Risk assessment chemical contaminants

Ron (L.A.P.) Hoogenboom
The Belgian dioxin crisis in 1999
General Food Law (EC No. 178/2002)

of 28 January 2002
laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Articles 37, 95, 133 and Article 152(4)(b) thereof,

the Member States. When Member States adopt measures governing food, these differences may impede the free movement of food, create unequal conditions of competition, and may thereby directly affect the functioning of the internal market.

▪ Basis for Food and feed safety management
Risk analysis food chain within the EU

Risk assessment
EFSA
Parma, Italy

Risk management
DG SANTE
Brussels, Belgium

Risk communication
EFSA: responsible for risk assessment

- 10 Panels with experts
- Not representation of Member States
- Supported by staff
- Science based risk assessments
- CONTAM Panel: dealing with contaminants
CONTAM Panel

- Dealing with contaminants in the food chain
- Persistent organic pollutants:
  - Dioxins and dl-PCBs, PFASs (PFOS/PFOA), chlorinated parafines
- Metals, Pb, Cd, Hg, As, Cr
- Processing contaminants like furans, acrylamide
- Non-allowed pharmacologically active substances, like chloramphenicol, malachite green and other dyes, nitrofurans
- Mycotoxins, plant toxins, marine biotoxins
  - DON, ZEN, tetrodotoxins
### Mandates

#### Register of Questions

<table>
<thead>
<tr>
<th>Mandate Number</th>
<th>Question Number</th>
<th>Subject</th>
<th>Unit</th>
<th>Panel</th>
<th>Status</th>
<th>Output Number</th>
<th>Last Updated</th>
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<td>Request for a scientific opinion on the presence of residues of fenicothion in horse meat</td>
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<td>Internal Mandate proposed by EFSA to the CONTAM Unit for a procurement on Alternaria toxins, included toxicokinetic and in vivo genotoxic study on Alternaria toxins</td>
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<td>M-2011-0102</td>
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<td>A study on the use of the EFSA scientific opinion on mercury and methyl mercury in food</td>
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<td>View</td>
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### Working groups

#### Chemical contaminants working groups

**Overview of planned meetings**

<table>
<thead>
<tr>
<th>Name</th>
<th>Minutes (last update)</th>
<th>Composition</th>
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<tr>
<td>3-MCPD update</td>
<td>23 May 2017</td>
<td>Members and declarations</td>
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<td>Dioxins in food and feed</td>
<td>26 April 2017</td>
<td>Members and declarations</td>
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<td>Fumonisins in feed</td>
<td>12 May 2017</td>
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<tr>
<td>Furan in food</td>
<td>16 May 2017</td>
<td>Members and declarations</td>
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</table>

**Subject area**

- **Chemical contaminants**

**Expert groups**

- CONTAM
  - Panel on Contaminants in the Food Chain

**See also**

- Working practices
- Declarations of interest
Opinions

Chemical contaminants

Scientific advice on chemicals that can be present unintentionally in food and feed due to food production, distribution, packaging or consumption, as well as those that might be present in the environment naturally or as a result of man-made activity. Reporting of data on veterinary drug residues and unauthorised substances in food and animals.

Latest publications

- Risks for public health related to the presence of tetrodotoxin (TTX) and TTX analogues in marine invertebrates and gastropods
  - Scientific Opinion | Chemical contaminants | Published: 20 April 2017

- Appropriateness to set a group health based guidance value for nivalenol and its modified forms
  - Scientific Opinion | Chemical contaminants | Published: 19 April 2017

- Generation of occurrence data on citrinin in food
Risk assessment process

- **Hazard identification:**
  - Which “adverse” effects?
  - Humans, animals

- **Hazard characterization**
  - At which dose? LOAEL/NOAEL/BMDL?

