Probabilistic Dietary Exposure Assessment

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Outline

• Deterministic and probabilistic
  – Variability and uncertainty
  – What are we trying to estimate?
• Needs and challenges in probabilistic assessment
• EFSA PPR Panel Guidance
• Future directions

A personal perspective
Deterministic vs. Probabilistic

• Deterministic
  – Uses *point estimates* for inputs (consumption, concentration, processing effects, etc.)
  – Generates point estimate of exposure

• Probabilistic
  – Uses *distributions* to take account of variability and uncertainty of inputs
  – Generates a distribution of exposures
Variability and uncertainty

variability of actual exposures

Cumulative % of population

Exposure mg/kg bw/day
Variability and uncertainty

variability of actual exposures

uncertainty in our knowledge of exposure
Variability and uncertainty

uncertainty in our knowledge of exposure

actual exposures are unknown
Deterministic assessment

Cumulative % of population

Exposure mg/kg bw/day

uncertainty in our knowledge of exposure

Deterministic point estimate
Based on conservative assumptions
A typical view of probabilistic assessment

- Option for refinement when concern at Tier 1
- More realistic estimates of exposure
- Avoids over-conservative first tier assumptions

- Load my data into available software and press ‘go’
- Compare 95\textsuperscript{th} percentile exposure to reference dose
- Good chance of solving my problem...
5% of EU population = 25 million

**Pesticides:** ‘shall not have any harmful effects on human health’ Reg. 1107/2009

**Additives:** ‘does not...pose a safety concern’ Reg. 1333/2008

Need to **characterise** the frequency & magnitude of upper tail exposures

95th percentile exposure compare to reference dose
Pesticides: ‘**shall not** have any harmful effects on human health’ Reg. 1107/2009

Additives: ‘**does not**...pose a safety concern’ Reg. 1333/2008

A high level of certainty is implied... need to show how much certainty there is

**Need confidence intervals for the distribution of exposures**
Many uncertainties are difficult to quantify probabilistically, e.g. for pesticides:
• limited samples of data
• distribution shapes uncertain (esp. tails)
• many non-detects
• dependencies between parameters

Use alternative assumptions to explore the impact of difficult uncertainties
Many uncertainties are difficult to quantify probabilistically, e.g. for pesticides:

- limited samples of data
- distribution shapes uncertain (esp. tails)
- many non-detects
- dependencies between parameters

Use alternative assumptions to explore the impact of difficult uncertainties

Compare to Reference Dose:

Further refinement required

Optimistic

Pessimistic

Stop

Stop
But... it is never possible to quantify all uncertainties

Need to *identify* and *evaluate* unquantified uncertainties
Parametric modelling may generate unrealistically high values.

Empirical bootstrap will underestimate upper tail.

Statistical methods may over- or underestimate upper tails.

Need ‘drill-down’ examination of estimates in upper tail.
Needs identified so far...

- Focus on characterising upper tail exposures, not on an arbitrary percentile of the distribution
- Give confidence intervals for quantified uncertainties
- Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically
- Evaluate the impact of unquantified uncertainties
- ‘Drill-down’ to check for over- and underestimation in upper tail
New PPR Panel Guidance

• Published 5 October 2012
• How does it address the needs identified above?
New PPR Panel Guidance

- Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically.

- *Start with Optimistic and Pessimistic assumptions for:*  
  - Residue distribution (bootstrap vs. lognormal)  
  - Sampling uncertainty (bootstrap vs. parametric)  
  - Unit-to-unit variability (none vs. conservative est.)  
  - Non-detects (zero vs. Limit of Reporting)  
  - Processing effects (zero vs. deterministic estimate)  
  - % crop treated (approx. estimate vs. 100%)  
  - Residues in water (zero, legal limit)  
  - etc...

- If important, quantify further in *refined assessment*
New PPR Panel Guidance

- Focus on characterising upper tail, not an arbitrary percentile
- Give confidence intervals for quantified uncertainties

<table>
<thead>
<tr>
<th>Exposure levels</th>
<th>Number of person-days per million exceeding exposure level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optimistic model run</td>
</tr>
<tr>
<td>% of ARfD</td>
<td>MoE*</td>
</tr>
<tr>
<td>1</td>
<td>10000</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>100***</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>50</td>
</tr>
<tr>
<td>500</td>
<td>20</td>
</tr>
</tbody>
</table>

Exposure levels expressed as % of reference dose and/or Margin of Exposure

Frequency of exceedance per million

Optimistic & Pessimistic assumptions

Estimated frequencies & confidence intervals

‘<‘ = below resolution of model
New PPR Panel Guidance

- Evaluate the impact of unquantified uncertainties
- ‘Drill-down’ to check for over- and underestimation in upper tail

