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CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON CONTAMINANTS IN FOODS

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The Hague, The Netherlands, 21 – 25 March 2011

DISCUSSION PAPER ON GUIDANCE FOR RISK MANAGEMENT OPTIONS ON HOW TO DEAL WITH THE RESULTS FROM NEW RISK ASSESSMENT METHODOLOGIES

(Prepared by Electronic Working Group led by the United States of America)

BACKGROUND

1. The 4th Session of the Codex Committee on Contaminants Foods (CCCF) agreed to establish an electronic Working Group to develop guidance on risk management options for dealing with the results from risk assessment approaches that are used by the Joint FAO/WHO Committee on Food Additives (JECFA) (ALINORM 10/33/41; paragraph 111). The Working Group participants are found in Annex I.

2. Traditionally in the food area, risk assessment is based on deterministic endpoints, i.e., use of the no observed adverse effect level (NOAEL) or no observed effect level (NOEL) and the mean or high level of exposure. Increasingly, more probabilistic and distributional methods are included, to characterize the hazard(s) as well as the exposure(s). These approaches allow for more description of variability in the population as well as uncertainty in the risk estimates. Moreover, additional risk assessment outcomes are being reported, such as the margin of exposure (MOE), which give a relative indication of the level of health concern without actually quantifying the risk. These expansions of risk assessment tools and information provided require additional risk management approaches.

3. Further, exposure information now has greater attention in the risk assessment of chemicals and different exposure scenarios (e.g., from different susceptible populations) are being compared to estimated risk. This more detailed comparison needs greater scrutiny by risk management as well as considerations for what fraction of the population will be affected by different measures.

4. The purpose of this discussion paper is to briefly describe the more traditional and the newer risk assessment methodologies (Annex II) and then, most importantly, provide options and directions for how the different risk assessment outputs can be considered by risk management.

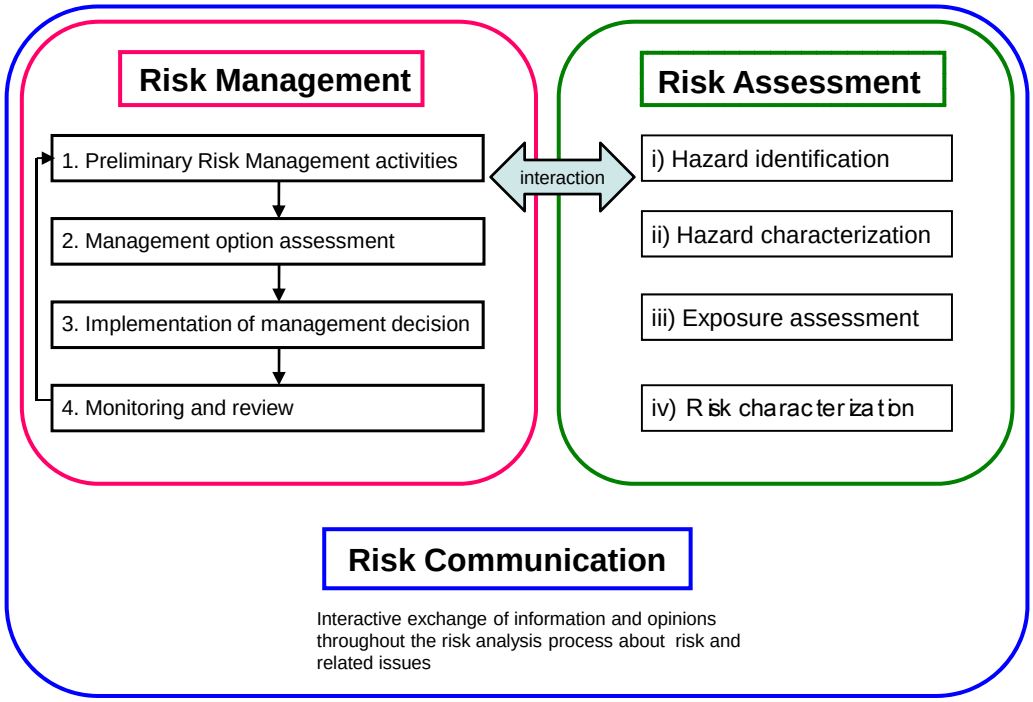
5. The eWG provides this discussion paper to CCCF for further evaluation and discussion during its fifth session. During the drafting of this paper, there were considerable comments provided and many recommendations about how to proceed, some of which were contradictory. This paper is drafted to balance the depth needed for some risk assessment context so that there is an understanding of what the subsequent risk management options mean more fully. This paper is presented to the CCCF to discuss what will be the future work on this paper. It is recommended that CCCF decide if work on this paper should continue, if some focus on risk assessment context as presented is appropriate, what (if any) case studies would be appropriate (see notes in Annex IV), and most importantly, what ideas can be provided to flesh out the risk management options sections.

Introduction

6. This discussion paper provides guidance to CCCF in addition to the working principles for risk analysis for application in the framework of the Codex Alimentarius (Codex) as found in the Codex

Alimentarius Commission Procedural Manual. Codex embraces the use of risk analysis in the development of risk-based approaches for the management of public health hazards in food. Risk analysis is made up of three components and Figure 1 illustrates the relationship between the three components of risk analysis.

FIGURE 1
Codex schematic framework for risk analysis



[Note: Japan suggests replacing the chart by the second one immediately above that explains the Codex schematic framework for risk analysis following "Working Principles for Risk Analysis For Application in the Framework of the Codex Alimentarius" in the Codex Procedural Manual. According to Article 2.2 of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), Risk management (sanitary measures) is based on scientific principles and is not maintained without sufficient scientific evidence. In the Codex Procedural Manual, it is stated that "The food standards, guidelines and other recommendations of

Codex Alimentarius shall be based on the principle of sound scientific analysis and evidence …". Although Risk Management itself involves policy development, it should be based on science.

