Terrestrial vertebrates
Guidance Document for Birds and Mammals
The PPR panel of the EFSA produced an opinion how to assess the risk of plant protection products (181 pages and 32 appendices with ± 550 pages).

This document was not a real a guidance document.

In the course of the revision of the Guidance document it became apparent that the task embraced several risk management issue which are not within EFSA’s and the PPR Panel’s remit.

The Panel adopted a two stage approach:
1) an opinion with the science behind the guidance document,
2) a joint working group of representatives of the EFSA, the Commission and the Member States that will consider the risk management issues to finalise the new guidance document.
Birds and mammals opinion / guidance document

- Development of generic focal species
- Acute risk assessment using LD50/m²
- Dietary exposure of nestling birds
- Combined effects of simultaneous exposure to several active substances
- Extrapolated LD50 values from limit dose tests
- Use of the geometric mean rather than lowest endpoint when toxicity data are available from multiple species
- Phase specific approach to avian and mammalian reproductive risk assessment
- Interpretation of protection goals and evaluation of the level of protection
Development of generic focal species
Acute risk assessment using LD50/m²
Dietary exposure of nestling birds
Combined effects of simultaneous exposure to several active substances
Extrapolated LD50 values from limit dose tests
Use of the geometric mean rather than lowest endpoint when toxicity data are available from multiple species
Phase specific approach to avian and mammalian reproductive risk assessment
Interpretation of protection goals and evaluation of the level of protection
Indicator species versus focal species
Indicator species

is not a real species but, by virtue of its size and feeding habits it is considered to have higher exposure than (i.e. to be protective of) other species that occur in the particular crop. It has a high food intake rate, and consumes one type of food which in turn has high residues on/in it.

Used in screening step of risk assessment

e.g. small herbivorous mammal or small insectivorous bird
Choice of indicator and focal species

Generic focal species

is, again, not a real species, however it is considered to be representative of all those species potentially at risk. It is based on ecological knowledge of a range of species that could be at risk. It may consume a mixed diet rather than just one as for the indicator species. However it is not tried to mimic the diet as good as possible.

*Used in first tier assessment*

*e.g. small granivorous bird (finch)*
Choice of indicator and focal species

Focal species

is a real species that actually occurs in the crop when the pesticide is being used. The aim of using a ‘focal species’ is to add realism to the risk assessment.

*Could be used in higher tier assessment*

e.g. the Robin
Choice of indicator and focal species

Plant material is eaten by voles and voles are found all over Europe, but not each vole species can be found in the whole of Europe.
Choice of indicator and focal species

Plant material is eaten by voles and voles are found all over Europe, but not each vole species can be found in the whole of Europe.
Choice of indicator and focal species

COMMON VOLE

*Microtus arvalis*

Total range area = 9,863,903 km²

**Range type:**
- Native Extant
- Introduced
- Native Reintroduced
- Probably Extinct
- Native - Possibly Present
- Prehistorically introduced

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Choice of indicator and focal species

FIELD VOLE

Microtus agrestis
Total range area = 10,765,759 km²
Range type
- Native Extant
- Introduced
- Native Reintroduced
- Probably Extinct
- Native - Possibly Present
- Prehistorically Introduced

IUCN 
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Choice of indicator and focal species

MEDITERRANEAN PINE VOLE

SAVI'S PINE VOLE

THOMAS'S PINE VOLE

EAST EUROPEAN VOLE OR SIBLING VOLE
### Choice of indicator and focal species

#### Agricultural habitats in which vole species can be found.

<table>
<thead>
<tr>
<th>English name</th>
<th>Grassland</th>
<th>Arable land</th>
<th>Pasture</th>
<th>Plantations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bank vole</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Field vole</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Common vole</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Cabrera’s vole</td>
<td>X</td>
<td>-</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Mediterranean pine vole</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Balkan pine vole</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Savi’s pine vole</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sibling vole</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Thomas’s pine vole</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
</tbody>
</table>
The common shrew has a wide distribution in the Palaearctic, occurring from Britain through central, northern and eastern Europe and Asia as far east as Lake Baikal and as far north as the Arctic coast.

**COMMON SHREW**

**GREATER WHITE-TOOTHED SHREW**

**BICOLOURED WHITE-TOOTHED SHREW**
Choice of indicator and focal species

WOOD MOUSE

STRIPED WOOD MOUSE
Choice of indicator and focal species

For the indicator and for the generic focal species it was proposed to use a body weight of 25 grams (a body weight comparable to the smaller species of voles).

There is no differentiation in food between the screening level and first tier assessment, because voles eat plant material and no other types of food.

The common shrew (9.7 grams) is proposed for insect eating mammals. Again no differentiation possible in food types.

