Technical stakeholder event on cumulative risk assessment of pesticides in food

Exposure assessment

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Evidence Management Unit
Methodology – Basic principles

Occurrence → Exposure → Consumption
Methodology – Primary input data

- **Consumption data:**
  - Comprehensive European Food Consumption Database
  - Converted to raw primary commodities
  - Surveys selected for adults (4), children (3) and toddlers (3)
  - Detailed records for 20,000 subjects (2-7 days)

- **Occurrence data:**
  - EU coordinated and national monitoring programs
  - Objective and selective sampling only
  - Reference period 2014-2016
  - 30 raw primary commodities + foods for infants and young children
  - Co-occurrence data for 120,000 samples
Methodology – Toxicological potency

<table>
<thead>
<tr>
<th>Sample</th>
<th>Analytical result</th>
<th>Relative potency</th>
<th>Adjusted concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Analytical result" /></td>
<td>X 1</td>
<td><img src="image2.png" alt="Adjusted concentration" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Analytical result" /></td>
<td>X 0.5</td>
<td><img src="image4.png" alt="Adjusted concentration" /></td>
</tr>
<tr>
<td>...</td>
<td><img src="image5.png" alt="Analytical result" /></td>
<td>X 0.75</td>
<td><img src="image6.png" alt="Adjusted concentration" /></td>
</tr>
<tr>
<td>...</td>
<td><img src="image7.png" alt="Analytical result" /></td>
<td>X 1</td>
<td><img src="image8.png" alt="Adjusted concentration" /></td>
</tr>
<tr>
<td>...</td>
<td><img src="image9.png" alt="Analytical result" /></td>
<td>X 0.25</td>
<td><img src="image10.png" alt="Adjusted concentration" /></td>
</tr>
</tbody>
</table>

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Note: The table and images are placeholders and the actual content should be replaced with the correct data and images.
Methodology – Chronic exposure

Simulations and imputations
- Left-censored data
- Processing factors
- Variability factors
- Missing data

2-Dimensional
- 100 distributions

Consumption data
- 20,000 subjects

Occurrence data
- 120,000 samples

Observed Individual Means (OIM) Approach
- Mean consumption x Mean occurrence
- Repeated for each subject (i.e. 20,000 times)

2-Dimensional
- 100 bootstraps

Exposure distribution
- Confidence P99.9

P2.5

P97.5
Methodology – Acute exposure

**Simulations and imputations**
- Left-censored data
- Processing factors
- Variability factors
- Missing data

**Monte Carlo simulation**
- Random day x Random sample
- 100 000 iterations

**2-Dimensional**
- 100 bootstraps
- 100 distributions

**Exposure distribution**
- Confidence P99.9
  - P2.5
  - P97.5

**Consumption data**
- 50 000 days

**Occurrence data**
- 120 000 samples
Overview

- General methodology
- Assumptions and tiers
- Results and interpretation
- Key observations
Alignment with risk management principles

- Standing Committee on Plants, Animals, Food and Feed (SC PAFF)
- Development of a tiered approach
- Generic and tier-specific assumptions
- Discussed and agreed at the meeting of 19 September 2018

Tier I

- Conservative assumptions which are less resource-intensive
- Screening of the exposure with low risk for underestimation

Tier II

- More refined assumptions which are more resource-intensive
- Still intended to be conservative
## Assumptions and tiers – Main simulations

<table>
<thead>
<tr>
<th>Unspecific definitions</th>
<th>Tier I</th>
<th>Tier II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most potent active substance is allocated to each sample</td>
<td>Random allocation of authorized active substances to each sample</td>
</tr>
<tr>
<td>Left-censored data</td>
<td>½ LOQ for food-substance combinations with quantifiable findings</td>
<td>½ LOQ based on estimated use frequencies, assuming 100% crop treatment</td>
</tr>
<tr>
<td>Missing measurement</td>
<td>Highest values assigned to the most contaminated samples</td>
<td>Random assignment of missing measurements to available samples</td>
</tr>
<tr>
<td>Drinking water</td>
<td>Imputed at 0,1 µg/l for the 5 most potent active substances</td>
<td>Imputed at 0,05 µg/l for the 5 most potent active substances</td>
</tr>
<tr>
<td>Processed foods</td>
<td>Use processing factors when available. Otherwise, assume all pesticides in the raw primary commodity will reach the end consumer without any loss of residues.</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **LOQ**: Limit of Quantification

**Notes:**
- **Tier I** simulations assume worst-case scenarios with the most potent active substances assigned to each sample.
- **Tier II** simulations use a random allocation of authorized active substances, with half the LOQ based on estimated use frequencies, assuming 100% crop treatment.
- Missing measurements are imputed at different levels depending on the tier.

**Definitions:**
- **Unspecific**: General categories without specific criteria.
- **Tier I**: Initial tier with censored data and missing measurements.
- **Tier II**: Second tier with more refined allocations and imputation strategies.

