Introduction in the Quantification of Dietary Exposure to Toxic Compounds

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Contents

- Dietary exposure assessment: acute and chronic
- Probabilistic modelling
- MCRA
- US EPA policy on tiered approach / EU
Dietary Exposure Assessment

- Risk assessment: hazard identification, hazard characterisation, exposure assessment and risk characterisation
- Dietary exposure assessment:
  - \((\text{consumption level} \times \text{residue level}) \div \text{bw}\)
  - comparison of intake with a reference dose, e.g. acceptable daily intake (ADI) or acute reference dose (ARfD)
    - intake > ref level → population may be at risk
    - intake ≤ ref level → population may not be at risk
  - acute vs chronic dietary exposure
Acute Dietary Exposure

- Results from a relatively short period of exposure:
  - acute: 1 hour until 24 hours
  - sub-acute: 1 day until 30 days

- Examples of acute toxic effects: headache, eye irritation, cholinesterase inhibition

- Reference dose: acute reference dose (ARfD) = amount of a substance that can be ingested during one meal or one day, without appreciable health risk (animal / human studies)
Chronic Dietary Exposure

- Results from a longer period of exposure:
  - sub-chronic: 1 month until 6 months
  - chronic: More than 6 months

- Examples of chronic toxic effects: cancer, heart disease

- Reference dose: acceptable daily intake (ADI) = amount of a substance which can be ingested daily over a lifetime without appreciable health risk
Exposure Calculations (1)

- Similar methods / different parameters
- Point estimate:
  - acute:
    - (high consumption \times high residue level) \div body weight
    - single commodity consumption
  - chronic:
    - (mean consumption \times residue level) \div body weight
    - mean, median, MRL residue level
    - summing intakes per food for overall exposure
Exposure Calculations (2)

- ‘Simple’ distributions
  - acute:
    - a single high residue level
    - a distribution of consumption or visa versa
    - single commodity consumption
  - chronic:
    - a single residue level (mean, median)
    - a distribution of consumption, or visa versa
    - summing intakes per food for overall exposure
Exposure Calculations (3)

- Probabilistic modelling
  - Acute:
    - a distribution of residue and consumption levels
    - whole diet
  - Chronic:
    - a distribution of residue and consumption levels
    - whole diet
    - more consumption days (≥ 2 d) per person
Exposure Calculations (4)

Point estimate is used most world-wide:

- Easy to calculate and understand
- However:
  - addresses only one food item at the time (acute)
    (consumers eat several food items)
  - addresses one chemical at a time
    (no cumulative exposure assessment)
  - too many worst-case assumptions? Overestimation?
  - no information about the likelihood that a certain exposure level will occur in the population
Overestimation

1) Measured intake and calculated intake monitoring
2) EPA: monitoring and field trial data

\[
(U \cdot HR \cdot P \cdot \text{Variability factor}) + (LP \cdot U \cdot HR \cdot P) \times \frac{\text{average body weight}}{\text{Overestimation factor}}
\]
→ growing interest in the use of probabilistic modelling when addressing the exposure to toxic chemicals via the diet
Dietary exposure assessment: acute and chronic
Probabilistic modelling
MCRA
US EPA policy on tiered approach / EU
Probabilistic Modelling (1)

random sampling from a residue and consumption database

residue database

consumption database

exposure = consumption \times \text{residue}

99, 99.9, and/or 99.99 percentile
Probabilistic Modelling (2)

50th percentile of exposure
= 50 g/kg bw/d

90th percentile of exposure
= 75 g/kg bw/d

99.9th percentile of exposure
= 88 g/kg bw/d

exposure (g/kg bw/d)
Probabilistic Modelling (3)

- A distribution of residue level: all levels including levels below LOQ / LOD / LOR or zero’s
- A distribution of consumption: all levels including non-consumers
- Whole diet can be addressed
- Result is the probability of possible exposure levels
Probabilistic Modelling (4)