The present description in the first chart could cause misunderstanding on this point.]

7. Although it is desirable to separate the functional activities of risk assessment from those of risk management in order to ensure scientific independence, it is acknowledged that risk managers should communicate and interact with risk assessors throughout the process, particularly during the problem formulation and planning and scoping phases at the beginning of the risk analysis process. This will help focus and direct the risk assessment on the appropriate risk management issue(s) and question(s). Thus, the relationship between risk assessment and risk management is an interactive, often iterative, process. An important part of this interaction is development of a risk assessment policy. The Codex Procedural Manual defines risk assessment policy as follows: "Documented guidelines on the choice of options and associated judgments for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained." This procedure aims at ensuring that the risk assessment is systematic, complete, unbiased, and transparent. The mandate given by risk managers to risk assessors should be as clear as possible.

8. Of equal importance is the communication between the risk assessors and the risk managers at the end of the risk assessment when communicating the outcomes to the risk managers. These outcomes will help the risk managers determine what food safety decisions may or may not be needed. It is this point in the risk analysis process that this discussion paper will emphasize. This purpose is consistent with the intent of the Codex Procedural Manual (Section IV: Risk Analysis, Section 2. CCFA/CCCF and JECFA) that encourages the two bodies to continue to develop procedures to enhance communication between the two committees.

9. As detailed in the Codex Procedural Manual (Section IV: Risk Analysis, Sections 3. CCFA/CCCF and 4, JECFA), there is an interrelationship between the two committees which requires comprehensible and transparent communication. JECFA is primarily responsible for providing CCCF with science-based risk assessments, comprised of the four components (i) hazard identification, (ii) hazard characterization (including dose response assessment), (iii) exposure assessment, and (iv) risk characterization. This serves as the basis for CCCF's food safety discussions and recommendations for management actions, such as maximum limits (MLs) in foods, to the Codex Commission.

10. For further discussion on the risk analysis process/framework and the components of risk analysis, refer to the Codex Procedural Manual, the International Programme on Chemical Safety (IPCS) document EHC 240: Principles and Methods for the Risk Assessment of Chemicals in Food (FAO/WHO, 2009), and the FAO Food and Nutrition Paper 87: Food Safety Risk Analysis – A Guide for National Food Safety Authorities (WHO/FAO, 2006), among many possible references.

11. Several glossaries provide definitions to the terms relevant to this paper, which serve as useful references, and two main sources were used in this discussion paper:

FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization). 2009. Environmental Health Criteria 240: Principles and methods for the risk assessment of chemicals in food. At: http://www.who.int/ipcs/food/principles/en/index1.html

U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS). At: http://www.epa.gov/ncea/iris/help_gloss.htm

Risk Assessment Outcomes

12. Risk assessment is a process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (IPCS Risk Assessment Terminology; WHO, 2004). There are many outcomes that are possible from a risk assessment ranging from a qualitative description of possible risks, to prioritization of risks, to a quantitative estimation of the risk at specified exposure levels. Most of the outcomes discussed here focus on quantitative derivations of risk.

Health-Based Guidance Values (HBGVs)

13. The setting of health-based guidance values, such as ADI/TDI or ARfD, provides quantitative information from a risk assessment for risk managers, enabling them to make decisions concerning the protection of human health. HBGVs developed by JECFA (and JMPR) for substances found in food, and also drinking water, are the quantitative expression of the range of oral exposure (either acute or chronic) that would be expected to be without appreciable health risk. HBGVs are calculated by dividing the point of departure (POD) by suitable safety/uncertainty factors.

14. HBGVs are established for compounds that produce adverse effects via a mechanism that demonstrate a non-linear dose-response relationship, i.e, an exposure level where an adverse effect cannot be discerned above background.

Point of Departure (POD)

15. The critical endpoint(s) and critical study(ies) (i.e., based on the most sensitive species, most sensitive endpoint of relevance to humans, nonreversible adverse health effect) are identified from which the appropriate doses for risk assessment can be selected (e.g., NOAEL). For doses responses that can be modelled, subsequent estimates of risk are made. From such dose response models, a point of departure (POD) for extrapolation to doses of anticipated human exposure(s) is identified.

16. Traditionally, the NOAEL for the critical effect from the critical study represents the traditional POD for health risk assessment of chemicals. The NOAEL is the highest experimental dose level for which the response is not statistically significantly different compared with the response in the control group. Expert judgment is involved in the determination of the NOAEL value. It is selected from the study that has been determined by experts to be most relevant for extrapolation to human risk. If a NOAEL cannot be identified from the most relevant study, then the lowest-observed-adverse-effect-level (LOAEL) is selected as the POD.

17. In order to use more information on the dose response relationship and as an improvement over the NOAEL approach, the benchmark dose (BMD) method is increasingly used where data allow. The BMD method has a number of advantages, including the use of the full dose response data in the statistical analysis, which also allows the quantification of the uncertainty in the data. Higher uncertainty in the data, for example, due to small group sizes or high variation within a group, would be reflected in lower health based guidance values (EHC 240; WHO, 2009).

18. Briefly, the BMD method involves fitting a series of dose response models to the data, and a BMD is estimated from each model as the dose corresponding to a specified change in risk/effect over background (i.e., the benchmark response, BMR). The lower one-sided 95% confidence bound on the BMD is calculated, i.e. the BMDL, to account for uncertainty in the data. From all models that provide an acceptable fit to the data the BMDLs are calculated and the range of BMDLs expressed. In the risk assessment, the lower end of the range of BMDLs is used in a conservative and hence more health protective approach.

