OVERVIEW OF COMMENTS

CONTAM Opinion on PCDD/Fs and DL-PCBs in food and feed

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efsa
European Food Safety Authority

Overview

Comments from 9 European Countries

- Finland
- Germany
- Iceland
- Ireland
- Italy
- Norway
- Spain
- Sweden
- The Netherlands

Overview

- Areas covered by the comments:

- Scope of the mandate
- Exposure assessment – humans
- Experimental animal studies
- Critical effect and epidemiological studies
- TEF scheme
- Toxicokinetic modelling
- Interpretation of the TWI
- Uncertainties

Scope of the mandate

... this opinion **must necessarily be accompanied by an updated risk-benefit report** to facilitate the risk management in the Member States and to be able to make suitable consumption recommendations...

... a set of **risk-benefit analyses** for each of the main groups of diets and alimentary habits/traditions in Europe should be performed...

... there is a **need for risk-benefit evaluations** of e.g. fish consumption related to PCDD/F exposure

... we rerun our **health benefit-risk assessment** model with the new outcomes proposed by the CONTAM Panel

OUT OF THE SCOPE OF THE MANDATE

The mandate did not include a risk-benefit assessment of fish consumption

Scope of the mandate

…general observation on the publication plan and the **delay of the publication**, which we see as unfortunate (...) there is a risk that the delay of publication can cast doubt on independence and transparency, even though there is no reason for it.

STRATEGIC DECISION OF EFSA

Given the new scientific information contained in the opinion and its sensitivity, it was decided to postpone the publication and **organise an exchange of views with MS**

Human exposure assessment

... can EFSA include the **exposure results per survey**, as well as the main food groups contributing to the exposure?

... why the chronic exposure has not been assessed using **statistical models**?

... why **FoodEx2 was not used** in the opinion to refine the linkage between the foods analysed and those consumed?

... exposure estimates are based on pooled European occurrence data (...) It is anticipated that **actual exposure in xxxx is much lower than estimated by EFSA**.

Presentation on:

Occurrence data and exposure assessment

Studies in experimental animals

... **only studies using pure TCDD** have been taken into account because of uncertainty about the TEF factors (...) can EFSA explain the **reasons for not applying this approach for the human studies**, other than wishing not to limit the availability of human studies?

Presentation on:

Methodology

Presentation on:

Studies in exp animals

Critical effect and epi studies

Sperm concentration

... studies in humans on semen quality are **difficult to control** and have to deal with many methodological aspects and other **factors potentially influencing the results**

... huge **inter- and intraindividual variability** in sperm concentration

... **mode of action** for the effect on sperm concentrations?

... the **evidence for a causal effect** of TCDD on sperm concentration is **limited**

... contribution of **other factors** on semen quality?

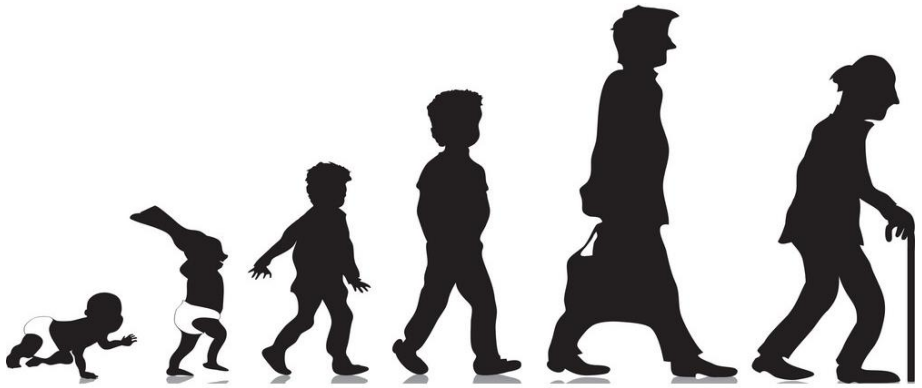
Critical effect and epi studies

Window of exposure

... what is the age period of the **relevant critical window**?

