Codex Alimentarius: Guidelines for Rapid Risk Analysis Following Instances of Detection of Contaminants in Food Where There Is No Regulatory Level

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Conflict of Interest Statement

- Views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the Food and Drug Administration.
Objectives

- Introduce the Codex Alimentarius Commission
  - What it is, what it does, the Codex process
- Introduce the Codex Committee on Contaminants in Foods
  - Terms of reference
- Introduce the Codex “Guidelines for Rapid Risk Analysis Following Instances of Detection of Contaminants in Food Where There Is No Regulatory Level”
Codex Alimentarius Commission (CAC)

- Established by Food and Agriculture Organization (FAO) and World Health Organization (WHO) in 1963
- Goals
  - To protect the health of consumers
  - To ensure fair practices in the food trade
- Develops harmonized international food standards, guidelines, and codes of practice for publication in the Codex Alimentarius
  - Documents and Codex information online at http://www.fao.org/fao-who-codexalimentarius/en/
Codex Committees

• CAC establishes subsidiary committees, including general and commodity committees.
  – Commodity committees (active): Fats and Oils, Spices and Culinary Herbs, Fish and Fishery Products, Fresh Fruits and Vegetables
  – Coordinating committees and task forces
• CAC must endorse new work proposals and final work products of committees.
• USDA Codex Office is central contact point for Codex activities in the US; FDA leads the US Delegation to CCCF (alternate delegate from USDA FSIS).
Codex Committee on Contaminants in Foods (CCCF)

- CCCF Terms of reference:
  - to establish or endorse permitted maximum levels or guideline levels for contaminants and naturally occurring toxicants in food and feed
  - to consider and elaborate standards or codes of practice for related subjects
  - to consider methods of analysis and sampling for the determination of contaminants and naturally occurring toxicants in food and feed
  - to prepare priority lists of contaminants and naturally occurring toxicants for risk assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)
  - to consider other matters assigned by the Commission
CCCF Develops MLs and COPs

• General Standard for Contaminants and Toxins in Food and Feed (GSCTFF, CODEX STAN 193-1995)
  – Lists maximum levels (MLs) and guideline levels (GLs), and associated sampling plans of contaminants and natural toxicants in food and feed recommended by the CAC to be applied to commodities moving in international trade.
  – Covered contaminants include metals, mycotoxins, radionuclides.
  – Also includes main principles recommended in dealing w/contaminants, e.g., criteria for setting MLs.
CCCF Develops MLs and COPs

- Codes of Practice (COP) on preventing and reducing contaminants in foods, including arsenic, lead, mycotoxins, dioxins, hydrocyanic acid, MCPD, 3-MCPD and glycidyl esters.
Codex Rapid Risk Analysis Guidelines

• The **Guidelines** provide an approach to assist governments in rapid risk analysis of instances of detection of chemical contaminants in food where there is no regulatory level.

• Incorporate a rapid risk analysis approach using a **cut-off value** and the **Threshold of Toxicological Concern (TTC)**, to assess low levels of chemical exposures, and to identify if further data are required to assess human health risk.
Rapid Risk Analysis Guidelines

• Scope includes:
  - Contaminants that may occur in materials used or created during processing of food and that may be inadvertently present in the food (e.g., printing inks, cleaning compounds, etc.)
  - Chemicals used to mitigate specific environmental, sustainability, and climate change issues (e.g., nitrification and urease inhibitors), which have not been anticipated to be present in food.
• Scope excludes contaminants detected in situations where risk manager is investigating the possibility of intentional adulteration of food.
Outline of Guidelines

1. Introduction
2. Purpose
3. Scope
4. Principles
5. Roles
6. Reporting of Detections
   1. Contaminants with established HBGVs, PODs or BMDLs (Step 1)
   2. Exclusionary contaminant categories (Step 2)
   3. Application of the cut-off value (Step 3)
   4. Information sharing from the competent authorities of exporting country (Step 4)
   5. Request for rapid risk assessment (Step 5)
   6. Toxicological data collection (Step 6)
   7. Selection of the TTC value/establishment of a HBGV/POD/BMDL, exposure assessment, and risk characterization (Steps 7-10)
   8. Reporting (Steps 11-12)
   9. Decision by the risk manager

