CONCEPTUAL FRAMEWORK FOR A TIERED APPROACH TO RISK RANKING AND PRIORITIZATION

Ian C. Munro, Ph.D., F.A.T.S., FRCPath
Workshop: Tools for Prioritizing Food Safety Concerns
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# CATEGORIES OF FOOD SAFETY CONCERNS

<table>
<thead>
<tr>
<th>Single Chemical Entities</th>
<th>Complex Mixtures</th>
<th>Major Ingredients/Whole Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and color additives</td>
<td>Botanicals</td>
<td>Starches</td>
</tr>
<tr>
<td>Packaging materials</td>
<td>Natural flavour complexes</td>
<td>Proteins</td>
</tr>
<tr>
<td>Processing aids</td>
<td>Processing reaction products</td>
<td>Fats &amp; Oils</td>
</tr>
<tr>
<td>Bioactive substances</td>
<td></td>
<td>Fibres</td>
</tr>
<tr>
<td>Flavors</td>
<td></td>
<td>Whole foods (GMO’s)</td>
</tr>
<tr>
<td>Contaminants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pesticide residues</td>
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</tbody>
</table>
PRESENTATION OUTLINE

• Prioritization Elements
• Key Data Requirements
• Approaches to Evaluation
PRIORITIZATION ELEMENT
– SINGLE CHEMICAL ENTITIES

• Intake
• Structure and presumed metabolic fate
• Structure activity relationships (SAR) (e.g., Redbook)
• Existing toxicity data and data on related structures
PRIORITIZATION ELEMENTS – COMPLEX MIXTURES

- Compositional data
- Intake of total mixture and individual components
- Toxicity and metabolic data on major components
- Toxicity data on the mixture where compositional data does not exist
PRIORITIZATION ELEMENTS – MAJOR INGREDIENTS AND WHOLE FOODS

- Compositional data
- Intake
- History of use
- Substantial equivalence
- Toxicity and metabolic data
SINGLE CHEMICAL ENTITIES
– ESTABLISHING PRIORITIES FOR TESTING

• WHO, EHC-70
• FDA, Redbook
ENVIRONMENTAL HEALTH CRITERIA – 70
GENERAL PRINCIPLES AND APPROACH TO EVALUATION

• Data on composition and specifications
• Fate of the substances in food matrices including residues
• Estimated intake
• Metabolic disposition and fate in biological system
• Toxicity data
FDA CONCERN LEVELS

- Based on intake, structural/molecular features
- Three structure categories A, B, C
- FDA developed Concern Levels I, II and III
CONCERN LEVELS AS RELATED TO CHEMICAL STRUCTURE AND EXPOSURE

Structure Category

Increasing Concern

Exposure (µg / kg-bw)

A  B  C

2.5  1.25  0.62

50  25  12.5

CL = Concern Level I (II or III)

CL III
CL II
CL I

CL = Concern Level I (II or III)
DEVELOPMENT OF A REFERENCE DATABASE

• Total of 2,944 NOELs entered into database for >612 substances
• Included food additives and pesticides
• Substances were grouped into Cramer et al. (1978) structural class in order to correlate structure with toxicity
• Most sensitive species, sex and endpoint for each substance were selected
• Cumulative distribution of NOELs for each structural class was plotted
NUMBER OF SUBSTANCES IN THE DATABASE

<table>
<thead>
<tr>
<th>Cramer et. al. Structural Class</th>
<th>No. of Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>137</td>
</tr>
<tr>
<td>II</td>
<td>28</td>
</tr>
<tr>
<td>III</td>
<td>447</td>
</tr>
</tbody>
</table>
CUMULATIVE DISTRIBUTIONS OF NOELs

NOEL (mg/kg/day) vs Percent

Class I
Class II
Class III
Fitted Distribution
DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS

- For each structural class, the 5th percentile NOEL was estimated.
- The 5th percentile NOEL provides 95% probability that any other substance in the same structural class as those comprising the reference database would have a NOEL greater than the 5th percentile for that particular structural class.
DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS (CONT'D)

Human exposure thresholds were derived by dividing the 5th percentile NOEL for each structural class by a 100-fold safety factor.