Uncertainty and Variability

19. Uncertainty occurs because of a lack of knowledge. It is not the same as variability. For example, a risk assessor may be very certain that different people drink different amounts of water but may be uncertain about how much variability there is in water intakes within the population. Uncertainty can often be reduced by collecting more and better data, whereas variability is an inherent property of the population being evaluated. Variability can be better characterized with more data, but it cannot be reduced or eliminated. Efforts to clearly distinguish between variability and uncertainty are important to characterize risk.

20. Variability refers to true heterogeneity or diversity. For example, among a population that drinks water from the same source and with the same contaminant concentration, the risks from consuming the water may vary. This may be due to differences in exposure (i.e., different people drinking different amounts of water and having different body weights, different exposure frequencies, and different exposure durations) as well as differences in response (e.g., genetic differences in resistance to a chemical dose). Those inherent differences are referred to as variability. Differences among individuals in a population are

referred to as inter-individual variability, differences for one individual over time is referred to as intra-individual variability.

21. Any parameters or predictions estimated from a given model are only point estimates and, to a larger or smaller extent, uncertain. This uncertainty arises from at least three sources: 1) the sampling error arising from inferences about a larger population from a single experiment; 2) the reality that dose–response estimates often differ among experiments with different experimental design, protocol or uncontrolled circumstances; and 3) the fact that the "true" model is not known, which results in additional uncertainty when interpolating between doses, but even more so when extrapolating outside the dose range containing observations. These uncertainties may all be represented in a dose response assessment through the use of probability distributions or probability trees. The latter technique involves using multiple alternative plausible assumptions about what data sets or models are to be used to produce an estimate, which results in a range of plausible estimates (FAO/WHO, 2009).

22. The Codex Procedural Manual provides guidance where constraints, uncertainties, and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty and variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable.

23. Sensitivity analysis can provide some insight to uncertainty. This analysis helps determine how changes in various inputs (data or assumptions) affect the outcomes of a risk assessment. An insight gained is an estimation of how much the uncertainty or variability associated with each input factor contributes to the overall uncertainty and variability in the risk estimate. Input distributions where uncertainty has the greatest impact on the outcome can be identified.

Uncertainty/Safety Factors

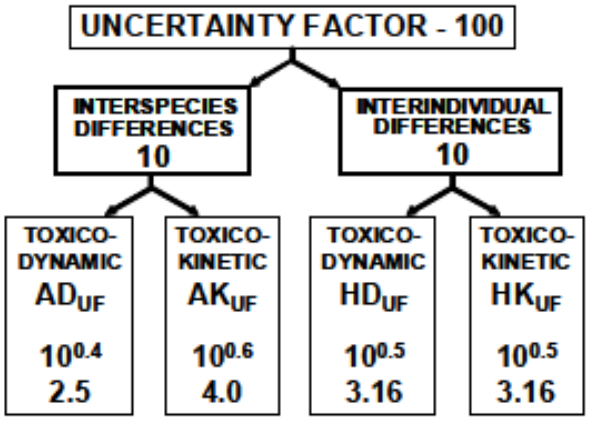
24. Uncertainty, or safety, factors are used to address the uncertainty and variability surrounding the data being used to estimate risk. An uncertainty/safety factor is usually a composite factor by which the selected POD is divided to derive a HBGV, which is considered a dose without appreciable health risk, corresponding to a safe level of exposure.

25. The default uncertainty/safety factor of 100 consists of the product of two separate 10-fold factors that allow for 1) differences between the average responses in the experimental animals used in the study identified to derive the POD and those in average humans and 2) the variability in responses between average humans and those who are highly sensitive (IPCS, 1987). The recognition that the original 100-fold uncertainty factor could be considered to represent two 10-fold factors allowed some flexibility, because different factors could be applied to the POD from a study in humans and the POD from a study in experimental animals. For example, if data from well-conducted studies in the human population are the basis for the risk estimate, a factor of 10 has been considered appropriate as a default value (IPCS, 1994).

26. A refinement has been used in which the two default 10-fold factors can be subdivided to incorporate appropriate data on toxicodynamics or toxicokinetics where these exist (Renwick, 1993). Subdivision of each factor of 10 into toxicokinetic and toxicodynamic components would allow part of the default value to be replaced by relevant, chemical-specific data, when these are available.

27. From this the concept of chemical-specific adjustment factors (CSAF) has been derived.

Figure 2: Subdivision of the usual uncertainty factor of 100. Chemical specific data can be used to replace a default uncertainty/safety factor by an adjustment factor (AF) (WHO 2005)



AD_{UF} = Uncertainty factor for animal to human differences in toxicodynamics
AK_{UF} = Uncertainty factor for animal to human differences in toxicokinetics
HD_{UF} = Uncertainty factor for human variability in toxicodynamics
HK_{UF} = Uncertainty factor for human variability in toxicokinetics

CSAFs for interspecies differences and human variability can be incorporated into a composite factor (CF). The CF is the product of four different factors, each of which could be a CSAF or a default uncertainty factor:

$CF = [AK_{AF} \text{ or } AK_{UF}] \times [AD_{AF} \text{ or } AD_{UF}] \times [HK_{AF} \text{ or } HK_{UF}] \times [HD_{AF} \text{ or } HD_{UF}]$

- A represents the animal to human extrapolation factor (based on quantitation of interspecies differences)
- H represents the human variability factor (based on quantitation of interindividual differences)
- K stands for toxicokinetic differences
- D stands for toxicodynamic differences
- AF is the adjustment factor calculated from chemical-specific data
- UF is the uncertainty factor, a default value that is used in the absence of chemical-specific data.