- **Estimate exposure (different age groups)**
  - Data on levels in food/feed
  - Data on food/feed consumption

- **Risk characterization:**
  - Derive HBGV: ARfD/TDI
  - margin of exposure (MOE); MOE large enough?
Hazard identification

- Which effects to take into account?
- Studies with experimental animals
  - Rats, mice but occasionally also pigs
- Studies with humans,
  - Accidents
  - Background exposure
- In vitro studies (mode of action)
  - E.g. genotoxicity
Hazard characterisation

- Which dose is critical?
  - i.e. showing effects
- Classical approach: NOAEL/LOAEL
- New approach: BMD-modelling

“It’s the dose that determines the poison”
BMDL-approach
BMDL-approach
Different models for curve fitting

- Previously BMDL based on model with acceptable curve fit and lowest BMDL
  - BMR 10% affected animals for quantal data
  - BMR 5% for continuous data
- Now curve fits evaluated and weighted
  - BMDL-BMDU intervals combined based on weight
  - Model averaging
- Less conservative approach
- Only possible for animal data, not human data
- BMDL used as PoD
Health based guidance values

- Which point of departure (Reference Point)?
- Preference for human data
  - Reduce uncertainty like inter- and intraspecies differences
- If not available, use animal studies (“mildest effect”)
- If not available either: “Threshold of Toxicological Concern (TTC)”
Health based guidance values

- Use of default “Uncertainty Factors (UFs)”
  - interspecies variability in toxicokinetics: 4.0
  - interspecies variability in toxicodynamics: 2.5
  - intraspecies variability in toxicokinetics: 3.16
  - intraspecies variability in toxicodynamics: 3.16

- May be reduced based on information

- Regarded as conservative
  - but not necessarily the case (TTX?)
Hazard characterisation

- Evaluate exposure (example on DON)
- Compare with TDI/ARfD
- Conclude on the risks
- Evaluate the uncertainties in the assessment
- Risk communication
Risks for farm animals

- Relatively few studies, compared to experimental animals
- For some compounds NOAELs/LOAELs determined
- No uncertainty factors applied
- Exposure assessment based on reported levels
  - Use of P50, and P95
- Exposure based on compound feed, or on feed ingredients, if numbers for feed too low
  - No database available, like for humans
In addition

- **Transfer feed to food**
  - Normally not taken into account for setting MLs
  - Exception is aflatoxin M1
  - For other compounds: ML for feed not necessarily low enough to ensure that food is below ML

- **Mode of action**
  - Important to understand toxic effects
  - Normally not used in Risk assessment
  - Exception is genotoxicity
Mycotoxins and plant toxins (examples)
Recent work from EFSA on mycotoxins

- Opinions on aflatoxins, OTA, nivalenol, sterigmatocystine, ergot alkaloids, enniatins, T2/HT2, masked forms (ZEN, NIV, T2/HT2, FUMs)
- Recent (2017) opinion on deoxynivalenol (DON)
  - Including ADONs and D3G (modified forms)
- Recent (2016) opinion on zearalenone (ZEN)
  - Including (potential) modified forms
- Opinion on moniliformin (in press)
- Working on DAS, fumonisins
Deoxynivalenol

- In particular detected on wheat
  - Co-occurrence with other Fusarium toxins
- Often also 3- and or 15-acetyl-DON and DON-3-glucoside (levels lower than DON)
- Can be transformed into DON in GI-tract
- Typical effects are vomiting at high doses (e.g. mink, pigs)
- and decreased growth in mice and feed intake
- At higher doses immunotoxic

EFSA, 2017
Critical study deoxynivalenol

- **NOAEL female mice**: 0.1 mg/kg bw/day
BMD modelling and TDI

- TDI of 1 µg/kg bw/day, based on BMDL_{05} of 0.11 mg/kg bw/day (both sexes combined); UF of 100
  - BMDL05 similar to NOAEL of 0.1 mg/kg bw/day
- ARfD of 8 µg/kg bw/day
Exposure assessment

- Data collected from member states
- Data set cleaned, a.o. for too high LOQs
- P50 and P95 determined

- In addition MSs provided food consumption data for different age groups
### Consumption surveys from MSs

#### Table D.1: Dietary surveys used for the estimation of acute and chronic dietary exposure

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey acronym</th>
<th>Survey period</th>
<th>N of days per subject</th>
<th>N of subjects/N of days</th>
<th>Infants</th>
<th>Toddlers</th>
<th>Other children</th>
<th>Adolescents (mean age)</th>
<th>Adults</th>
<th>Elderly</th>
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<td>Netherlands</td>
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Exposure assessment

