SAFETY ASSESSMENT OF FOOD CONTACT MATERIALS
Threshold of Toxicological Concern | Lisette Krul
OUTLINE

- Challenges safety assessment Food Contact Materials
- Threshold of Toxicological Concern (TTC): principles, developments and application
- Applying TTC in assessment of complex matrices – CoMSAS
- Future research activities
INCREASING SAFETY CHALLENGES

改善分析方法

复杂生产链

1 2 3 4 5

回收材料
TRADITIONAL SAFETY ASSESSMENT

Hazard Identification

Hazard Characterisation

Exposure Assessment

Risk Characterisation

Migration testing

Toxicological Assessment

Food Intake Assessment

Risk Assessment

4 | Safety assessment of food contact materials
SAFETY ASSESSMENT IS A BOTTLENECK FOR INNOVATION

- Often substance specific and requiring full identification of substances
- Traditional safety assessment of new food products and food packaging materials is expensive and time- and animal-consuming

Hampers innovation and improvement in food and food packaging

Unnecessary research for low-exposure substances
EXPOSURE-BASED SAFETY ASSESSMENT

- **Threshold of Toxicological Concern (TTC)**
  - Establishing an exposure threshold for substances below which there is a very low probability of an appreciable risk for humans (Kroes et al., 2004) – for life long exposure
  
  - TTC has been developed to assess safety of single substances for which structural information is available, but toxicological information is lacking

- Pragmatic approach for substances to which exposure is low

- Used by European Food Safety Authority (EFSA) as screening and prioritization tool for safety assessment of substances in food (EFSA, 2016)
THRESHOLD OF TOXICOLOGICAL CONCERN

- Based on a large database containing chronic toxicity and carcinogenicity data of about 600 chemicals

Pinalli et al., 2011: distribution of recalculated NOAELs of 232 food contact materials was similar to substances in Munro database

- Threshold based on 5th percentile of No Observed Adverse Effect Levels (NOAELs) per class
TTC – DECISION TREE

Excluded substances:
- Aflatoxin-, azoxy- and nitroso-like substances
- Proteins
- Non-essential metals
- Dioxin-like substances

Exposure thresholds:
- Structural alerts for genotoxicity => 0.15 µg/person/day (0.0025 µg/kg bw/day)
- Organophosphate or carbamate => 18 µg/person/day (0.3 µg/kg bw/day)
- Cramer class III (most substances) => 90 µg/person/day (1.5 µg/kg bw/day)
- Cramer class II => 540 µg/person/day (9 µg/kg bw/day)
- Cramer class I => 1800 µg/person/day (30 µg/kg bw/day)

EFSA: Cramer class III threshold is applicable
Several developments since introduction TTC thresholds:

- Separate threshold for organophosphates and carbamates (out of Cramer class III)
- Cramer class II database limited => Cramer class III threshold applies
- Additionally: Organohalogens might be considered as separate class

TTC thresholds were not adapted due to these changes

TNO assessed chronic toxicity dataset underlying Cramer class III substances => derived other thresholds for (sub)classes of Cramer class III substances

Based on the exclusion of organophosphates, carbamates and organohalogens from this class
### TTC THRESHOLDS

<table>
<thead>
<tr>
<th>Chemical class</th>
<th>TTC threshold (μg/kg bodyweight/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substances with a structural alert for genotoxicity</td>
<td>0.0025 (unchanged, not part of this evaluation)</td>
</tr>
<tr>
<td>Organophosphates and carbamates</td>
<td>0.30</td>
</tr>
<tr>
<td>Organohalogenes</td>
<td>1.5</td>
</tr>
<tr>
<td>Cramer class III substances, without organophosphates, carbamates, and organohalogenes</td>
<td>4.0</td>
</tr>
<tr>
<td>Cramer class II substances</td>
<td>9* (unchanged, not part of this evaluation)</td>
</tr>
<tr>
<td>Cramer class I substances</td>
<td>30 (unchanged, not part of this evaluation)</td>
</tr>
</tbody>
</table>

* Note that the Cramer class II substances are not considered by the EFSA (2012).

EFSA, 2016: acknowledges that a new threshold could be determined for Cramer class III (without the OP and carbamates), but recommends update of databases with new information prior to a review.
APPLICATION TTC FOR FCM

- Not a guidance document, intended as input for risk management discussion European Commission

- TTC thresholds used in tiered approach: demands for toxicity testing depending on exposure
- Tiered approach applies in principal for all substances including Non Intentionally Added Substances (NIAS)

- For NIAS assessment non-testing methods like TTC recommended to be used on a case-by-case basis for priority setting and preliminary toxicological assessment
- If exposure to a NIAS is below 0.0025 µg/kg bw/day (0.15 µg/person/day), no genotoxicity data needed
FOOD AS A COMPLEX MATRIX

- (Increasing) complexity of food/FCMs is a challenge
- How to identify and assess all substances?
- Assess whole product at once?