- Well-defined consumption database is needed representative of population studied: individual consumption levels (not e.g. household budget)
- Residue data needed relevant for the foods consumed by the population studied
- Statistically sound methods to assess risks
When going from point estimate to probabilistic approach

- better use of available data, which results in more realistic estimates of exposure
- need of more resources (e.g. software, well-defined food consumption databases)
Validation study EU-project Monte Carlo

- Duplicate diet collection of infants (8 – 12 months)
- Food consumption of infants
- Analytical measurements at 1 ppb level for 18 pesticides
- Monitoring residue levels from KAP-database

Probabilistic model is valid (or fit for use) when
point estimate exposure > probabilistic exposure > real intake
Validation: probabilistic model > real intake

Pirimicarb, prob model vs. real intake

<table>
<thead>
<tr>
<th></th>
<th>p50</th>
<th>p90</th>
<th>p95</th>
<th>p97.5</th>
<th>p99</th>
<th>p99.9</th>
<th>p99.99</th>
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<tbody>
<tr>
<td>DD</td>
<td>0.0129</td>
<td>0.0267</td>
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<td>0.296</td>
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<td>1.017</td>
<td>2.945</td>
<td>4.59</td>
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<td>0.077</td>
<td>0.23</td>
<td>0.401</td>
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<td>1.837</td>
<td>7.136</td>
<td>12.415</td>
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<tr>
<td>MC pvn all</td>
<td>0.249</td>
<td>0.415</td>
<td>0.543</td>
<td>0.899</td>
<td>1.859</td>
<td>6.716</td>
<td>11.75</td>
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</tbody>
</table>
Validation study EU-project Monte Carlo

Probabilistic model is valid (or fit for use) when point estimate exposure > probabilistic exposure > real intake
Validation: probabilistic model < point estimate

**Diagram:**

**Pirimicarb, prob model vs. point estimate**

<table>
<thead>
<tr>
<th>Fruit</th>
<th>p50</th>
<th>p90</th>
<th>p95</th>
<th>p97.5</th>
<th>p99</th>
<th>p99.9</th>
<th>p99.99</th>
<th>IESTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>0</td>
<td>0.015</td>
<td>0.204</td>
<td>0.399</td>
<td>0.729</td>
<td>1.903</td>
<td>2.626</td>
<td>23.33</td>
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<td>Pear</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.034</td>
<td>0.477</td>
<td>0.648</td>
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<tr>
<td>Strawberry</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0.003</td>
<td>0.479</td>
<td>1.042</td>
<td>7.183</td>
</tr>
<tr>
<td>Endive</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.072</td>
<td>2.315</td>
<td>4.101</td>
<td>99.55</td>
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<tr>
<td>Spinach</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.057</td>
<td>0.247</td>
<td>1.079</td>
</tr>
</tbody>
</table>
Validation study EU-project Monte Carlo

Probabilistic model is valid (or fit for use) when

**point estimate exposure > probabilistic exposure > real intake**
Conclusions validation

- Validation seems OK in general
  (point estimate > probabilistic model > real intake)
- Real exposure levels were low, in general below probabilistic model
- Results probabilistic model << point estimate
- [www.rikilt.wur.nl/Publications/Publicationscompleet.html](http://www.rikilt.wur.nl/Publications/Publicationscompleet.html) (click on reports and select report with nr 2003 002)
Contents

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Monte Carlo Risk Assessment (software)
(see http://mcra.rikilt.wur.nl/mcra/mcra.html)

Monte Carlo Risk Assessment

Stochastic modelling of chemical intake from food

On this website you find a demo version of MCRA, the program for Monte Carlo Risk Assessment, developed in collaboration between RIKILT and Biometrics in the context of the Dutch Programme for the Quality of Agricultural Products (KAP).

In a Monte Carlo dietary risk assessment the risk of exposure to pesticides or other chemicals from the diet is quantified by combining database information on food consumption with database information from monitoring programs for residues of chemicals in food.