- Many data <LOQ, especially for modified forms
- When assuming LOQ levels for non-detects, large overestimation exposure
- Based on detected levels, relative contribution of these forms estimated
  - 10, 15 and 20% for 3-ADON, 15-ADON and D3G
  - Applied to non-detects to determine the sum
- Use of P50 (chronic)/P95 (acute) values
- Combine with consumption data
  - Results in range of mean intake for surveys
  - Both lower- and upperbound
Exposure assessment

- Use of P50 (chronic)/P95 (acute) values
  - Both lower- and upperbound
- Combine with consumption data
  - For each person in each survey
  - Determine mean and P95 for each survey
- Results in range (min-max) of mean and P95 intake for surveys
Chronic exposure assessment DON

<table>
<thead>
<tr>
<th>Age group (a)</th>
<th>Mean dietary exposure (µg/kg bw per day)</th>
<th>95th percentile dietary exposure (µg/kg bw per day)</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Minimum</td>
</tr>
<tr>
<td>Infants (b)</td>
<td>6</td>
<td>0.3 (0.1-0.5)</td>
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<tr>
<td>Toddlers</td>
<td>11</td>
<td>0.6 (0.3-1.1)</td>
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<tr>
<td>Other children</td>
<td>20</td>
<td>0.5 (0.5-0.6)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>20</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Adults</td>
<td>24</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>Elderly</td>
<td>16</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>Very elderly</td>
<td>14</td>
<td>0.3 (0.2-0.5)</td>
</tr>
</tbody>
</table>

- Combining P50 occurrence levels with all different consumption surveys (lowerbound: <LOQ equal to zero)
Exposure assessment

### Table 33: Summary statistics of probabilistic acute dietary exposure assessment to the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside (at the lower, middle and upper bound) across European dietary surveys (µg/kg bw per day) by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>n</th>
<th>Minimum</th>
<th>Maximum</th>
<th>95th percentile dietary exposure (µg/kg bw per day)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>6</td>
<td>1.0 (0.9–1.0)</td>
<td>2.9 (2.8–3.2)</td>
<td></td>
<td>2.7 (2.6–2.8)</td>
<td>6.7 (6.2–7.1)</td>
</tr>
<tr>
<td>Toddlers</td>
<td>11</td>
<td>1.5 (1.2–1.9)</td>
<td>2.2 (2.0–2.6)</td>
<td></td>
<td>3.5 (3.3–3.6)</td>
<td>5.4 (4.5–6.5)</td>
</tr>
<tr>
<td>Other children</td>
<td>20</td>
<td>1.2 (1.1–1.3)</td>
<td>2.0 (1.9–2.0)</td>
<td></td>
<td>2.6 (2.5–2.7)</td>
<td>4.5 (4.2–4.9)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>20</td>
<td>0.6 (0.6–0.6)</td>
<td>1.2 (1.1–1.3)</td>
<td></td>
<td>1.3 (1.3–1.4)</td>
<td>2.9 (2.7–3.2)</td>
</tr>
<tr>
<td>Adults</td>
<td>24</td>
<td>0.5 (0.5–0.5)</td>
<td>1.0 (1.0–1.0)</td>
<td></td>
<td>1.5 (1.4–1.6)</td>
<td>2.8 (2.8–2.8)</td>
</tr>
<tr>
<td>Elderly</td>
<td>16</td>
<td>0.5 (0.5–0.5)</td>
<td>0.8 (0.8–0.9)</td>
<td></td>
<td>1.3 (1.1–1.6)</td>
<td>2.2 (1.9–2.6)</td>
</tr>
<tr>
<td>Very elderly</td>
<td>14</td>
<td>0.5 (0.5–0.5)</td>
<td>0.9 (0.8–1.0)</td>
<td></td>
<td>1.3 (1.2–1.4)</td>
<td>2.2 (1.7–2.9)</td>
</tr>
</tbody>
</table>

- Combining P50 or P95 occurrence levels with all different consumption surveys (upperbound: <LOQ equal to LOQ/LOD) (95% CIs also provided)
Mean exposure (TDI = 1)

