UNCERTAINTY AND RECOMMENDATIONS

CONTAM Opinion on dioxins and DL-PCBs in food and feed

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Uncertainty Analysis

The CONTAM Panel performed the evaluation of the inherent uncertainties in the assessment of exposure to PCDD/Fs and DL-PCBs:

- following the EFSA Guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2007)

- considering the WHO/IPCS report on ‘Characterizing and Communicating Uncertainty in Exposure Assessment’ (WHO/IPCS, 2008)

Furthermore, uncertainties were reflected in:
- Hazard identification and characterization
- Dose-response assessment and HBGV derivation
- Risk characterization
Summary of Uncertainty Analysis - **EXPOSURE**

Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of exposure of PCDD/Fs and DL-PCBs in food

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapolation of the occurrence data to the whole of Europe</td>
<td>+/-</td>
</tr>
<tr>
<td>Consumption data: different methodologies / representativeness / underreporting / misreporting / no portion size standard</td>
<td>+/-</td>
</tr>
<tr>
<td>Use of data from food consumption surveys covering only a few days to estimate high percentiles (95th) long-term (chronic) exposure</td>
<td>+</td>
</tr>
<tr>
<td>Occurrence samples not sufficiently described (e.g. classified only at the 1st level of FoodEx) were excluded</td>
<td>+/-</td>
</tr>
<tr>
<td>Imputation of missing fat percentages of certain foods in the Comprehensive Database</td>
<td>+/-</td>
</tr>
<tr>
<td>Effect of cooking/processing not taken into account</td>
<td>+/-</td>
</tr>
<tr>
<td>Contribution of other persistent AHR agonists</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = uncertainty with potential to cause over-estimation of exposure/risk
- = uncertainty with potential to cause under-estimation of exposure/risk
## Summary of Uncertainty Analysis – **HAZARD ID/HC**

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty in the relative potency of PCB-126</td>
<td>+</td>
</tr>
<tr>
<td>Uncertainties in WHO\textsubscript{2005}-TEFs being rounded figures based on a wide range of relative potencies in animal and cell based studies</td>
<td>+/-</td>
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</table>

### Epidemiological studies

<table>
<thead>
<tr>
<th>Source of uncertainty</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty about systemic TEFs</td>
<td>+/-</td>
</tr>
<tr>
<td>Lack of measurements on PCDD/Fs and DL-PCBs other than TCDD</td>
<td>+</td>
</tr>
<tr>
<td>Non differential misclassification of exposure</td>
<td>-</td>
</tr>
<tr>
<td>True exposure being higher or lower than the estimate of exposure</td>
<td>+/-</td>
</tr>
<tr>
<td>True outcome is more or less prevalent than the estimate of the outcome</td>
<td>+/-</td>
</tr>
<tr>
<td>Confounding by other factors</td>
<td>+/-</td>
</tr>
<tr>
<td>Low number of epidemiological studies on the critical endpoint at low exposure</td>
<td>+/-</td>
</tr>
</tbody>
</table>

### Critical study

<table>
<thead>
<tr>
<th>Source of uncertainty</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-exposure to other compounds which may impair semen quality</td>
<td>+</td>
</tr>
<tr>
<td>Uncertainty regarding critical window for effect on semen quality outcome</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Toxicokinetic modelling

- Existing kinetic models not suitable to take into account variations in levels of PCDD/Fs and DL-PCBs during pregnancy and lactation
  - Milk intake of 800 mL per day applied throughout breastfeeding period
  - May result in overestimation of child exposure and a more conservative TWI (but rounded TWI robust for these effects)

- Body fat content was kept constant for infants and children
  - Known to be low at birth but rapidly increasing
  - Initial serum level at birth underestimated
  - Peak serum levels and subsequent decrease less affected
  - May affect relative amount stored initially in the liver
Toxicokinetic modelling

- Variations in body weight and fraction of body fat in mothers not taken into account by the modelling
  - may affect exposure and serum levels infants (both directions)

- Models developed for TCDD
  - less accurate for other relevant PCDD/Fs and DL-PCBs
  - the half-lives of PeCDD and 2,3,4,7,8-PeCDF are longer than for TCDD, those for other shorter

- The models are likely to underestimate the serum levels for these compounds but overestimate that for other congeners
  - Decided not to apply another uncertainty factor
Conclusion of the Uncertainty Analysis

The CONTAM Panel considered that:

- the impact of the uncertainties on the risk assessment of PCDD/Fs in food is moderate
- the impact of the uncertainties in the risk assessment for the sum of PCDD/F and DL-PCBs in food is high, due to the uncertainty in the relative potency of PCB-126 in humans

Overall, the assessment is likely to be conservative
Recommendations (I)

In order to improve the risk assessment for both humans and animals and reduce the uncertainties, the CONTAM Panel recommends that:

- The current WHO$_{2005}$-TEFs should be re-evaluated in order to take into account new in vivo and in vitro data. In particular, more insight into the relative potency of PCB-126 in humans is required.

- There is a specific need to derive systemic TEFs for PCDD/Fs and DL-PCBs for use in epidemiological studies, also taking into account the results from human cells.

- There should be an evaluation of the relative exposure contribution of other persistent chemicals, acting as agonists on the AHR, taking into account their toxic potencies.

- To evaluate the applicability of the TEQ-principle, more research and understanding is needed on reported congener-specific effects of PCDD/Fs and DL-PCBs, including their relevance at low doses.
Recommendations (II)

- Further **improvement of toxicokinetics models** is needed, including parameters dealing with pregnancy, breastfeeding and occasional exposure to high levels. Inclusion of PCDD/Fs, other than TCDD, and DL-PCBs is required. The use of in vitro models for further refinement should be considered.

- Data from both experimental animal and epidemiological studies should be reported in a way that allows a better **dose-response evaluation** in order to improve the risk assessment. There is a need to develop a **consensus methodology for data sharing** between individual researchers and public health authorities.

- There is a need for **prospective developmental epidemiological studies** on PCDD/Fs and DL-PCBs at low to moderate doses on, in particular, male reproductive outcomes and effects on the thyroid system. **Follow-up studies on existing and previous cohorts** with good information on pre- and postnatal exposure should be considered.
Recommendations (III)

- Validated and cost-effective methods are needed to assess exposure in small amounts/volumes of biological samples of animals and humans.

- To better understand the adverse effects of PCDD/Fs and DL-PCBs, more insight is needed into the mode of action, especially in relation to observed critical effects.

- Mechanistic studies on transgenerational (third generation) effects are needed.

- To improve human exposure estimation, more occurrence data are needed on food of plant origin, especially where individual results of certain foods indicate potential higher contamination.

- More data are needed on feed, provided by a greater number of European countries.
Recommendations (IV)

- There is a need for an updated benefit-risk assessment of fish consumption that takes exposure to PCDD/Fs and DL-PCBs into account.

Noting that,

_The EFSA Scientific Committee in its statement on the benefits of fish/seafood consumption of methylmercury recommended that:_

**each country needs to consider its own pattern of fish consumption; especially the species of fish consumed,**

_and carefully assess the risk of exceeding the HBGV while obtaining the health benefits from consumption of fish/seafood._

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