**Key Points:**
- Processed foods assume that all pesticides reach the end consumer without loss.
- Drinking water considerations include imputation based on specific thresholds.
- Unspecific definitions apply broadly across tiers.
### Threshold for regulatory consideration

<table>
<thead>
<tr>
<th><strong>Who defined it?</strong></th>
<th>Standing Committee on Plants, Animals, Food and Feed (SC PAFF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How is it calculated?</strong></td>
<td>Total margin of exposure (MOET), i.e. toxicological reference dose/estimated exposure</td>
</tr>
<tr>
<td><strong>Reference point?</strong></td>
<td>99.9&lt;sup&gt;th&lt;/sup&gt; percentile of the exposure distribution</td>
</tr>
<tr>
<td><strong>Numerical threshold?</strong></td>
<td>Should be ≥ 100</td>
</tr>
<tr>
<td><strong>Additional conditions?</strong></td>
<td>Assumptions used under Tier II should be “sufficiently conservative”</td>
</tr>
</tbody>
</table>

#### Results – Margin of exposure

<table>
<thead>
<tr>
<th>Exposure distribution</th>
<th>MOET distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Exposure distribution graph with P&lt;sub&gt;99.9&lt;/sub&gt; at 0 and P&lt;sub&gt;0.1&lt;/sub&gt; at 100" /></td>
<td><img src="image2.png" alt="MOET distribution graph with P&lt;sub&gt;0.1&lt;/sub&gt; at 100" /></td>
</tr>
</tbody>
</table>
Results – Confidence interval

- 97.5th Percentile
- 3rd Quartile
- Mean
- 1st Quartile
- 2.5th Percentile
Hypertrophy, hyperplasia and neoplasia of C-cells

German adults

Tier II

Dutch toddlers

Tier II

95% confidence intervals on the total margin of exposure calculated at different percentiles in adults (Germany)

95% confidence intervals on the total margin of exposure calculated at different percentiles in toddlers (Netherlands)
Results – Chronic exposure

Hypothyroidism

German adults
Tier II

Dutch toddlers
Tier II

95% confidence intervals on the total margin of exposure calculated at different percentiles in adults (Germany)

95% confidence intervals on the total margin of exposure calculated at different percentiles in toddlers (Netherlands)

[Graphs showing confidence intervals for German adults and Dutch toddlers]
Brain and/or erythrocyte AChE inhibition

German adults
*Tier II*

Dutch toddlers
*Tier II*

95% confidence intervals on the total margin of exposure calculated at different percentiles in adults (Germany)

95% confidence intervals on the total margin of exposure calculated at different percentiles in toddlers (Netherlands)
Results – Acute exposure

Alterations of the motor division

German adults

Tier II

Dutch toddlers

Tier II

95% confidence intervals on the total margin of exposure calculated at different percentiles in adults (Germany)

95% confidence intervals on the total margin of exposure calculated at different percentiles in toddlers (Netherlands)
Key observations – Risk drivers

**Limited number of substances**
- Hypertrophy, hyperplasia and neoplasia of C-cells: thiram
- Hypothyroidism: bromide ion
- AChE inhibition: chlorpyrifos, triazophos, omethoate
- Motor division: triazophos, thiram, deltamethrin

**Other factors driving the acute exposure distribution**
- Single substances in a specific commodity (75% of the upper part)
- Samples exceeding the MRL (40 to 95% of the upper part)

**What about 2017-2019 (retrospective assessment)?**
- Single substance assessments have revealed similar risks
- Measures already taken by risk managers for chlorpyrifos
Missing processing factors
- Sensitivity analysis assuming no residues in processed foods
- Potential overestimation by a factor of 2 to 5 (!)
- Need for consolidation of EU Processing Factor Database

Left-censored (LC) data
- Sensitivity analyses assuming LC data equal 0 or ½ LOQ
- Most relevant for chronic exposure assessment
- Data on use frequency to be collected

<table>
<thead>
<tr>
<th>Exposure assuming LC = 0</th>
<th>Exposure using Tier II</th>
<th>Exposure assuming LC = ½ LOQ</th>
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<tr>
<td>0</td>
<td></td>
<td></td>
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</table>

Exposure assuming LC = 0
Exposure using Tier II
Exposure assuming LC = ½ LOQ
Key observations – Main uncertainties (2)

- **Foods for infants and young children (FIYC)**
  - Sensitivity analysis excluding FIYC
  - Contribution of FIYC to the exposure is negligible
  - Consistent with previous opinion of the PPR Panel

- **Unspecific residue definitions**
  - No sensitivity analysis was carried out...
  - ... but several risk drivers (e.g. thiram and omethoate) resulting from unspecific residue definitions
  - Data on use frequency to be collected
Exposure calculated with two different software

- EFSA used SAS® Software
- RIVM used MCRA Software
- Minor divergencies attributed to random effects of probabilistic methodologies

What are the advantages?

**MCRA**
- Scope
- Accessibility
- Usability

**SAS®**
- Flexibility
- Openness
- Data integration

Action plan for MCRA under elaboration
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