Table 33: Summary statistics of probabilistic acute dietary exposure assessment to the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside (at the lower, middle and upper bound) across European dietary surveys (µg/kg bw per day) by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Mean dietary exposure (µg/kg bw per day)</th>
<th>Mean dietary exposure (µg/kg bw per day)</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Minimum (95% CIs)</td>
<td>Minimum (95% CIs)</td>
<td>Maximum (95% CIs)</td>
</tr>
<tr>
<td>Infants(b)</td>
<td>6</td>
<td>0.3 (0.1-0.5)</td>
<td>1.0 (0.9-1.0)</td>
<td>2.9 (2.8-3.2)</td>
</tr>
<tr>
<td>Toddlers</td>
<td>11</td>
<td>0.6 (0.3-1.1)</td>
<td>1.5 (1.2-1.9)</td>
<td>2.2 (2.0-2.6)</td>
</tr>
<tr>
<td>Other children</td>
<td>20</td>
<td>0.5 (0.5-0.6)</td>
<td>1.2 (1.1-1.9)</td>
<td>2.0 (1.9-2.0)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>20</td>
<td>0.3 (0.3-0.4)</td>
<td>0.6 (0.6-0.6)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Adults</td>
<td>24</td>
<td>0.2 (0.2-0.3)</td>
<td>0.5 (0.5-0.5)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
<tr>
<td>Elderly</td>
<td>16</td>
<td>0.2 (0.2-0.3)</td>
<td>0.5 (0.5-0.6)</td>
<td>0.8 (0.8-0.9)</td>
</tr>
<tr>
<td>Very elderly</td>
<td>14</td>
<td>0.3 (0.2-0.5)</td>
<td>0.5 (0.5-0.6)</td>
<td>0.9 (0.8-1.0)</td>
</tr>
</tbody>
</table>

- Combining P50 occurrence levels with all different consumption surveys (95% CIs also provided)
High exposure (P95) (TDI = 1)

- Combining P95 occurrence levels with all different consumption surveys (95% CIs also provided)

<table>
<thead>
<tr>
<th>Age group(a)</th>
<th>95th percentile dietary exposure (µg/kg bw per day)</th>
<th>95th percentile dietary exposure (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Minimum</td>
</tr>
<tr>
<td>Infants(b)</td>
<td>6</td>
<td>1.7 (1.6-1.8)</td>
</tr>
<tr>
<td>Toddlers</td>
<td>11</td>
<td>1.8 (1.6-2.0)</td>
</tr>
<tr>
<td>Other children</td>
<td>20</td>
<td>1.5 (1.4-1.6)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>20</td>
<td>0.8 (0.7-0.9)</td>
</tr>
<tr>
<td>Adults</td>
<td>24</td>
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<tr>
<td>Elderly</td>
<td>16</td>
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</tr>
<tr>
<td>Very elderly</td>
<td>14</td>
<td>0.7 (0.5-1.0)</td>
</tr>
</tbody>
</table>
LOD/LOQs of (multi)methods

- High number of samples below LOQ causes uncertainty
  - Low LOQs required
- Tendency for rapid analysis and many compounds
  - As a result high LOD/LOQs
- Also problem for trend analysis
- And potentially for deriving maximum levels based on “strict but feasible”
Zearalenone (EFSA, 2016)

- TDI: 0.25 µg/kg bw per day
  - Based on oestrogenic effects in pigs (NOAEL 10.4 µg/kg bw per day; UF of 4x10)
- Expressed as ZEN equivalents for ZEN and its modified forms
Metabolites

- Also conjugated forms
- Can be transformed to parents in GI-tract
- α-ZEL most potent animal metabolite, detected in milk by Huang et al., 2014
Relative potencies