28. The development of CSAFs may not always be possible or even necessary. For example, if the margin between the POD and anticipated human exposure is very wide, the generation of the more sophisticated data necessary to replace part of a default uncertainty factor would not warrant the necessary experimentation in animals and humans and the associated resource expenditure. However, where this margin is small, development of additional chemical-specific quantitative data may be justified to refine the dose response analyses and scientific credibility of the outputs, such as acceptable daily intakes (ADIs)/tolerable daily intakes (TDIs), and margins of exposure (MOEs).

29. Additional uncertainty/safety factors can be used "case-by-case," mainly to account for deficiencies in the database, to extrapolate from sub-chronic to chronic exposure, or to extrapolate from a NOAEL to a LOAEL.

30. Critical in the application of uncertainty/safety factors is always the transparent description and explanation for the selection of all factors applied.

Margin of Exposure (MOE)

30. Substances that are both genotoxic and carcinogenic would generally not be considered acceptable for use as food additives, pesticides or veterinary drugs. For genotoxic and carcinogenic substances, the traditional assumption is that there is a linear dose response down to zero dose and that some degree of risk

may exist at any level of exposure. Thus, JECFA does not establish HBGVs for substances, such as certain contaminants, that are known to be both genotoxic and carcinogenic.

31. In order to advise risk management, the MOE concept has been applied to several such contaminants (e.g., acrylamide). The MOE is the ratio between a POD and the estimated human exposure. The MOE takes relative cancer potency and exposure estimates into account, and thus gives an indication of the level of concern. The higher the MOE, the lower the health concern, and vice versa.

32. This approach provides advice to inform risk managers of how close human exposures are to those that produce a measurable effect in laboratory animals or humans. In addition, MOEs for different substances can be compared to assist risk managers in prioritizing risk management actions (EFSA, 2005a; FAO/WHO, 2005; O'Brien et al., 2006). The level of regulatory or non-regulatory intervention will then take account of the size of the MOE.

33. It should be noted, however, that some chemicals increase the incidence of cancer in experimental animals by non-genotoxic mechanisms, and establishing a reference value would be appropriate for such chemicals (FAO/WHO, 2009). However, for substances with a non-linear dose response, but for which the database is really too incomplete to set a reference value, the MOE approach is also used in relation to a specific endpoint for which there are some data.

Quantitative Risk Estimates

34. If sufficient data are available, JECFA can also perform a fully quantitative risk assessment, describing the quantitative risk estimate at defined levels of exposure. To date this has been done for aflatoxins only, where the cancer risk (i.e., number of estimated cancer cases per year) per ng of aflatoxin ingested was estimated for different populations at risk. Such detailed risk assessments require a large amount of data that are often not available. [Note: it was commented that a quantitative risk assessment was done by JECFA for fumonisins in 2001].

Risk Management Options

35. The manner in which HBGVs (also called reference values) such as the ADI, TDI, and RfD are estimated usually generates deterministic values in that they imply a demarcation between what is a "safe" level of exposure (i.e., exposures below the value) versus a "non-safe" level (i.e., exposures above the value). In many instances over the years, these deterministic values have been used as a common "bright line" approach to managing risk. Decision makers and competent authorities use these reference values to set standards and regulations for what are appropriate exposures. However, it should be kept in mind that due to uncertainty and variability, these apparent "bright lines" in reality are not as precise (i.e., not as sharp a boundary between safe and non-safe) as they appear to indicate. There should be an understanding that there is a distribution of uncertainty (as much as an order of magnitude for RfDs for instance) that must be understood. Probabilistic modelling (e.g., with distributions around the values) provides risk managers more detailed dose response modelling with greater transparency of the uncertainty surrounding many of these values. To aid the decision, the risk assessment should provide information on the nature and magnitude of uncertainties in both the toxicological and exposure data that make up the inputs to the distributions being modelled.

36. For risk managers, the distribution around the reference value and its probabilities and uncertainties makes decision making more complicated, particularly about who specifically or what portion of a population to protect. Considerations need to be made regarding whether the most sensitive individual(s) needs to be protected or the bulk of the general population (e.g., to decide on a goal that at least 95 % of any population should not exceed the TDI (in some cases this could be a long term goal)). For some contaminants, it may be useful to establish more than one reference value (e.g., a TDI or RfD for the general population and an ARfD for pregnant women).

Maximum Level (ML) by Codex

38. In the case of chemical contaminants, MLs are established by CCCF, with advice from JECFA, to be compatible with tolerable intake levels and are based on the lowest level of contamination that can be reasonably achieved without removing the food from the food supply. The Codex Procedural Manual states

that CCCF shall endorse maximum levels only for those contaminants for which 1) JECFA has completed a safety assessment or has performed a quantitative risk assessment, and 2) the level of the contaminant in food can be determined through appropriate sampling plans and analysis methods. The setting of an ML for a contaminant may be considered where the risk is high and when it occurs in foods which make a significant contribution to total exposure. The Codex ML for a contaminant in a food or feed commodity is the maximum concentration of that contaminant recommended by Codex to be legally permitted in that commodity.

39. Although MLs are mainly set for primary commodities, it may be appropriate to set an ML for processed foods where the setting of an ML for the primary commodity is judged to be ineffective or where the contaminant arises as a result of processing (e.g., chloropropanols) or where appropriate processing may result in the removal of a toxin. In cases where the source of the contamination is sporadic, such as with biotoxins in bivalve mollusks, setting an ML can serve as an effective control against occasional poisoning outbreaks if regular monitoring is undertaken, while other control mechanisms try to minimize the occurrence of these outbreaks.

40. For a contaminant that has a chronic toxic effect and a lognormal distribution, the setting of an ML for that chemical in the food in which it occurs often has little impact on the mean exposure of the population. If a reduction in exposure is desired, a significant proportion of the food would have to be removed from the market in order to shift the mean value. In addition, in cases where the mean exposure to a chemical is well below the toxicological reference value, establishing an ML in the food is unlikely to have any impact in terms of public health.

