There are various classes of food contaminants for which TIs can be developed. These include heavy metals, environmental contaminants, mycotoxins), impurities in food additives, solvents used in processing, packaging material migrants and residues arising from use of animal feed additives or the non-active components of veterinary drug formulations.

48. The principles used to determine ADIs also apply for TIs. There are also epidemiological studies available that can be used to establish TIs and define PODs for contaminants. JECFA also applies the concept of CSAFs when establishing TIs for contaminants, when assessing inter-species and inter-individual differences in toxicokinetics, or using PBTK modelling for this purpose.

49. JECFA's assessment of a weekly or monthly TI considers the possibility of food containing above-average levels of the contaminant, thus leading to exceedance.

Group ADIs/TIs

50. Group ADIs and TIs are established when there are several substances that produce similar toxic effects. Considering substances as a group aims to limit their overall intake.

51. In order to establish a group ADI or TI, the substances should produce the same adverse outcome, by a similar mode of action. One member of the group of substances can be identified as an index compound, with exposure to each member of the group being adjusted according to its potency relative to that of the index compound. One POD will need to be selected when determining a group ADI or TI, if a conservative approach is adopted the group ADI/TI should be based on the lowest POD. Other factors to consider when establishing a group ADI/TI or selecting an index compound are the quality and duration of the studies and in some cases group ADIs can be based on metabolic information.

Establishing acute reference doses (ARfDs)

52. The WHO defines an ARfD of a chemical as the amount of substance that can be ingested in a period of 24 hours or less with reasonable certainty of no harm.

53. It is decided if an ARfD is necessary based on the hazard profile of a substance and end-points relevant to acute effects. Effects of human exposure

should be reviewed using a weight of evidence approach to determine if adverse effects seen in repeated-dose toxicity studies might be relevant to single exposures.

54. A toxicological ARfD is determined in the same manner as an ADI or TI, which involves selection of a POD and application of an uncertainty factor.

55. Alternatively, if an ARfD is based on an effect on the human gut microflora, the approach used will closely follow the approach used to establish a microbiological ADI. JECFA has previously concluded that it is unlikely that a single exposure to a substance will change the susceptibility of the bacterial population within the microbiome.

56. The difference between a microbiological ARfD and microbiological ADI is the estimate of the concentration of substance in the lumen of the colon. For the ARfD it is assumed intake of the active substance results in a single exposure and transits down the gastrointestinal tract into the colon, which would contain no other ingested substance. With regards to chronic exposure it is assumed that ingestion of a substance daily would make exposure of intestinal bacteria to microbiologically active concentrations *in vivo* lower than that occurring for regular ingestion of the same dose.

57. An ARfD cut-off value is determined when it is considered unnecessary to establish an ARfD due to the acute toxicity of a substance being so low that the exposure would be well below the value that would normally be assigned to the ARfD. The ARfD cut-off proposed by JMPR is 5 mg/kg bodyweight, which equates to a POD of 500 mg/kg bodyweight per day, if acute toxicity was seen below this dose it would be considered unnecessary to establish an ARfD. Although, there is an exception for veterinary drugs, where exposure is high at the injection site and acute effects above the cut-off value should be assessed and may therefore result in high ARfD.

58. The WHO outlined following the steps to take when establishing an ARfD. The first step is to evaluate the total database for a substance and establish a toxicological and antimicrobial profile. The next step involves considering the various principles for not needing to establish an ARfD. An explanation is needed if it is decided that an ARfD does not need to be established. If an ARfD is needed it should be established using the most appropriate end-point and uncertainty factors.

59. Toxicological ARfD are calculated in the same way as a standard HBGV, explained in (paragraph 32). Whereas, microbiological ARfD based on *in vitro* data is calculated as follows:

$$\text{ARfD} = \frac{MIC_{calc} \times \text{correct factors x colon volume}}{\text{Fraction of oral dose available to microbiota} \times 60}$$

60. Where correction factors take into account considerations not used for the microbiological ADI but may be applicable to the microbiological ARfD.

61. When microbiological ARfDs based on a POD from in vivo data, ARfDs are calculated in the same manner as a standard HBGV, explained in (paragraph 32).