The wood mouse (21.7 gram) is proposed for omnivorous mammals. In the screening level it is assumed that this indicator species will only eat plant material, which will result in the highest exposure. In the first tier it is assumed that the generic version will eat 25% plant material (leaves), 50% seeds and 25% insects.
## Screening level shortcuts

<table>
<thead>
<tr>
<th>Crop</th>
<th>Indicator species</th>
<th>Short cut value for mean RUDs</th>
<th>Short cut value for 90th percentile RUDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare soil</td>
<td>Small granivorous mammal</td>
<td>6.6</td>
<td>14.4</td>
</tr>
<tr>
<td>Bush and cane fruit</td>
<td>Small herbivorous mammal</td>
<td>43.4</td>
<td>81.9</td>
</tr>
<tr>
<td>Bulbs and onion like crops, cereals, oilseed rape, potatoes, root and stem vegetables, strawberries, sugar beet, and sunflower</td>
<td>Small herbivorous mammal</td>
<td>48.3</td>
<td>118.4</td>
</tr>
<tr>
<td>Cotton, fruiting vegetables, grassland, leafy vegetables, legume forage, maize, orchards, ornamentals/nursery, pulses, and vineyard</td>
<td>Small herbivorous mammal</td>
<td>72.3</td>
<td>136.4</td>
</tr>
</tbody>
</table>
# First tier short cuts for Crop Growth stage

<table>
<thead>
<tr>
<th>Crop</th>
<th>Growth stage</th>
<th>Generic focal species</th>
<th>Short cut for mean</th>
<th>Short cut for 90th percentile.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes BBCH 10-19</td>
<td>Small insectivorous mammal “shrew”</td>
<td>4.2</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH ≥ 20</td>
<td>Small insectivorous mammal “shrew”</td>
<td>1.9</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH ≥ 40</td>
<td>Small herbivorous mammal &quot;vole&quot;</td>
<td>21.7</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH 10-40</td>
<td>Large herbivorous mammal “lagomorph”</td>
<td>14.3</td>
<td>35.1</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH ≥ 40</td>
<td>Large herbivorous mammal “lagomorph”</td>
<td>4.3</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH 10-19</td>
<td>Small omnivorous mammal “mouse”</td>
<td>7.8</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH 20-39</td>
<td>Small omnivorous mammal “mouse”</td>
<td>7.5</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>Potatoes BBCH ≥ 40</td>
<td>Small omnivorous mammal “mouse”</td>
<td>2.4</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>
### Residue unit doses for different food types

<table>
<thead>
<tr>
<th>Crop/category of insects</th>
<th>Crop stage</th>
<th>mean</th>
<th>Standard deviation</th>
<th>90&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>n</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass+cereals</td>
<td>BBCH 10-30</td>
<td>54.2</td>
<td>55</td>
<td>102.3</td>
<td>132</td>
<td>ECPA database&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-grass weeds</td>
<td>Whole season</td>
<td>28.7</td>
<td>27.5</td>
<td>70.3</td>
<td>230</td>
<td>ECPA database&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Small fruits from orchards&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Fruiting period</td>
<td>3.3</td>
<td>2.6</td>
<td>6.5</td>
<td>33</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Large fruit from orchards&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Fruiting period</td>
<td>19.5</td>
<td>16.8</td>
<td>41.1</td>
<td>33</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Berries&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Fruiting period</td>
<td>8.3</td>
<td>7.2</td>
<td>16.7</td>
<td>9</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Tomato</td>
<td>Fruiting period</td>
<td>12.8</td>
<td>14.6</td>
<td>30.6</td>
<td>86</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Gourds</td>
<td>Fruiting period</td>
<td>34.3</td>
<td>54.7</td>
<td>61.5</td>
<td>19</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Grains/ear</td>
<td>Fruiting period</td>
<td>15</td>
<td>25.4</td>
<td>13.0</td>
<td>21</td>
<td>Baril et al. (2005)</td>
</tr>
<tr>
<td>Seeds</td>
<td>Fruiting period</td>
<td>40.2</td>
<td>50.6</td>
<td>87.0</td>
<td>108</td>
<td>EC (2002)</td>
</tr>
<tr>
<td>Ground dwelling invertebrates without interception&lt;sup&gt;4&lt;/sup&gt;</td>
<td>ground directed applications</td>
<td>7.5</td>
<td>12.0</td>
<td>13.8</td>
<td>21</td>
<td>ECPA</td>
</tr>
<tr>
<td>Ground dwelling invertebrates with interception&lt;sup&gt;5&lt;/sup&gt;</td>
<td>applications directed to crop canopies</td>
<td>3.5</td>
<td>3.8</td>
<td>9.7</td>
<td>28</td>
<td>ECPA&amp;CSL</td>
</tr>
<tr>
<td>Insects (foliar dwelling invertebrates&lt;sup&gt;8&lt;/sup&gt;)</td>
<td>Whole season</td>
<td>21.0</td>
<td>21.6</td>
<td>54.1</td>
<td>35</td>
<td>ECPA&amp;CSL (-aphids)</td>
</tr>
</tbody>
</table>
Dietary intake versus LD$_{50}$ per m$^2$
Dietary risk assessment