You can run the MCRA demo program by clicking here. At present the website is under construction, so occasionally you may encounter difficulties.

MCRA provides the following options:
- acute risk assessment
- chronic risk assessment
- parametric or non-parametric modelling of residue levels
- modelling of processing effects
- modelling of unit variability
- modelling of nondetects levels
- restrictions on age and/or consumption days
- calculate exposure distribution for consumption days only
- bootstrap sampling of consumers and/or residue levels to access the uncertainty of percentiles
- EIESTI values

username/password and training required!
MCRA: selection population addressed

**Consumer population**

Check individual characteristics for subset selection

<table>
<thead>
<tr>
<th>variable</th>
<th>levels in current selection</th>
<th>check if you want to select levels</th>
<th>select from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>age:</td>
<td>min=1; max=97</td>
<td>□</td>
<td>current selection</td>
</tr>
<tr>
<td>weight:</td>
<td>min=8; max=150</td>
<td>□</td>
<td>current selection</td>
</tr>
<tr>
<td>sex:</td>
<td>n = 2</td>
<td>□</td>
<td>current selection</td>
</tr>
</tbody>
</table>

Number of individuals currently selected: 6250

- show/select levels for checked variables
- use total population (no consumer subset selection)
MCRA: main menu (1)

Selection of model (acute or chronic intake)

Exposure model

Risk

Perform an acute or chronic risk assessment?  

[ acute ]  [ chronic ]
MCRA: main menu (2)

options related to residue data

Residues

Concentration data ?
Full data ?
Empirical or parametric modelling of acute risks ?
Empirical modelling? ?
Treatment of nondetects ?
Replace nondetects by LOR: ?
Processing factors ?
Use processing factors (no = factors are 1)? ?
Unit variability ?
Model unit variability? ?
Distr. of Positive Intakes (2.8%) for carbaryl

total exposure distribution (acute intake)
MCRA: Output Examples (2)

Contribution of foods to total intake distribution

Statistics of the 2 Largest Contributions

- Grape: 91.3%
- Nectarine
- Others
### Percentiles, maximum and average intake

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Percentiles of ALDICARB (microgr/kg bw/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.00</td>
<td>0.00000</td>
</tr>
<tr>
<td>95.00</td>
<td>0.00000</td>
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<tr>
<td>99.00</td>
<td>0.00064</td>
</tr>
<tr>
<td>99.90</td>
<td>0.00329</td>
</tr>
<tr>
<td>99.99</td>
<td>0.00996</td>
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</table>

percentiles of exposure
### MCRA: Output Examples (4)

#### Uncertainty of percentiles (Confidence limits)

<table>
<thead>
<tr>
<th></th>
<th>2.5%</th>
<th>25%</th>
<th>75%</th>
<th>97.5%</th>
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<td>0.0000</td>
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</tr>
<tr>
<td>95.00</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>99.00</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0010</td>
<td>0.0020</td>
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<tr>
<td>99.90</td>
<td>0.0000</td>
<td>0.0007</td>
<td>0.0044</td>
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<tr>
<td>99.99</td>
<td>0.0000</td>
<td>0.0011</td>
<td>0.0058</td>
<td>0.0183</td>
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<table>
<thead>
<tr>
<th></th>
<th>maximum</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.021</td>
<td>0.0000</td>
<td>0.0010</td>
<td>0.0050</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th></th>
<th></th>
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</thead>
<tbody>
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<td>0.000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**P99.9 = 0.00329**

**Confidence intervals of the percentiles**
MCRA used for food safety issues (few examples)

- Dietary exposure assessment of Dutch pesticide monitoring programme on a regular basis
- Exposure assessment mycotoxins, dioxins etc. (chronic intake)
- WHO expert consultation on acrylamide, HEATOX
- EU Standing Committee on Plant Health and Animal Nutrition
- CODEX Commission on Pesticide Residues
- Cumulative exposure assessment of pesticides
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Tiered approach: US EPA (1)