8. Further Risk Management Activities

9. Risk Communication
Threshold of Toxicological Concern (TTC)

- Developed outside of Codex; Guidelines cite TTC.
- Risk characterization approach for chemicals with insufficient toxicological data.
- Based on grouping chemical substances into three Cramer structural classes.
- For each structural class, a TTC value was derived, based on 5th percentile No Observed Effect Level and safety factors.
- Substance is reasonably expected to be safe if its intake is less than or equal to its Cramer structural class TTC value.
- Some chemicals are excluded altogether (e.g., high potency carcinogens).
Application of Decision Tree, Part 1

**Decision Tree for Rapid Risk Analysis**

**Detection of a contaminant within the scope of the guidelines in food**

1. **Is there an established HBOV/PCD/BMDL? (Section 7.1)**
   - Yes: Potential food safety concern. Further risk analysis action necessary
   - No: 2. **Is the contaminant in a TTC exclusionary category? (Section 7.2)**
     - Yes: Potential food safety concern. Further risk analysis action necessary
     - No: 3. **Apply the cut-off value of 1 μg/kg\(^1\) (Section 7.3)**
       - Below: No risk management measures about the consignment are required. Other follow-up actions may be taken (e.g. surveillance)
       - Above: 4. **Notify stake-holder(s); including the exporting country if notification arrangements exist; and seek information sharing if appropriate. (Section 7.4)**

\(^1\)Application of the cut-off value should be considered case by case for consignments which may represent greater than 10% of the diet in certain sub-populations.

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**Cut-off value**
Application of Decision Tree, Part 2

5. Commission rapid risk assessment (Section 7.5)

Insufficient data, or time, to establish an ad hoc HBGV/POD/BMDL

7. Select appropriate TTC reference value (Section 7.7)

6. What toxicology data are available? (Section 7.6)

Enough data and time to establish an ad hoc HBGV/POD/BMDL

8. Calculate an ad hoc HBGV/POD/BMDL (Section 7.7)

9. Conduct rapid exposure assessment (Section 7.7)
Application of Decision Tree, Part 3

11. Report findings to risk manager (Section 7.8)
   - No
     - Other risk management options (e.g. surveillance)
     - No risk management measures required
   - Yes
     - 10. Risk characterization indicates potential public health concern? ²
       - No
         - 11. Report findings to risk manager (Section 7.8)
       - Yes
         - 12. Report findings to risk manager (Section 7.8)

²Equivocal public health concern may be reported either by a scientific opinion on the degree of uncertainty or conservatism in the results.

Documentation of the risk management decision, including the risk assessment

Appropriate risk management measures implemented and communicated. Including notify exporting country if notification arrangements exist. (Section 7.9)
Exclusionary Contaminant Categories (Step 2)

- Certain contaminant categories may not be suitable for rapid risk assessment given their chemical or toxicological properties. Unless there is prior experience with... these groupings, a risk manager, seeking expert advice where required, should not apply the decision tree to the following categories of contaminants:

<table>
<thead>
<tr>
<th>High potency carcinogens</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemicals of unknown or unique structure</td>
<td>Nanomaterials</td>
</tr>
<tr>
<td>Inorganic chemicals</td>
<td>Radioactive substances</td>
</tr>
<tr>
<td>Metals and organometallics</td>
<td>Organo-silicon compounds</td>
</tr>
<tr>
<td>Proteins</td>
<td>Chemicals that are known or predicted to be persistent and bioaccumulate</td>
</tr>
</tbody>
</table>
Cut-Off Value

• The cut-off value (1 µg/kg) is a guideline indicating whether or not a specific risk management action might be taken on the basis of the concentration of the contaminant in the consignment tested.

• For values above the cut-off, application of these guidelines would result in the risk manager deciding to progress with a rapid risk analysis.

• For measured levels below the cut-off value, a risk management decision can be made that the consignment does not require a specific risk management response.
  – Even though the consignment does not require a response, other follow-up actions may be taken (e.g., surveillance).