• The choice was between:
  - The LD$_{50}$ per square meter approach, or
  - The TER approach

Input only application rate and toxicity value

\[
\text{TER} = \text{Toxicity Exposure Ratio} = \frac{\text{LD}_{50}}{\text{ETE}}
\]

\[
\text{ETE} = \frac{\text{FIR}}{\text{BW}} \times C \times \text{PT} \quad \text{(mg/kg BW/d)}
\]

In which:
ETE = Estimated theoretical exposure
FIR = Food intake rate of indicator species (g fresh weight /d)
BW = Body weight (g)
C = Concentration of compound in fresh diet (mg/kg)
PT = Fraction of diet obtained in treated area (number between 0 and 1)
**Dietary risk assessment**

\[
FIR = \frac{DEE}{(FE \times (1 - \frac{MC}{100})) \times \frac{AE}{100}}
\]

In which:

- **DEE** = Daily energy expenditure of the indicator species (kJ/d)
- **FE** = Food energy (kJ/dry g)
- **MC** = Moisture content (%)
- **AE** = Assimilation efficiency (%)

The risk managers preferred to have one method for the different assessments, as well for birds and mammals and as for acute and reproductive assessments.
Geometric mean versus lowest available toxicity value
Geometric mean approach

The advice of the PPR panel of the EFSA was to use the geometric mean of the available toxicity values instead of the lowest available toxicity value.

It was shown that this value together with the safety factor (as defined in 91.414) would ensure at least the same level of protection as implied in the directive.

The Joint Working Group recognized the scientific logic and robustness of the geomean approach to addressing endpoints from multiple toxicity studies for different species.

However, there were concerns for situations where species sensitivity distribution was particularly wide.
Geometric mean approach

Toxicity value available

<table>
<thead>
<tr>
<th>Difference between lowest and highest toxicity value</th>
<th>1-10</th>
<th>10-100</th>
<th>100-1000</th>
<th>≥ 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of compounds</td>
<td>122</td>
<td>100</td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>
The Joint Working Group decided on the following approaches:

- The geometric mean should be used for the acute assessment, except when the lowest species is more than a factor of 10 below the geometric mean.
- Where this is the case, then the most sensitive species will be used for the risk assessment but generally without an assessment factor (unless there are specific reasons to believe that this is not appropriate).

The Joint Working Group decided that the reproductive assessment should continue to be based on the most sensitive species pending additional research. The PPR Panel will therefore be asked to consider further the applicability of the geometric mean for NOEC from reproductive studies.
Geometric mean approach (some examples)

Suppose you have a number of LD50s and the geomean is 100, and the lowest LD50 is 20.

\[ \frac{100}{10} = 10 \] which is lower than 20, therefore, 10 will be used in the risk assessment.

Now suppose the lowest was 5.

This is lower than the geomean of \[ \frac{100}{10} = 10 \], therefore, 5 will be used in the risk assessment.
Phase specific assessment

versus

former reproductive assessment
Reproductive assessment

In the opinion it was proposed to use a new method: the phase specific risk assessment.

<table>
<thead>
<tr>
<th>Breeding phase</th>
<th>Test endpoint used as surrogate</th>
<th>Short-term exposure</th>
<th>Long-term exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair formation/breeding site selection</td>
<td>1/10 of LD50 or specific NAOEL</td>
<td>1, 2 or 3 days Time weighted average Dietary Daily Dose</td>
<td>21 day time weighted average daily dose</td>
</tr>
<tr>
<td>Copulation and egg laying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incubation and hatching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile growth and survival until fledging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-fledging survival</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reproductive assessment

Move phase-specific approach to higher tier

Single tox endpoint:
- Mammals - lowest relevant endpoint from 2-gen rat
  - or outcome of teratogenetic study if lower
- Birds – lowest or geomean of relevant endpoints

Single exposure estimate:
- Use Long Term Exposure as default
- Use Short Term Exposure when evidence for substance in hand

Questions to PPR Panel:
- Criteria for when to use short term exposure estimates,
- Use of 1/10th LD50 for birds needs to be confirmed
- TWA period for LTE – study duration or 21d?
Acknowledgement

Members of the G&D working groups:

Members of Risk managers working group:
Apolonia Novillo (Spain), Brian Woolacott (United Kingdom), Elisabeth Dryselius (Sweden), Her de Heer (The Netherlands), Manousous Foudoulakis (Greece), Martin Streloke and last meeting Andreas Höllrigl-Rosta (Germany), Lilian Tornqvist (chair, DG SANCO).

All members of PPR panel of the EFSA and in particular Christine Füll