41. Another aspect of MLs helps risk managers determine what different risk management may be considered. Different hypothetical MLs can be examined for a contaminant under its exposure scenarios and help provide insight to risk management options and the ultimate ML established (e.g., aflatoxin in tree nuts).

Interpretation of the Margin of Exposure

42. In order to decide on the necessity for risk management action in cases where the outcome of the risk assessment is an MOE, the level of health concern needs to be interpreted.

43. There is no general guideline for the interpretation of the MOE. The acceptability of a MOE depends on its magnitude and is ultimately a risk management decision (IPCS, 2009a). To aid to that decision, the risk assessment should provide information on the nature and magnitude of the inherent uncertainties and variability in both the toxicological and exposure data (Barlow et al., 2006). There are some points regarding the acceptability of a MOE that can be considered.

- Empirically, when comparisons between the linear low dose extrapolation historically used for genotoxic carcinogens are made to estimate MOEs, the risk of one in a million cancer risk from the low dose extrapolation is found at MOEs of approximately 100,000. This might be considered an upper value for which greater MOE values would be considered of low risk. When there are adequate data to determine the mode of action for carcinogenicity is a genotoxic one, EFSA has suggested that a MOE of 10,000 or greater would be appropriate (EFSA, 2005).

- For compounds with less severe endpoints (i.e., not genotoxic carcinogens, severe reproductive/developmental toxicants), consideration of whether the identified MOE presents a concern for human health could follow a process similar to selection of appropriate uncertainty factors to be used in establishing a reference value (e.g., factor of 10 for interspecies differences, 10 for human variability and additional factors for important gaps in the database). Therefore, a MOE of 100 might be considered a lower value for contaminants with a low relative risk.

- When the estimated MOE falls between these values with attendant toxicities of concern, it becomes more difficult for risk managers to decide on the acceptability of that MOE. Usually decisions on the acceptability of that MOE are made on a case by case basis depending on the level of public health protection needed or desired and the extent and nature of the population of people being exposed. Again, when the uncertainties and variability are clearly and transparently analyzed, this will assist the decision

on what is an acceptable MOE for that contaminant. Some considerations can assist the risk manager regarding the MOE level:

- *The number of assumptions and amount of uncertainty*. Larger number of assumptions and greater uncertainty in the data probably needs a larger MOE.
- *The number of responses (adverse effects)*. A smaller MOE may be called for when a compound induces one type of response versus several responses, which would likely result in a larger MOE.
- *The nature of the response(s)*. Depending upon the severity of the effect (e.g., enzyme level change versus frank tumor), whether the response is a precursor effect in the mode of action or a frank apical effect, and the slope of the dose response curve (e.g., steep versus shallow rise; over what range of doses it rises) will help discern an acceptable MOE.
- *Number(s) and different kinds of mode(s) of action*. When a contaminant is demonstrated to have more than one mode of action, a larger MOE may be necessary. This also depends on the nature of response induced by those modes of action. For example, a smaller MOE may be acceptable if the only response/mode of action is a reversible change of liver weight increases with no other observed response. A genotoxicity mode of action probably argues for a larger MOE.
- *Persistence of compound*. Information about the contaminant's persistence in the body would suggest a larger MOE for those compounds that persist longer in the body.
- *Sensitive populations/lifestages*. The risk manager may decide that sensitive populations (e.g., children at risk) need to be considered and a larger MOE may be appropriate to take their sensitivities into account.

44. Information on the exposure(s) to the contaminant may help determine the MOE. If a great number of people are exposed versus a very small number, a larger MOE may be necessary for the first case. However, the size of the MOE depends not only the number of people exposed, but the nature of the exposure, the timing and length of the exposure, and who is more or less sensitive to the exposure, among many exposure variables.

General Considerations for Risk Management

45. The decision as to whether the appropriate risk management strategy/option is regulatory or non-regulatory or a combination of both will depend on a number of factors, including the severity of the health risk, the probability of its occurrence, the number of individuals potentially affected, the level of protection required or desired, and the anticipated effectiveness of the proposed risk management strategy. Since risk assessments may be qualitative or quantitative in nature, it is necessary to consider how the type of risk assessment will impact the way it is used in risk management. Different types of quantitative risk assessment can be applied, generally following either deterministic or probabilistic approaches. Deterministic approaches are usually based on single value inputs and outputs (which may be bounded by confidence intervals) and provide a relatively straightforward means of using a risk assessment to develop risk management options (e.g., setting of maximum levels). However, this comes at a cost in providing less accurate information, e.g., limited insights into uncertainty (even if accompanied by confidence intervals) and a tendency to focus on extreme situations such as worst-case scenarios. Probabilistic approaches provide the means to overcome some of these deterministic disadvantages. The inputs and outputs of the probabilistic approaches are distributions of values and can incorporate both uncertainty and variability. However, this poses a challenge of how to express the outcome as an option to be achieved by appropriate food safety control measures.

46. Regardless of approach, many risk management options for contaminants rely on estimates of tolerable exposure levels for avoiding adverse health effects (as described in earlier sections). For chemical contaminants, the output of the risk assessment generally includes an estimate of a tolerable intake, such as a TDI or PTWI which are generally based on an estimate made by the risk assessment of a dose level that is reasonably certain to have no adverse health effect(s). For probabilistic outputs, an acceptable/tolerable level is in most instances decided by risk managers to take into account a sizable portion of the distribution to help

maximize the level of protection (e.g., the 95th or 99th percentile of a distribution). The range of risk management options that could achieve that level can be selected for implementation, e.g., enforcing good agricultural practices (GAPs) at the farm level to minimize contamination and/or setting MLs for contaminants in specific foods. Risk management options are implemented by a variety of parties, including government, the food industry, and consumers, each of which has different responsibilities depending on the risk management option being used.