- 100-fold safety factor is inherently applied in establishing safe intake levels.
DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS (CONT'D)

- Use of 5th percentile NOEL is more conservative than arithmetic mean
- Substantive margin of safety since human exposure thresholds are based on approximately 612 compounds with good supporting toxicity data
## HUMAN EXPOSURE THRESHOLDS FOR CRAMER ET AL. STRUCTURAL CLASSES

<table>
<thead>
<tr>
<th>Structural Class</th>
<th>No. of Chemicals</th>
<th>5th Percentile NOEL (µg/kg/day)</th>
<th>Human Exposure Threshold (µg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>137</td>
<td>2,993</td>
<td>30</td>
</tr>
<tr>
<td>II</td>
<td>28</td>
<td>906</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>447</td>
<td>147</td>
<td>1.5</td>
</tr>
</tbody>
</table>
CONCERN LEVELS AS RELATED TO CHEMICAL STRUCTURE AND EXPOSURE

Structure Category

Increasing Concern

Exposure (µg / kg-bw)

A: 2.5
B: 1.25
C: 0.62

30 25 12.5

50 25 12.5

Human Exposure Thresholds

CL = Concern Level I (II or III)

CL III

CL II

CL I

CONCERN LEVELS AS RELATED TO CHEMICAL STRUCTURE AND EXPOSURE
TOXICITY TESTS RECOMMENDED FOR DIFFERENT CONCERN LEVELS BY FDA

<table>
<thead>
<tr>
<th>Test</th>
<th>Concern Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term Tests for Genetic Toxicity</td>
<td>X X X</td>
</tr>
<tr>
<td>Metabolism and Pharmacokinetic Studies</td>
<td></td>
</tr>
<tr>
<td>Short-term Toxicity Tests with Rodents</td>
<td>X X X</td>
</tr>
<tr>
<td>Subchronic Toxicity Tests with Rodents</td>
<td></td>
</tr>
<tr>
<td>Subchronic Toxicity Tests with Non-Rodents</td>
<td>X X X</td>
</tr>
<tr>
<td>Reproduction Study with Teratology Phase</td>
<td>X X X</td>
</tr>
<tr>
<td>One-year Toxicity Test with Non-Rodents</td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity Study with Rodent</td>
<td>X X X</td>
</tr>
<tr>
<td>Chronic Toxicity/Carcinogenicity Study with Rodents</td>
<td></td>
</tr>
</tbody>
</table>
COMPLEX MIXTURES

- Food additive preparations
- Herbs, botanicals, spices and extracts
- Natural flavor complexes – essential oils and oleoresins
SOME GENERAL PRINCIPLES

- Source, specifications and manufacture
- Composition, identification of principal constituents
- Intended conditions of use
- Level of intake
- Toxicological evaluation
SUGGESTED EVALUATION SCHEMES

- Botanicals
- Natural flavor complexes
1. Is the ingredient or product a botanical traditionally used in food in the same form as in the proposed application?

yes  →  Accept

no  →  Accept After Nutritional and Toxicological Assessment

3. Is the product or ingredient an extract or derivative of a traditional food or ingredient (e.g., garlic oil, rosemary extract, tea polyphenols)?

yes  →  Accept After Nutritional and Toxicological Assessment

no  →  Accept After Nutritional and Toxicological Assessment

5. Can the product or ingredient be compared to a traditional food except for specified differences?

yes  →  Accept After Nutritional and Toxicological Assessment

no  →  Accept After Nutritional and Toxicological Assessment

6. Is the product or ingredient a plant or portion of a plant with a history of use as a herbal medicine?

yes  →  Accept After Nutritional and Toxicological Assessment

no  →  Characterize and Evaluate

7. Are the active principles identified or characterized?

yes  →  Accept After Nutritional and Toxicological Assessment

no  →  Characterize and Evaluate

8. Are there any indications of adverse side-effects in medicinal use?

no  →  Accept After Nutritional and Toxicological Assessment

yes  →  Risk/Benefit Assessment
JECFA Procedure for the Safety Evaluation of Flavors and Natural Flavoring Complexes

1. Determine the structural class

2. Can the flavoring agent or congeneric group of flavoring agents be predicted to be metabolized to innocuous products?

A3. Intake greater than the threshold of concern for the structural class?