Typical chromatogram for foods visualising the substances present in a specific food product.
INTRODUCTION

Most relevant data to start with:

- Identity (purity, size, shape, surface area, etc…)
- Physico-chemical properties (chemical reactivity, (photo-)catalytic reactivity, surface charge, etc…)

Changes in either identity and/or physico-chemical properties may introduce specific hazards.

Current approach CoMSAS

- Focus on full identification
  - Identify & quantify all components
  - Hazard & safety assessment for each individual component
  - Unidentified substances cannot be assessed

CoMSAS

- Focus on toxicological relevance
  - Targeted analysis for certain groups of (highly) potent components
  - Exclude genotoxicity
  - Identification and safety assessment only for substances above exposure threshold
COMSAS

- Exposure driven safety assessment for complex food matrices
- Step-wise strategy combining analytical techniques with the TTC concept
- Exposure threshold and strategy is based on the TTC decision tree (Kroes et al 2004) updated according to latest insights (e.g. Munro et al, 2008 and EFSA, 2012 and 2016)
Based on Cramer class III

**STEP 1**
Translate response into intake and identify peaks corresponding with intakes of more than 90 µg/p/d

**STEP 2**
- proteins (or assess safety)
- non-essential/heavy metals
- metal containing compounds
- dioxin-like chemicals
- high potent genotoxic compounds
- organophosphates

**STEP 3, exclude:**
(structural alerts for) genotoxicity

**STEP 4**
Identify and assess compounds with intakes >90 µg/p/d and non-excluded compounds

**STEP 5 assess allergenicity**
FROM THEORY TO PRACTICE...

Development of approach:

- Step 1 and 2 => developing analytical techniques
- Step 1 => convert peaks to intake
- Step 3 => sensitive genotoxicity screening (bio) assay
- Challenges related to application of TTC (for mixtures)
CHALLENGES FOR APPLYING TTC APPROACH TO UNKNOWNS?

- **Combination toxicity**
  - Synergistic effects only when 2 or more compounds are above effect level (not likely at low TTC exposure)
  - Dose addition at low concentrations cannot be excluded
  - But…
    - Cumulative effect is depending on potency
    - TNO has assessed the relative potency for acute and chronic effects for certain classes of substances (e.g. organophosphates, triazoles)
    - Conclusion: Health relevance of possible cumulative effects at 90 µg/day is considered to be low, need for correction factor very low to absent

Leeman *et al.* 2013, *Food and Chemical Toxicology*
CHALLENGES FOR APPLYING TTC APPROACH TO UNKNOWNS?

- **Bio-accumulating substances**
- EFSA, 2016: substances that are known or predicted to accumulate should be excluded from TTC
  - Research questions:
    - How to predict bioaccumulation? Log Po/w sufficient?
    - Is TTC protective for bioaccumulating substances?
  - Conclusion:
    - Log Po/w in combination with H-bond acceptor best predictive for bioaccumulation
    - TTC thresholds are derived from a dataset containing bioaccumulating substances => toxicity of bioaccumulating substances is taken into account in the TTC thresholds.

Leeman *et al.* 2016 *Regulatory Toxicology and Pharmacology*
FROM THEORY TO PRACTICE...

Democases:

- Food contact material – carton (Koster et al., 2014 *Food additives and Contaminants*)

- Non-selective extracts of fruit/vegetables (Koster et al., 2015 *Food and Chemical Toxicology*)
  - Project performed in collaboration with Christian Hansen, The Coca-Cola Company and the Netherlands Food and Product Safety Authority (NVWA)
FROM THEORY TO PRACTICE...

- **Stakeholder acceptance**
  - EFSA/WHO, 2016 on use of TTC:
    - TTC can be applied for unknowns in mixtures if sufficient information confirms no TTC excluded substances are present.
    - In case presence of genotoxic substances, organophosphates or carbamates can be excluded the Cramer class III threshold can be applied.
  - ILSI- Europe guidance, 2015 on Non-Intentionally Added Substances (NIAS) in Food packaging
    - In case NIAS cannot be identified the CoMSAS approach can be applied
SUMMARIZING...

- TTC: pragmatic safety assessment for low-exposure substances

- CoMSAS:
  - Enables quick safety screening (5-10 days) without need for full analysis
  - Only assessment needed of substances exceeding exposure threshold
  - Only approach to assess safety matrices containing unknowns
  - Flexible approach

- Application:
  - Product design
  - Safety assessment final product
    - As such
    - By comparing with reference product
CIRCULAR ECONOMY: NEW CHALLENGES

Mineral oils in paper and carton  Recycled rubber for artificial grass

Towards a sustainable planet is essential, but safety should be warranted

Challenge: deal with incontinuous compositions and many unknowns
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