62. If both a toxicological and microbiological ARfD have been determined, these are compared and the lower is established as the ARfD for the substance.

63. It is preferable to have one single ARfD to cover the whole population. However, the ARfDs based on developmental (embryo/fetal) effects only apply to pregnant women or women on child bearing age and is therefore irrelevant and very conservative for other population subgroups.

Margin of Exposure (MOE) approach

64. The MOE is defined as Ratio of the POD to the exposure dose (ED). It is applied when assessing a DNA-reactive mutagenic and carcinogen, if there is insufficient data for deriving a HBGV and for additives used in infant formula at high inclusion levels. The MOE should be rounded to two significant figures and is calculated as follows:

$$MOE = \frac{POD}{ED}$$

MOE for DNA-reactive mutagenic carcinogen

65. JECFA uses the MOE approach for DNA-reactive mutagenic and carcinogenic substances and has used the $BMDL_{10}$ for carcinogenicity derived from animal studies as the POD. Potency of genotoxic carcinogens have also been directly calculated from epidemiological data, but epidemiological data do not allow determination of potency.

66. Linear extrapolation from a BMDL to estimate cancer risk at relevant levels of human exposure can be used, although an MOE approach is preferred.

67. Uncertainties that need to be considered in interpretation of an MOE include human exposure, extrapolating from animals to humans and additional uncertainties in the process of carcinogenesis.

MOE due to insufficient data

68. MOE of exposure can be used in instances where limitations and uncertainties in the available dataset preclude establishment of a HBGV.

MOE in the evaluation of additives used in infant formulas

69. An MOE approach is used for additives in infant formulas as the ADI concept does not apply to infants up to the age of 12 weeks as they may be at more risk at lower exposure levels compared with older age groups.

70. Reproductive and developmental toxicity studies include direct oral administration to neonatal animals arising through in utero and lactational exposure. However, they do not include direct oral administration to neonatal animals, which are required for the evaluation of food additives in infant formula. This type of study uses doses that are small multiples of human infant exposure, as intended levels of additives in infant formula may be too high to be feasible in animal studies. For this reason, MOEs of food additives used in infant formulas can be quite low (i.e. 0.8-12).

71. The following considerations for interpretation of the MOE relevant to infants are highlighted: maturity of the process of ADME, effects observed in animal models and the relevance to human infants. Additional considerations include, clinical study design and outcome, adverse reactions in post-marketing surveillance. Final considerations relate to dietary exposure assessments, these include that formula is the only source of nutrition for the first 12 weeks of life, there is variability of exposure among infants is small and duration of exposure is for a limited time, and exposure decreases on a body weight basis during the exposure period.

Conclusion

72. Chapter 5 outlines how dose-response assessment should be performed for various data types. It also discusses how the NOAEL and BMD approach are used to determine the POD and how HBGVs and MOEs are established. The key differences between the updated draft chapter and the previous version are the added discussions on DRM for counts and ordinal categorical measures. Other additions include a more in-depth discussion of the MOE approach and its application.

Questions for the committee

- Do members have any comments on the WHO public consultation on the JECFA/JMPR update of Chapter 5?

Secretariat
January 2020

Abbreviations

ADI	Acceptable daily intake
ARfD	Acute deference Dose
BMD	Benchmark-dose
BMDL	Benchmark-dose level
BMR	Benchmark response
CSAF	Chemical-specific adjustment factors
DRA	Dose response assessment
DRM	Dose response modelling
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MOE	Margin of exposure
PMTDI	Provisional maximum tolerable daily intake
PTMI	Provisional tolerable monthly intake
PTWI	Provisional tolerable weekly intake
TDI	Tolerable daily intake

TOX/2020/01/Annex 1

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

WHO public consultation on the JECFA/JMPR update of Chapter 5 (EHC 240) (Deadline: 31 Jan 2020)

This Annex contains the full draft of WHO public consultation on the JECFA/JMPR update of Chapter 5 (EHC 240) and is available at:

https://www.who.int/docs/default-source/food-safety/chapter-5-public-consultation.pdf?sfvrsn=fafb70eb_2

Secretariat
January 2020