TTC Applications: approaches and challenges

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Outline

- JECFA
- Application of TTC in flavours assessment
- Achievements to date for flavours assessment
- Future outlook for other compounds
JECFA: Joint FAO/WHO Expert Committee on Food Additives

- Over 50-year history (since 1956)

- Risk assessment/safety evaluation of
  - Food Additives
  - Processing aids (considered as food additives)
  - Flavouring agents (by groups of related compounds)
  - Contaminants
  - Natural toxins
  - Residues of Veterinary Drugs in animal products

- Specifications and analytical methods, Residue definition, MRL proposals (veterinary drugs)

- Development and improvement of general principles
1956: 1. JECFA meeting, procedures for the testing of food additives
1958: Specifications for Identity and Purity of Food Additives
1961: First ADI for antioxidants and preservatives
1967: First Meeting to deal with contaminants
1987: Principles for the Safety Assessment of Food Additives and Contaminants (EHC 70)
1987: First meeting dedicated to veterinary drug residues (individual compounds evaluated in earlier meetings)
1995: Start of systematic assessment of flavouring agents
2010: Principles and methods for the risk assessment of chemicals in food (EHC240)
Flavours – application of TTC

Evaluation of groups of related compounds

Threshold of toxicological concern:

“The threshold of toxicological concern (TTC) is a principle, which refers to the establishment of a human exposure threshold value for all chemicals, below which there would be no appreciable risk to human health.”


- based on the dose-response data for compounds sharing structural characteristics
- taking conservative exposure estimates into account
The safety evaluation of flavouring agents

- Over 3000 different chemicals used as flavours
- Wide variety of different chemical structures
- Intake of most is extremely low and self-limiting
- Safety assurance or risk assessment is necessary

Assuming each would need chemical-specific genotoxicity data + a 90-day OECD-type study (about $400,000 and 100+ rats) this would cost $1,200 million ($1.2 billion) and 300,000+ rats!
JECFA evaluation of flavours

Principles:

- evaluation by groups of related compounds (structurally and metabolically)

- structural classes by Cramer decision tree

- exposure thresholds for Cramer classes based on Munro database

- systematic evaluation via decision tree for compounds without structural alerts for genotoxicity and carcinogenicity
JECFA decision tree for flavours:
compounds without structural alerts for genotoxicity and carcinogenicity

- Step 1: structural class – based on CRAMER et al (1978) decision tree

Class thresholds based on Munro 1997:

<table>
<thead>
<tr>
<th>Class</th>
<th>5%ile NOEL (mg/kg/day) (μg per day)</th>
<th>Human threshold (mg/kg/day)</th>
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<tbody>
<tr>
<td>I</td>
<td>3.0</td>
<td>1800</td>
</tr>
<tr>
<td>II</td>
<td>0.91</td>
<td>540</td>
</tr>
<tr>
<td>III</td>
<td>0.15</td>
<td>90</td>
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</table>

5th percentile NOEL
JECFA decision tree for flavours:
compounds without structural alerts for genotoxicity and carcinogenicity

1. Decision tree **structural class**

2. Can the substance be predicted to be **metabolised** to innocuous products?

   - **YES**
     - **Side A**
       - There are no safety concerns if the estimated intake is below the relevant threshold
       - Data on structural analogues can be used if the estimated intake is above the relevant threshold
   - **NO**
     - **Side B**
       - Data on structural analogues can be used if the estimated intake is below the relevant threshold
       - Data must be available on the compound or closely related substances to perform a safety evaluation if the estimated intake is above the relevant threshold

INITIAL STEPS IN THE JECFA DECISION TREE FOR FLAVOURS
1. Structural Class

2. Metabolized to innocuous products?

A3. Exposure > threshold of concern for class?

B3. Exposure > threshold of concern for class?

A4. Is the substance or its metabolites endogenous?

B4. NOEL available with an adequate margin of safety?

A5. NOEL available with an adequate margin of safety?

B5. Is exposure > 1.5 µg/d?

No safety concern

Additional data required

Additional data required
Innocuous:

- Innocuous products are products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agents.

Endogenous:

- Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated;

Excluded: hormones and other substances with biochemical or physiological regulatory functions.
Intake considerations

- Conservative (but realistic) estimate

- The estimated intake of a flavouring agent, or its metabolite, should not give rise to perturbations outside the physiological range
Intake considerations

- **MSDI (maximum survey-derived intake):**
  - Based on reported poundage data
  - Taking underreporting (e.g. 0.8) and consumers only (assuming 10% of population) into account
  
  \[
  \text{mg/person/day} = \frac{\text{Annual volume of production (kg) x 109 (mg/kg)}}{\text{Population of consumers x 0.8 x 365(days)}}
  \]

- **SPET (Single portion exposure technique) (since 2009):**
  - Assumes daily consumption of a single portion (standard portion size) of food category likely to contribute highest exposure
  - Added use levels as reported by industry

- **Combined exposure:**
  - Previously simple addition of MSDI estimates per group and class
  - Refinement: addition of MSDI estimates based on common metabolites or homologous series
## JECFA Flavours Assessment: Achievements through 2010

<table>
<thead>
<tr>
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<th>Count</th>
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<tbody>
<tr>
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<tr>
<td>Class I</td>
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</tr>
<tr>
<td>Class II</td>
<td>446</td>
</tr>
<tr>
<td>Class III</td>
<td>207</td>
</tr>
</tbody>
</table>

No safety concern at current estimated levels of intake:

1944 (97%)

Additional data required (3%):

<table>
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<tr>
<th>Class</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
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</tr>
<tr>
<td>Class II</td>
<td>30</td>
</tr>
<tr>
<td>Class III</td>
<td>21</td>
</tr>
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</table>
JECFA Procedure for Flavours

- Practical safety evaluation method for flavouring agents using available data on potential for toxicity and exposure
- Integrates data on exposure, chemical structure, metabolism and toxicity
- Identifies substances for which estimated intakes are not a safety concern - and those requiring further evaluation
- Conserves resources by focusing on flavouring substances with the greatest potential for adverse effects
- Has provided a simplified, structured and methodical approach for the safety assessment of about 2000 substances
- Provides a scheme whereby conclusions are reached early on for compounds with very low exposure – preserving resources without compromising on safety
- Considers combined exposures to flavours
Veterinary drug residues in food:

- A hypothesis driven decision tree approach for the safety evaluation of residues of veterinary drugs (70th JECFA, 2008)
  - identifies additional tools and options (e.g. TTC, MOE) that may be of value in the evaluation of veterinary drug residues

- Veterinary drug residues diverse group of compounds, e.g. antimicrobials; receptor-mediated pharmacological effects

(Process-)Contaminants, Packaging migrants in food:

- Compounds with possible structural alerts for genotoxicity and carcinogenicity

- Compounds with potential for (hormone)-receptor interaction
Conclusion

- TTC is an important concept to predict potential toxicity based on limited compound-specific information.
- Scientific concept taking toxic potential (based on SAR) and conservative exposure estimates into account.
- Applicability to compounds with low exposure from food.
- Extension/update of existing databases, including various end points, necessary for further application.