47. In some cases, a single option may have the potential to successfully manage the risks associated with a particular food contaminant. In other cases, a combination of options may be necessary. In general, to the extent practicable, it is valuable to consider initially a relatively broad range of possible options, then to select the most promising and feasible one(s) to implement. The Codex Alimentarius assists competent authorities with its development of food standards, guidelines, and related texts as codes of practice.

Establish Regulatory Requirements

48. One of the major risk management options is for a competent authority to establish regulatory requirements. For contaminants, a regulatory level is usually based on the Codex ML for a contaminant in a food or feed commodity that is understood to be the maximum concentration of that substance recommended by the Codex Alimentarius Commission to be legally permitted in that commodity. Codex standards usually relate to product characteristics and may deal with all government-regulated characteristics appropriate to the commodity, or only one characteristic. MLs for contaminants in foods are examples of standards.

49. The competent authority establishes the regulatory level through legislation and/or rule making (the process usually entails proposing the new level in a policy statement and then soliciting stakeholder/public input on the proposed new policy before instituting the regulatory level). Codex member countries usually adopt or adapt the Commission's adopted standard, and members can establish a different standard if there is a scientific-based reason to do so for their national situation.

50. Competent authorities can establish control measures specifying relevant requirements that allow attainment of the regulatory level. These may be necessary for industries that do not have the means to establish appropriate measures themselves or who adopt such control measures, including appropriate measures at specific stages of the food/feed chain where they are of critical importance to the performance of the overall chain.

51. Competent authorities can establish requirements for inspection and audit procedures, and certification or approval procedures to ensure that regulatory levels are attained. Codex methods of analysis and sampling, such as those for contaminants in foods, are Codex standards that competent authorities or industry can adopt or adapt in their requirements for inspection and auditing.

52. Another major regulatory option is a strategy to eliminate the potential for risk(s). Examples of this can include a ban on the sales of an imported food with a history of high levels of contamination, prohibiting the use of a carcinogenic chemical that may contaminate food, or severely restricting the use of a chemical).

Publish Guidelines/Guidances

53. Non-regulatory risk management options can be considered, generally when the health risk is lower such that the development of a regulatory measure is not warranted or where the setting of an ML is unlikely to be effective. This may be in the form of a best practice guideline document or a code of practice (practices discussed in next section).

54. Codex guidelines provide principles that set out policy in certain key areas; and guidelines for the interpretation of these principles or for the interpretation of the provisions of the Codex general standards. In the case of contaminants, the basic principles governing the regulation of these matters are built into the relevant standards and codes of practice. Competent authorities can utilize Codex guidelines to publish guidances, notices, or directives to address food safety issues (these can be new or updated policies that aren't rule making). Such guidance documents do not establish legally enforceable responsibilities like regulatory levels or actions discussed above. Instead, guidances describe the current thinking on a topic and should be viewed as recommendations, unless specific regulatory requirements are cited. For example,

notices and directives can be written instructions for government personnel, but serve as informational sources to industry and the public since these guidances generally are publicly available.

Establish Good Practices

55. Codes of practice may also supplement a food regulatory measure, e.g., when advice is needed to facilitate compliance. Controls other than regulatory measures are often appropriate to reduce or eliminate the possibility of food contamination, e.g., controls on waste management and disposal, on water quality, on zoning, and other environmental safeguards. In some cases, these controls may eliminate the need for additional specific controls on the food itself. Codex codes of practice, e.g., codes of hygienic practice, define the production, processing, manufacturing, transport, and storage practices for individual foods or groups of foods that are considered essential to ensure the safety and suitability of food for consumption. Competent authorities can develop (or encourage the development of) specific documents and guides, e.g., good agricultural practices (GAPs), good manufacturing practices (GMPs), good hygienic practices (GHPs), and Hazard Analysis and Critical Control Point (HACCP) plans.

56. Where CCCF has developed such codes of practice for adoption by the Codex Commission, these can serve as models for the adoption or adaptation of codes and guides for their national situation. For example, the introduction of agricultural management practices can be an effective risk management control measure. For instance, soil conditions such as pH and the level of organic matter significantly influence the uptake into plants of metals such as cadmium. Similarly, storage conditions such as humidity and temperature significantly influence aflatoxin levels in peanuts.

57. The competent authorities, the food industry, or a 3rd party expert body can draft more specific guidances to further explain how industry can implement these good practices. For example, these documents could identify those points between production and consumption where food safety measures could be implemented to: prevent or limit initial levels of contaminants in raw materials (e.g., select ingredients that do not have presence of a known contaminant); reduce potential for environmental contamination or cross contamination (e.g., mandate food processing controls); and/or reduce contaminant levels in foods (e.g., physical inspection processes). Industry-led quality assurance programs at the producer level are other examples of good practices.

Communication Measures

58. An important risk management strategy is to ensure good communication with all stakeholders and impacted parties regarding the food safety measure(s) being taken. Communication can take many guises, through advisories, public meetings (often to inform and also to solicit input), technical meetings (with industry, other agencies, consumer groups; usually to solicit input), and constituent updates.

59. Public meetings may be structured as simply informative, e.g., the competent authority announces a new policy and invites written and oral comment. Public meetings can be also in the form of break-out groups as experts from all sectors are invited to participate in brain storming sessions with the outcome in the form of proposed action items for one or all parties to take or a revised policy. The competent authority can solicit input from neutral 3rd party expert group where risk management options to deal with a particular food safety issue are discussed and technical experts from academics/research/industry/government brought together in on data presented and provide recommendations.