<table>
<thead>
<tr>
<th>Exposure levels</th>
<th>Number of person-days per million exceeding exposure level</th>
<th>Additional considerations &amp; uncertainties\textsuperscript{65}</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of ARfD</td>
<td>MoE*</td>
<td>Optimistic model run</td>
</tr>
<tr>
<td>1</td>
<td>10000</td>
<td>2000 (500 – 7000)</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>500 (200 – 1200)</td>
</tr>
<tr>
<td>50</td>
<td>200</td>
<td>50 (10 – 500)</td>
</tr>
<tr>
<td>100**</td>
<td>100</td>
<td>10 (&lt;10 – 50)</td>
</tr>
<tr>
<td>200</td>
<td>50</td>
<td>&lt;10 (&lt;10 – 10)</td>
</tr>
<tr>
<td>500</td>
<td>20</td>
<td>&lt;10 (&lt;10 – &lt;10)</td>
</tr>
</tbody>
</table>

*Specify MoE for additional uncertainty checks.*

\textsuperscript{65}Indicate overall direction and magnitude of additional uncertainties, e.g., by inserting summary text from bottom row of uncertainty table (see Section 8).

Identify or omit results that are based on clearly unrealistic extremes of input distributions.

Use ‘<’ to indicate results that are below the sensitivity of the model.
New PPR Panel Guidance

- Evaluate the impact of unquantified uncertainties

<table>
<thead>
<tr>
<th>Assessment component</th>
<th>Approach in pessimistic model run</th>
<th>Subjective evaluation of impact on the upper tail exposures</th>
<th>Brief explanation of evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Modelling food consumption</td>
<td>Empirical + bootstrap; examine which commodities contribute to upper tail exposures</td>
<td>• (common foods and large survey) - - / • (small survey and/or rare foods)</td>
<td>Model is limited to intakes observed in survey. With large surveys this will cause no underestimation for common foods. Tendency to underestimation if there is limited data for the foods driving exposure</td>
</tr>
<tr>
<td>2. Use of old food consumption survey data</td>
<td>Not considered</td>
<td>• (sometimes -/+))</td>
<td>Little effect unless consumption has recently changed for a food with high residues</td>
</tr>
</tbody>
</table>
An additional need...

• Effective communication with risk managers

• Characterisation of upper tail exposures:
  – Person-days per million exceeding effect level
  – Confidence intervals for quantified uncertainties
  – Potential impact of unquantified uncertainties

• Question for *toxicologists*:
  – Characterise severity of effects at this level

• Question for *risk managers*:
  – Is all this consistent with ‘not any harmful effects’?
Another key need: Calibrate deterministic assessment

- Uncertainty in our knowledge of exposure
- Deterministic point estimate
  - Based on conservative assumptions
  - + unquantified uncertainties

Cumulative % of population

Exposure mg/kg bw/day
Calibrating the deterministic Tier 1

uncertainty in our knowledge of exposure

Based on conservative assumptions + unquantified uncertainties

Example:

EFSA PPR Panel (2007): IESTI equation for pesticides

Ratio IESTI/ARfD

Level of protection (% consumption-days < ARfD)

DE pome fruits
DE grapes
DE others
NL apples/pears
NL table grapes
NL others

0
>99.99
99.9
99
90

Children only:
DE 2-<5
NL 1-6
Some future directions

- Probabilistic calibration of deterministic approaches
- Simulation studies on treatment of unit-to-unit variability of pesticide residues for PPR Guidance
- Methods & software for cumulative and aggregate exposure assessment (FP7 project ACROPOLIS)
- Improved statistical methodology:
  - Usual intakes and life time exposure
  - Modelling upper tail exposures

EU project ACROPOLIS

- Improved cumulative exposure assessment and cumulative hazard assessment;
- To integrate cumulative and aggregate risk models in a web-based tool, including accessible data for all stakeholders;
- Improving the understanding of cumulative risk assessment methodology of different stakeholders.
- For more information: http://acropolis-eu.com/
Summary

• Focus on characterising upper tail exposures, not on an arbitrary percentile of the distribution
• Give confidence intervals for quantified uncertainties
• Use alternative assumptions to assess uncertainties that are difficult to quantify probabilistically
• Evaluate the impact of unquantified uncertainties
• ‘Drill-down’ to check for over- and underestimation in upper tail
• Communicate effectively with risk managers
• Calibrate first tier deterministic approaches