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative potency factor (RPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEN</td>
<td>1.0</td>
</tr>
<tr>
<td>ZENGlc and ZENSulf</td>
<td>1.0</td>
</tr>
<tr>
<td>α-ZEL</td>
<td>60</td>
</tr>
<tr>
<td>α-ZELGlc and α-ZELSulf</td>
<td>60</td>
</tr>
<tr>
<td>β-ZEL</td>
<td>0.2</td>
</tr>
<tr>
<td>β-ZELGlc and β-ZELSulf</td>
<td>0.2</td>
</tr>
<tr>
<td>ZAN</td>
<td>1.5</td>
</tr>
<tr>
<td>ZANGlc and ZANSulf</td>
<td>1.5</td>
</tr>
<tr>
<td>α-ZAL</td>
<td>4.0</td>
</tr>
<tr>
<td>α-ZALGlc, α-ZALSulf</td>
<td>4.0</td>
</tr>
<tr>
<td>β-ZAL</td>
<td>2.0</td>
</tr>
<tr>
<td>β-ZALGlc, β-ZALSulf</td>
<td>2.0</td>
</tr>
<tr>
<td>cis-ZEN</td>
<td>1.0</td>
</tr>
<tr>
<td>cis-ZENGlc and cis-ZENSulf</td>
<td>1.0</td>
</tr>
<tr>
<td>cis-α-ZEL</td>
<td>8.0</td>
</tr>
<tr>
<td>cis-α-ZELGlc and cis-α-ZELSulf</td>
<td>8.0</td>
</tr>
<tr>
<td>cis-β-ZEL</td>
<td>1.0</td>
</tr>
<tr>
<td>cis-β-ZELGlc and cis-β-ZELSulf</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Potential consequence milk

- Guidance Value for dairy cows: 0.5 mg/kg feed
  - Suppose 2 kg feed means intake of 1 mg ZEN
  - If 1% excreted in milk as α-ZEL: 0.01 mg or 10 µg
  - In 20 litres milk gives level of 0.5 µg/L
- So equivalent to 30 µg ZENeq/L with RPF of 60
- If child of 10 kg drinks 0.5 L: 1.5 µg ZENeq/kg bw/day
- TDI: 0.25 µg/kg bw per day
- So 6-fold exceedance of TDI
- Children(young boys) sensitive to hormones
Consequences

- Based on 0.5 L milk by 10 kg bw child:
  - Level should be below $2.5/0.5/60=0.08$ µg/L (ppb)

- If 1% transfer is correct:
  - Intake cow $< 166$ µg ZEN
  - If 2 kg feed Guidance value dairy cows $< 83$ µg/kg (6x lower)

- Therefore urgent need for transfer studies and sensitive methods for α-ZEL in milk
Recent work from EFSA on plant toxins

- Opinion on tropane alkaloids (food)
  - Detected in cereals
  - Lower ARfD established based on human studies
  - Potential risk especially for children
- Opinion on phorbol esters Jatropha (detoxification/feed)
- Opinion on cyanogenic alkaloids
- Opinion on tetrahydrocannabinol
- Report on pyrrolizidine alkaloids (PAs)
  - New BMDL$^{10}$ established for riddelliine
- Working on opium alkaloids
Pyrrolizidine alkaloids (PAs)

- Liver effects like veno-occlusive disease in animals and humans (various incidents)
- Carcinogenic in rats (hepatocellular carcinomas and haemangiosarcomas)
- Genotoxic properties
- Therefore: no threshold so no TDI
Structures of pyrrolizidine alkaloids
## Model outcomes

### Table with summary of the fitted models

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of parameters</th>
<th>Log-likelihood</th>
<th>AIC</th>
<th>BMD</th>
<th>BMDL</th>
<th>BMDU</th>
<th>Converged</th>
<th>Accepted AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>1</td>
<td>-119.66</td>
<td>241.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>6</td>
<td>-38.90</td>
<td>89.80</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Logistic</td>
<td>2</td>
<td>-40.32</td>
<td>84.64</td>
<td>363</td>
<td>299</td>
<td>431</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Probit</td>
<td>2</td>
<td>-39.63</td>
<td>83.26</td>
<td>328</td>
<td>270</td>
<td>386</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>3</td>
<td>-38.95</td>
<td>83.90</td>
<td>278</td>
<td>216</td>
<td>345</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Log-probit</td>
<td>3</td>
<td>-38.90</td>
<td>83.80</td>
<td>270</td>
<td>215</td>
<td>323</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Weibull</td>
<td>3</td>
<td>-39.00</td>
<td>84.00</td>
<td>290</td>
<td>218</td>
<td>366</td>
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<td>yes</td>
</tr>
<tr>
<td>Gamma</td>
<td>3</td>
<td>-38.92</td>
<td>83.84</td>
<td>277</td>
<td>216</td>
<td>337</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Two-stage</td>
<td>3</td>
<td>-41.12</td>
<td>88.24</td>
<td>208</td>
<td>182</td>
<td>240</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