60. Competent authorities can hold regular meetings with constituent groups for the purpose of allowing them to ask specific questions to the authority relative to a new or change in policy or regulation. This is opportunity for the constituents to become educated about new expectations.

Dietary advice

61. Competent authorities can issue advisory documents on safe intake levels (for instance, quantity/portion of each food item, in the context of trade-off of risks and benefits in food consumption (e.g. methylmercury in fish)) for certain food products across specific demographics (e.g., pregnant women, children, elderly, immunocompromised). Authorities can require labelling to inform consumer groups who may be especially susceptible, e.g., people allergic to nuts, or pregnant women exposed to methymercury in fish. This provides information to consumers so that they can voluntarily limit exposure.

Mitigation strategies

62. Competent authorities may work with industry to reduce human exposure to contaminants by setting appropriate targets and establishing strategies to comply with such targets. Increased inspection of establishments, collection and analysis of samples, and/or monitoring of imports can be implemented to ensure mitigation of any potentially harmful exposures to contaminants.

Recalls/Public Health Alerts

63. Competent authorities (where they have the authority) and industry can invoke recalls of commodities when they are determined to be unsafe food products. Monitoring of adverse event reports and consumer complaints help in the determination if there are public exposures of potentially unsafe food products.

Education/Training

64. An important risk management strategy is education and training for all stakeholders involved in food safety. Education can occur for those in competent authorities, in industry, and in the public. Appropriate training for those in food safety should be a priority for competent authorities and industry to institutionalize. Extension services, including provisions for practical educational training at colleges and universities, could be mobilized to support educating industry and the public. All manners of reaching out to stakeholders should be considered to maximize the education message(s), e.g., on-line capabilities and networks, public meetings, advisories.

65. Consumer education is a major risk management option. Education can provide guidance in terms of avoiding or limiting exposure to certain foods (e.g., methylmercury in fish), advising on cooking practices (e.g., correct preparation of kidney beans to break down phytohaemagglutinin or cassava to avoid cyanuric acid), and consumer education for handling foods in the home.

66. Technical training on proper food safety practices is paramount in ensuring safe food. All manners of reaching out to technical personnel should be considered to maximize training, e.g., webinars, on-line modules, on-site training, front line supervisor training, district level meetings.

67. Laboratory research can provide additional data for refining risk assessments and help better risk management decision(s) for determining food safety, but also provide education and training opportunities for those in food safety. Research can develop/improve methods for detecting contaminants in food, determine health effects of food contaminants, determine effects of processing on food composition and allergenicity, and determine health effects of dietary factors

Labelling

68. Proper labelling includes information that instructs the consumer regarding safe handling practices and, where appropriate, briefly informs the consumer of the food safety issue.

Other Factors

69. The selection of risk management options that are both effective and feasible should generally include consideration of: population(s) that may be exposed, suitability of the option for implementation, and the capacity of the industry to incorporate and manage the option(s).

70. Technical information on the feasibility and practicality of implementing different options should be carefully weighed.

71. When selecting a risk management option, there should be a link between the risk management option being evaluated and the level of risk reduction and/or consumer protection that is being provided. The desire is to maximize risk reduction while ensuring that the option(s) implemented are efficient and effective and not overly restrictive. For example, the relative impacts of different controls on reducing risks and their stated benefits need to be objectively evaluated.

72. Cost-benefit analysis is often difficult. Estimating the magnitude and distribution of benefits and costs of particular risk management options may require addressing a myriad of concerns, e.g., changes in

the availability or nutritional quality of foods; impacts on access to international food markets; impacts on consumer confidence in the safety of the food supply or in the food regulatory system; and other societal costs and consequences of both food safety risks and choices made in managing them. Such economic estimates often have great uncertainty associated with them, so cost-benefit analysis by itself cannot determine the best risk management option, but as a systematic way for collecting and evaluating data and data gaps, it informs the decision-making process.

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Annex II: Risk Assessment Methodologies [Dose response approach(es)]

Observable range of data points

1. Historically, the major risk assessment output was identification of a no-observed-(adverse)-effect level (NO(A)EL). The NO(A)EL is determined to be the greatest concentration or amount of a substance, found by experiment or observation, that causes no (adverse) alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

2. If due to experimental design, a NO(A)EL cannot be identified, then a lowest-observed-(adverse)-effect level (LO(A)EL) is determined from the dose response curve. The LO(A)EL is determined to be the lowest concentration or amount of a substance, found by experiment or observation, that causes an (adverse) alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

3. Increasingly, the benchmark response (BMR; i.e., the response from a selected dose response curve for which the benchmark dose is to be calculated) is being used. The benchmark dose (BMD) is typically a dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect (the dose associated with a specified measure or change of a biological effect).

   Guidelines have been developed for the BMD approach by different agencies (e.g., EFSA, 2009; USEPA, 2000). The central aspects in the BMD method is the selection of the benchmark response (BMR), the statistical approaches, including the selection of dose-response models, for estimating the BMD and its lower confidence bound, BMDL, as well as the establishment of the overall BMDL, representing the POD, for the critical data.

   Use of BMD methods involve fitting mathematical models to dose-response data and using the different results to select a BMD that is associated with a predetermined benchmark response (BMR), such as a 10% increase in the incidence of a particular lesion. BMD software (BMDS) facilitates these operations by providing simple data-management tools and an easy-to-use interface to run multiple models on the same dose-response data set.

   Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and the estimate of the lower-bound confidence limit on the BMD (BMDL). Model results are presented in textual and graphical output files which can be printed or saved and incorporated into other documents.