• The cut-off value does not necessitate the analytical laboratory achieving a limit of detection of 1 µg/kg.
Derivation of the Cut-Off Value

• The underlying premise of the cut-off value is that the contaminant is at the time of detection only observed in a single or limited number of consignments, and thus would only be present in a small fraction (e.g., one tenth) of a typical varied diet.

• For certain sub-populations where a consignment could represent more than a tenth of the daily diet intake, for example with foods for infants or sole source nutrition products, the cut-off value may not be appropriate.

• Such instances should be considered on a case-by-case basis and progressed for full risk assessment when there is uncertainty over the proportion of the diet... a food consignment may represent for these sub-populations.
### Examples: Comparison TTC Values to JECFA HBGVs/PODs*

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>JECFA HBGV/POD</th>
<th>Magnitude of protection from TTC Genotoxic/DNA reactive class (0.0025 μg/kg bw/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-MCPD/3-MCPD esters</td>
<td>4 μg/kg bw/day</td>
<td>1600x lower than HBGV</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>No HBGV - Genotoxic carcinogen; POD: BMDL(_{10}) 0.18/0.31 mg/kg bw/d</td>
<td>Margin of (10^4)-(10^5) to POD</td>
</tr>
<tr>
<td>DON</td>
<td>ARfD: 8 μg/kg bw PMTDI: 1 μg/kg bw/day</td>
<td>3200x lower than ARfD 400x lower than PMTDI</td>
</tr>
<tr>
<td>Ochratoxin A</td>
<td>PTWI: 0.112 μg/kg bw/week (0.016 μg/kg bw/day)</td>
<td>6x lower than PTWI</td>
</tr>
</tbody>
</table>

* From CX/CF 19/13/8
Case Studies

• Alternaria mycotoxins:

• Printing inks
US Comments on Final Draft of Guidelines

- Include language on “instances of detection of contamination” and “rapid” to be consistent with initial impetus of work; i.e., focus on rapid assessment of consignments with contaminants with no regulatory level.
- Avoid using the term “unregulated contaminants” because contaminants may be subject to regulatory framework even in the absence of explicit regulation.
- Avoid suggesting that TTC is the only scientifically valid approach that could apply where data are insufficient to establish a health-based guidance value (HBGV).
US Comments on Final Draft of Guidelines

• Clarify whether compounds with HBGVs should be included in the decision tree.
• Limit the inclusions list to several examples.
• Expand exclusions section based on currently available TTC databases.
• Include appropriate reference for additional information on TTC to provide further technical guidance.
• Avoid nebulous language like “meaningful reductions to adverse impact to public health” and “measures should be proportional to the . . . risk.”
• Clarify steps/flow in decision tree.
Viewpoints on Adoption in CCCF

**PRO**

- This guideline provides an important reference by a respected authority for use in discussion with regulatory agencies that are less familiar with standard food risk assessment practices.
- This guideline, like all Codex texts, creates alignment of practices across the world, which is important for multinational companies interacting with multiple regulatory agencies.
- The establishment of the cut-off value, based on well-founded toxicological principles, should guide development of fit-for-purpose analytical methods that have the goal of ensuring food safety, rather than methods that chase zero and detect concentrations of substances that are not relevant to human health.
Viewpoints on Adoption in CCCF

CON

• Some countries felt that the Guidelines could potentially cause disruption to international trade, due to differences in understanding and technical capacity to apply the principles, especially related to laboratory capacity.

• Some countries requested assistance with implementation related to the TTC concept.
Summary

- Codex adopted the *Guidelines for Rapid Risk Analysis Following Instances of Detection of Contaminants in Food Where There Is No Regulatory Level* in 2019.
- The Guidelines provide an approach to assist governments in the rapid risk analysis of instances of detection of chemical contaminants in food where there is no regulatory level.
- The Guidelines incorporate a rapid risk analysis approach using a cut-off value and the TTC to assess low levels of chemical exposures.
- The Scope covers contaminants detected in food where there is no regulatory level, where detections have not been previously reported, and where detections are in a specific lot or consignment.
References

- Codex CX/CF 19/13/8, Agenda Item 10, Draft Guidelines for Risk Analysis of Instances of Contaminants in Food Where There is No Regulatory Level of Risk Management Framework Established.
Acknowledgements

• US Delegation to CCCF