- Yes
  - Substance or congeneric group would not be expected to be of safety concern.
  - No
    - Yes
      - A4. Is the substance, or members of the congeneric group endogenous?
      - No
        - Yes
          - Additional data required
        - No
          - A5. Does a NOEL exist which provides an adequate margin of safety under conditions of intended use.
          - Yes
            - A6. Are all of the congeneric groups in the flavoring agent or NFC determined to be of no safety concern?
            - No
              - Flavoring agent or NFC would not be expected to be a safety concern.
            - Yes
              - Additional data required
1. Determine the structural class

2. Can the flavoring agent or congeneric group of flavoring agents be predicted to be metabolized to innocuous products?

B3. Intake greater than the threshold of concern for the structural class?

B4. Does a NOEL exist which provides an adequate margin of safety under conditions of intended use.

B5. Do the conditions of use result in an intake greater than 1.5 ug/day?

B6. Are all of the congeneric groups in the flavoring agent or NFC determined to be of no safety concern?
JECFA Procedure for the Safety Evaluation of Flavors and Natural Flavoring Complexes

1. Determine the structural class
   - Yes: A3. Intake greater than the threshold of concern for the structural class?
     - Yes: Substance or congeneric group would not be expected to be of safety concern.
     - No: B3. Intake greater than the threshold of concern for the structural class?
       - Yes: Additional Data must be available
       - No: B4. Does a NOEL exist which provides an adequate margin of safety under conditions of intended use.
         - Yes: Substance or congeneric group would not be expected to be of safety concern.
         - No: B5. Do the conditions of use result in an intake greater than 1.5 ug/day?
           - Yes: Substance or congeneric group would not be expected to be of safety concern. Following evaluation of all congeneric groups in the flavoring agent or NFC, proceed to B6.2
           - No: B6. Are all of the congeneric groups in the flavoring agent or NFC determined to be of no safety concern?
             - Yes: Flavoring agent or NFC would not be expected to be a safety concern.
             - No: Additional data required
       - No: A4. Is the substance, or members of the congeneric group endogenous?
         - Yes: A5. Does a NOEL exist which provides an adequate margin of safety under conditions of intended use.
         - No: A6. Are all of the congeneric groups in the flavoring agent or NFC determined to be of no safety concern?
           - Yes: Flavoring agent or NFC would not be expected to be a safety concern.
           - No: Additional data required
   - No: 2. Can the flavoring agent or congeneric group of flavoring agents be predicted to be metabolized to innocuous products?
     - Yes: A4. Is the substance, or members of the congeneric group endogenous?
     - No: B5. Do the conditions of use result in an intake greater than 1.5 ug/day?
       - Yes: Substance or congeneric group would not be expected to be of safety concern. Following evaluation of all congeneric groups in the flavoring agent or NFC, proceed to B6.2
       - No: B6. Are all of the congeneric groups in the flavoring agent or NFC determined to be of no safety concern?
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         - No: Additional data required
INGREDIENTS AND WHOLE FOODS – KEY ISSUES

- Often impossible to achieve 100x fold safety factor (LSRO)
- Nutritional status may be altered in test animals resulting in pseudotoxicty
- A different approach is required with less emphasis on toxicity testing and more emphasis on compositional and metabolic data
- Clinical trials can play a key role in macro ingredient safety evaluation
APPROACHES TO SAFETY EVALUATION

• Compositional data are essential

• Because of high exposure impurities and contaminants need to be emphasized

• Analytical comparison of the new product with a suitable naturally occurring counterpart is a key element of the safety assessment

• Animal toxicity tests need to be designed in a thoughtful manner. Standard Redbook procedures often cannot be used
Key to developing a credible approach to safety evaluation relies on having detailed compositional data. These data can be used to predict metabolic fate (e.g., resistant starches, chemically or enzymatically modified carbohydrates, fats and oils). 

*In vitro* metabolic and fermentation techniques can be used to evaluate potential *in vivo* metabolic fate. Limited toxicity testing may be used to confirm safety.
ADDITIONAL FACTORS TO CONSIDER IN SAFETY EVALUATION OF WHOLE FOODS AND INGREDIENTS

• Changes in food consumption patterns
  – Potential for nutritional effects
  – High intakes by certain sub-groups

• New foods/ingredients being introduced
  – Potential for allergenic reactions

• Post-market monitoring
  – Confirm expected consumption patterns
  – Assess potential shifts in nutrient intake
e.g. How much EPA/DHA is actually being consumed?
CONCLUSIONS RE FRAMEWORKS

• Three separate categories of concern
  – Single chemical entities
  – Complex mixtures
  – Whole foods and major ingredients

• Each category requires a unique approach; no single approach can be used across the entire spectrum of potential risks