Overview

- Role of uncertainty analysis
- Assessment for German adults
- Extrapolation to other populations
- EFSA conclusions on risk
Risk managers: “a threshold for regulatory consideration at the 99.9th percentile could be an acceptable target value, provided that the tier 2 assumptions are sufficiently conservative”
- Uncertainty analysis quantifies the degree of conservatism

Risk managers: “If in the second tier calculation a risk is identified above the threshold for regulatory consideration, then a risk management decision should be considered taking into account all aspects e.g. all sources of uncertainties and their magnitude or the fact that a result might be driven by outliers”

Role of uncertainty analysis

<table>
<thead>
<tr>
<th>Calculated MOETs</th>
<th>Uncertainty analysis</th>
<th>Risk characterisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Degree of conservatism</td>
<td></td>
</tr>
</tbody>
</table>
Calculated MOETs

- Calculated MOETs at the 99.9\textsuperscript{th} percentile
- 95\% confidence intervals quantify sampling uncertainty
- All extend below 100
- Calculation is designed to be conservative
- So: are the MOETs really below 100?

**CAG-NAN (brain and/or erythrocyte AChE inhibition):**

<table>
<thead>
<tr>
<th>Country</th>
<th>Population class</th>
<th>99.9\textsuperscript{th} Percentile MOET</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Adults</td>
<td>102</td>
<td>72 - 162</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Adults</td>
<td>120</td>
<td>87 - 176</td>
</tr>
<tr>
<td>Germany</td>
<td>Adults</td>
<td>95</td>
<td>73 - 120</td>
</tr>
<tr>
<td>Italy</td>
<td>Adults</td>
<td>96</td>
<td>75 - 149</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Other children</td>
<td>49</td>
<td>36 - 63</td>
</tr>
<tr>
<td>France</td>
<td>Other children</td>
<td>59</td>
<td>46 - 74</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Other children</td>
<td>52</td>
<td>45 - 62</td>
</tr>
<tr>
<td>Denmark</td>
<td>Toddlers</td>
<td>60</td>
<td>50 - 69</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Toddlers</td>
<td>40</td>
<td>33 - 50</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Toddlers</td>
<td>61</td>
<td>47 - 76</td>
</tr>
</tbody>
</table>
How different is the ‘true’ MOET?

- True MOET is lower - calculated MOET is unconservative
- True MOET is higher - calculated MOET is conservative

Lower MOETs  
Calculated MOET  
Higher MOETs
The true MOET is uncertain.

- True MOET might be lower.
- True MOET might be higher.

Confidence in the Calculated MOET is uncertain.
We quantify uncertainty using *probability*.

- Quantifies the *likelihood* of different degrees of conservatism.
“Sufficient conservatism” = low enough probability that the true MOET is less than 100
Assessing conservatism

- Identify sources of uncertainty and conservatism
- Quantify the overall uncertainty of the MOET
- Assess probability of MOET < 100
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Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)

Main uncertainties affecting exposure for CAG-NAN:
- Lack of data on processing (+)
- Effect of peeling and washing (+)
- Selective sampling (+)
- Analytical error (+/-)
- Conversion to raw primary commodity (-)
- Commodities not included in modelling (-)

+ Tend to make the true MOET higher
- Tend to make the true MOET lower
Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)

Main uncertainties affecting toxicology for CAG-NAN:

- NOAELs underestimate BMDL20 (+)
- Effect of gavage dosing (+)
- Use of repeated dose studies (+)
- Carryover between days (-)
- First-pass metabolism at low doses (+)
- Non-approved substances (limited -)
• Calculated MOET at 99.9%ile = 95 (95% CI 73 – 120)

• Combined impact of exposure and toxicology uncertainties on the MOET at 99.9%ile exposure for German adults

• 0.28% probability that true MOET is less than 100
  • Quantifies degree of conservatism
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Key findings:

- Additional uncertainties (green) much wider than those quantified by model (blue)
- Large impact of conservative assumptions
Final expert judgement for **CAG-NAN**, taking account of:
- dependencies between toxicological and exposure uncertainties
- differences between populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Probability from earlier steps</th>
<th>Final probability MOET&lt;100</th>
<th>Certainty that the threshold for regulatory consideration is not reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgian adults</td>
<td>0.20%</td>
<td>&lt; 1%</td>
<td>&gt; 99% certainty (almost certain)</td>
</tr>
<tr>
<td>Czech Rep. adults</td>
<td>0.07%</td>
<td>&lt; 1%</td>
<td>&gt; 99% certainty (almost certain)</td>
</tr>
<tr>
<td>German adults</td>
<td>0.28%</td>
<td>&lt; 1%</td>
<td>&gt; 99% certainty (almost certain)</td>
</tr>
<tr>
<td>Italian adults</td>
<td>0.25%</td>
<td>&lt; 1%</td>
<td>&gt; 99% certainty (almost certain)</td>
</tr>
<tr>
<td>Bulgarian children</td>
<td>6.8%</td>
<td>1 - 10%</td>
<td>90 - 99% certainty (very likely to extremely likely)</td>
</tr>
<tr>
<td>French children</td>
<td>2.8%</td>
<td>&lt; 5%</td>
<td>&gt; 95% certainty (extremely likely to almost certain)</td>
</tr>
<tr>
<td>Dutch children</td>
<td>4.6%</td>
<td>1 - 10%</td>
<td>90 - 99% certainty (very likely to extremely likely)</td>
</tr>
<tr>
<td>Danish toddlers</td>
<td>2.8%</td>
<td>&lt; 5%</td>
<td>&gt; 95% certainty (extremely likely to almost certain)</td>
</tr>
<tr>
<td>Dutch toddlers</td>
<td>12%</td>
<td>5 - 20%</td>
<td>80 - 95% certainty (likely to very likely)</td>
</tr>
<tr>
<td>United Kingdom toddlers</td>
<td>2.7%</td>
<td>&lt; 5%</td>
<td>&gt; 95% certainty (extremely likely to almost certain)</td>
</tr>
</tbody>
</table>
### Corresponding probabilities for other CAGs

<table>
<thead>
<tr>
<th>Population</th>
<th>Probability MOET &lt;100 at 99.9%ile exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAG-NAM: Motor Division</td>
</tr>
<tr>
<td>Belgian adults</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Czech Rep. adults</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>German adults</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Italian adults</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Bulgarian children</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>French children</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Dutch children</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Danish toddlers</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Dutch toddlers</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>United Kingdom toddlers</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>
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Overall, taking account of the available data and the uncertainties involved, it is concluded that:

- **cumulative exposure to pesticides that have acute effects on the nervous system** does not exceed the threshold for regulatory consideration established by risk managers

- **cumulative exposure to pesticides that have chronic effects on the thyroid** does not exceed the threshold for regulatory consideration established by risk managers
Thank you for your attention

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Flow chart of method from draft Reports

Uncertainty distributions for MOET at the 99.9\textsuperscript{th} percentile of exposure, produced by probabilistic modelling

Model output for each population

Individual uncertainties - toxicology

Individual uncertainties - exposure

Prioritise populations with highest probability of MOET < 100 at the 99.9\textsuperscript{th} percentile of exposure

Final assessment of P(MOET<100) for populations of most concern using approximate probabilities

Implications of results for EFSA PRIMo populations

EKE Q1: evaluation of each individual uncertainty FOR GERMAN ADULTS using +/- scale

EKE Q2: overall toxicology & exposure uncertainties FOR GERMAN ADULTS

Combine distributions by 1D Monte Carlo simulations assuming independence – one for each population

EKE Q3: overall uncertainty taking account of dependencies and population-specific issues

Considered in conclusion section of report