      The EPA's latest BMDS version (2.1.2) contains thirty (30) different models that are appropriate for the analysis of dichotomous (quantal) data (Gamma, Gamma-BgDose, Dichotomous Hill, Logistic, Logistic-BgResponse, Log-Logistic, Multistage, Multistage-BgDose, Probit, Probit-BgResponse, Log-Probit, Log-Probit-BgDose, Quantal-Linear, Weibull, Weibull-BgDose, Multistage-Cancer and Multistage-Cancer-BgDose), continuous data (Linear, Polynomial, Power, Hill and four (4) Exponential models), nested developmental toxicology data (NLogistic, NCTR, and Rai & Van Ryzin) and concentration-time data (ten Berge and Toxicodiffusion) (USEPA, 2010).

      By means of the Netherlands National Institute for Public Health and the Environment (RIVM) program PROAST (possible risk obtained from animal studies) the toxic effect can be estimated.

   The BMDL accounts for the uncertainty in the estimate of the dose response that is due to characteristics of the experimental design, such as sample size. The BMDL can be used as the point of departure for derivation of a health-based reference value or a margin of exposure.

4. The point of departure (POD) is the dose response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response. The POD is the point from the dose response curve that is used to make

extrapolations to lower dose risk estimates that are basis for health-based guidance values and to calculate a margin of exposure (MOE).

Possible outcomes of risk assessment, including health-based guidance values

5. The acceptable daily intake (ADI) has been used for many years as one of the main health-based reference values that are estimated from a risk assessment. The ADI is the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects. Alternatively, it is the estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk; e.g., the estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk (standard human 60kg) (WHO 1987).

   In a similar sense, the tolerable daily intake (TDI) is used. It is the estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk (standard human 60kg) (WHO 1987). It is similar to the ADI, but the term tolerable is used for agents that are not deliberately added, such as contaminants in food. Note that the JECFA uses the term provisional maximum tolerable daily intake (PMTDI). Further, the provisional tolerable weekly intake (PTWI) is used for contaminants with cumulative properties (e.g., heavy metals). The provisional tolerable monthly intake (PTMI) is typically used for contaminants with cumulative properties and very long half-life (e.g., dioxins).

6. The reference dose (RfD) came into use after the ADI, follows a similar approach as the ADI, and has become one of the major risk assessment methodologies. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Reference doses can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Historically, the RfD usually applied to lifetime exposures, however the RfD approach is increasingly being used for shorter exposure durations including acute, short-term, and subchronic in addition to chronic. These are detailed below:

   Acute reference dose (ARfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for an acute duration (24 hours or less) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

   Short-term reference dose: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a short-term duration (up to 30 days) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

   Subchronic reference dose: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a subchronic duration (up to 10% of average lifespan) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

   Chronic reference dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

   For inhalation dose response studies, a reference concentration (RfC) is usually estimated. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

7. Margin of Exposure (MOE; ratio between experimental no/low effect level and estimated exposure; e.g., genotoxic carcinogens (e.g., acrylamide, PAHs); other chemicals of concern). The MOE is calculated by

dividing the NOAEL, BMD, or other point of departure for the critical effect by the actual, theoretical, predicted, or estimated exposure dose or concentration of interest.

8. Linear dose response low dose extrapolation (e.g., increased relative cancer risk at defined level of exposure (e.g., aflatoxins)). The slope factor is usually the upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship when a linear dose response is demonstrated or assumed.

Annex III: Case Study - Lead

In its 73rd meeting, the JECFA concluded that the PTWI previously established for lead could no longer be considered health protective and withdrew it. Based on the dose response analyses, the Committee estimated that the previously established PTWI of 25 µg/kg body weight is in the range of exposures associated with a decrease of at least 3 intelligence quotient (IQ) points in children and an increase in systolic blood pressure of approximately 3 mmHg in adults.

According to the JECFA evaluation, the mean dietary exposure estimates of children aged about 1–4 years range from 0.03 to 9 µg/kg body weight per day. The health impact at the lower end of this range (0.03 µg/kg body weight per day) is considered negligible by the Committee because it is below the exposure level of 0.3 µg/kg body weight per day calculated to be associated with a population decrease of 0.5 IQ points. The higher end of the exposure range (9 µg/kg body weight per day) is higher than the level of 1.9 µg/kg body weight per day calculated to be associated with a population decrease of 3 IQ points, which is deemed by the Committee to be of concern.

For adults, the mean dietary lead exposure estimates range from 0.02 to 3.0 µg/kg body weight per day. The lower end of this range (0.02 µg/kg bodyweight per day) was considerably below the exposure level of 1.2 µg/kg body weight per day, calculated by the Committee to be associated with a population increase in systolic blood pressure of 1 mmHg. The Committee considered that any health risk that would be expected to occur at this exposure level is negligible. At the higher end of the range (3.0 µg/kg body weight per day), a population increase of approximately 2 mmHg in systolic blood pressure would be expected to occur.

This evaluation shows that there is a significant part of the population that is probably affected by the intake of lead, meaning that it is necessary to reduce the lead level in food.

Possible risk management actions could include:

- revision of the Good Agricultural Practices, especially for those vegetable species that have high potential of lead fixation, including the identification of the high contaminated food producing areas;
- revision of the current maximum levels in food categories that most impact the lead intake;
- dietary recommendations for critical population groups - children and adults with hypertension - aiming at reducing the consumption of food with high lead levels;
- monitoring programs to assess the lead level in food and recall contaminated products.

Additionally, it is important to define the margin of exposure (MOE) that represents an acceptable risk.

Annex IV: Case Study – Acrylamide

[Note: Several comments have identified acrylamide as a possible case study. Acrylamide, both genotoxic and carcinogenic, might be a good example to be discussed in the case study because acrylamide is assessed by JECFA through benchmark method and MOE approach, and CCCF has an experience in developing code of practice for the reduction of acrylamide in foods (CAC/RCP 67-2009).]

[Note: Another suggestion is to use aflatoxin B1 as a case study example.]