### Estimated model weights

<table>
<thead>
<tr>
<th>Logistic</th>
<th>Probit</th>
<th>Log-logistic</th>
<th>Log-probit</th>
<th>Weibull</th>
<th>Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.11</td>
<td>0.23</td>
<td>0.16</td>
<td>0.17</td>
<td>0.16</td>
<td>0.17</td>
</tr>
</tbody>
</table>

### Dose tumors N

<table>
<thead>
<tr>
<th>Dose</th>
<th>tumors</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>71</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>236</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>714</td>
<td>38</td>
<td>50</td>
</tr>
</tbody>
</table>
BMD modelling Riddelliine

- MOE > 10,000 so exposure < 25 ng/kg bw/day

<table>
<thead>
<tr>
<th>Dose</th>
<th>tumors</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>71</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>236</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>714</td>
<td>38</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMD</th>
<th>BMDL</th>
<th>BMDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>292.53</td>
<td>246.23</td>
<td>522.72</td>
</tr>
</tbody>
</table>

\( \mu g/kg \text{ bw/day} \)
Exposure to PAs from supplements, tea and honey

- Supplements of PA containing plants give highest exposure
- Followed by tea contaminated by weeds
- Third comes honey
- Animal derived products contribute less
Exposure $< 25$ ng/kg bw/day

In many cases too high exposure
Which weeds in tea?
Patterns green and black tea (>10 µg/l)
Patterns green and rooibos tea (>10 µg/l)
Patterns green and chamomile tea (>10/5 µg/l)

green

chamomile
What about farm animals?
## Animal feedstuffs: Alfalfa (lucerne)

<table>
<thead>
<tr>
<th>Year</th>
<th>No of samples</th>
<th>Positive</th>
<th>Average content (µg/kg)</th>
<th>Max (µg/kg)</th>
<th>Samples &gt;1000 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>6</td>
<td>83%</td>
<td>1440</td>
<td>3439</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>2007</td>
<td>13</td>
<td>85%</td>
<td>225</td>
<td>1409</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>2008</td>
<td>12</td>
<td>83%</td>
<td>716</td>
<td>6219</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>2009</td>
<td>17</td>
<td>88%</td>
<td>621</td>
<td>4507</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>2010</td>
<td>51</td>
<td>92%</td>
<td>225</td>
<td>2418</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>2011</td>
<td>50</td>
<td>86%</td>
<td>265</td>
<td>2027</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>2012</td>
<td>51</td>
<td>90%</td>
<td>356</td>
<td>4169</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

- In the Netherlands contamination of alfalfa with PAs remains high, notwithstanding the information provided to the industry.
Source?
Common groundsel rather than ragwort
Transfer to milk: study design

- 3 cows fed (fistula) 2x/day with tansy ragwort (*Senecio jacobaea*)
  - Week 1: no ragwort
  - Week 2: 2x 25 g ragwort
  - Week 3: 2x 50 g ragwort
  - Week 4: 2x 100 g ragwort (1% of feed intake)
  - Week 5: no ragwort

- Collected:
  - Milk
  - Some urine and feces
PAs in evening milk

![Graph showing the concentration of PAs in milk over time for three different cows.](graph_image)

- **Cow 1**: Dotted line with diamonds
- **Cow 2**: Dashed line with squares
- **Cow 3**: Solid line with triangles

The x-axis represents time (d), and the y-axis represents concentration (µg l⁻¹).
Milk versus plant material

Concentration (µg l⁻¹).

Concentration (mg kg⁻¹).

jacoline
PAs in eggs (Mulder et al., 2016)

- PAs primarily in yolk
Questions?