- US EPA = Environmental Protection Agency
- Responsible for registering pesticides and setting pesticide tolerances in the US
Tiered approach: US EPA (2)

Starts with a worst-case assessment and progresses to probabilistic assessments as the risk management situation dictates (tier 1 – 4)
Tiered approach: Tier 1 (deterministic)

- A single residue level for each food included:
  - tolerances
  - maximum field trial residue level (MRL)
- Entire distribution of consumption data
- Assumes 100% crop treated
- Result: distribution of exposures
- Exposure estimate at the P99.9 exceeds ARfD
  then refinement
Tiered approach: Tier 2 (deterministic)

- A single residue level for each food included
  - tolerances or MRLs for single-serving commodities
  - mean field trial residues (or P95 residue from monitoring) for processed / blended commodities
- Entire distribution of consumption data
- Assumes again 100% crop treated
- Result: distribution of exposures
- Exposure estimate at the P99.9 exceeds ARfD then refinement
Tiered approach: Tier 3 (probabilistic)

- For single-serving foods, utilises the entire range of field trial data points in probabilistic modelling
  - for processed / blended, mean field trial residues or residue distribution from monitoring
- Entire distribution of consumption data
- Residue distribution includes zero values proportional to the percentage of untreated crops
- Exposure still > ARfD? The Tier 4 assessment if applicable
Tiered approach: Tier 4 (probabilistic)

- Distribution of residue levels and consumption data
- Requires more extensive residue data
  (from market basket surveys on single serving sized items in stead of composite samples from field trials)
- Provides the most representative exposure picture
- Exposure still > ARfD? Then possibly risk mitigation
- Can only be applied for already existing compounds on the market
Tiered approach: Tier 4 (probabilistic)

- Risk mitigation
  - either pesticide is not registered for use or
  - EPA may work together with registrant
    - to reduce use rates or number of applications (for example, only 3 applications per season, not 4), or
    - to drop certain crops from the label
Tiered approach: EU

- In EU probabilistic approach not yet accepted as a tool to address acute exposure in the field of pesticide authorisation: point estimate

- PACT project (from the EU)
  - training for EU regulators
  - draft EU guidance document on how to include probabilistic approaches into acute exposure assessments as part of a tiered approach
Training was received well

All regulators from all Member States were well able to understand the principles of probabilistic modelling. They were also able to perform a Monte Carlo simulation themselves at their own office using the MCRA-software.

In many EU-countries consumption data were available, sometimes it was difficult to get access to consumption data.

Still a lot of work needs to be done to make consumption data compatible with residue measurements or field trial data.
Draft guidelines within EU (1)

- Tiered approach
  - Tier 1: Point estimates (worst-case)
  - Tier 2: Point estimates realistic (processing, variability)
  - Tier 3: Probabilistic assessment (worst-case)
  - Tier 4: Probabilistic assessment realistic (processing, variability)

Research on further refinement options is needed
Draft guidelines within EU (2)

- Recommendations were made related to
  - food consumption data (individual, recipe databases if available)
  - field trial data (all, levels below LOR as $\frac{1}{2}$ LOR)
  - food processing factors
  - variability factors
  - treatment of outliers
  - number of iterations
Other issues addressed are

- Quality check of data above P99.9 of exposure
- Rarely eaten food items and dilution of risk
- Possible solutions data shortage:
  - Pool data from different national databases (nectarines from IT, SE)
  - Pool data with similar products (e.g. nectarines and peaches)
Conclusions

- Probabilistic modeling is a more valid method to address dietary exposure compared to point estimate.
- Consumers eat combinations of fruits and vegetables, probabilistic modeling deals with all foods consumed.
- Training is very helpful for the understanding (and acceptance) of probabilistic risk assessment.
Thanks for your attention!