... no justification **why the age of 8-9 years was chosen** for the exposure assessment.

... remains **uncertain**, whether serum concentration at the **age of 8-9 years is a suitable time to assess effect** on semen quality at a later stage in life.

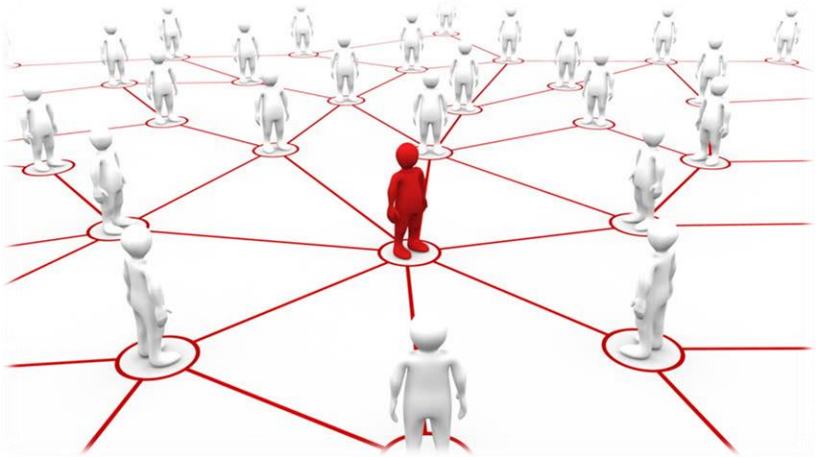


Critical effect and epi studies

Number of subjects

... of the 516 boys originally selected, only 133 participated at follow-up 10 years later. (...) how the **small number of boys followed up** may have affected the results?

... the **number of subjects in the studies considered seems to be too low**, and adjustment during statistical evaluation may not handle the many possible confounders adequately



Critical effect and epi studies

Confounders

... contamination of the environment with special pattern of dioxins, but also with **organochlorine pesticides, lead and probably other compounds with shorter half-lives** not detected in the study

... how was the **contribution of several co-contaminants in relation to the critical effect** investigated?

... **HCB- and HCH-exposure** are important confounders in the study and have been associated with onset of puberty. Is it possible that **onset of puberty has an impact on semen quality** and therefore should be included as a **confounder** in the semen parameters study?

... **HCB** levels were also associated with **delayed puberty** and **NDL-PCBs** were associated with **early puberty**. (...) How does this confounder and possible different congener pattern **affect the observed association**?

Critical effect and epi studies

Confounders

... the consumption of **alcohol and the smoke of tobacco** are two potential confounding factors related to the lifestyles (...) The questions used have a very high sensitivity in the detection of the two behaviours at risk, but also have a very low discrimination power, i.e. they do not address the issue of heavy consumption of these two substances, which is what most likely may be linked to an adverse (therefore confounding) effect on the semen quality.

… significant **association between Pb and a delay in the onset of puberty** (...) No specific study in this cohort on the association of Pb and semen quality (...) Pb could be a **confounder** (...) Proper control of this potential confounder would have required the analysis also of blood samples at the moment of semen collection.

Critical effect and epi studies

Associations

... **no associations for PCDF-TEQ and DL-PCBs-TEQ** is surprising and contradicts the theory of the binding affinity at the AhR

... the observed association between PCDD/F levels and lower sperm concentrations **does not seem to be plausible** with regard to a causal relation

... a relevant negative effect of dioxins on sperm concentrations in the background range, as suggested from results of the Russian Children's Study, **does not match with results of the global "sperm crisis"** in developed countries.

... the somewhat lower sperm quality in these higher quartiles of exposure may just be **chance finding**?

Critical effect and epi studies

Associations

... why did EFSA not perform a **dose-response analysis** (and derive a BMDL)?

... **why was a NOAEL derived** from a study lacking any dose-response?

... more information about the **shape of the association** would be of interest. How is the distribution of PCDD in the study population? Linearity/non-linearity? Results of **other percentiles**? Sensitivity analyses (e.g. results restricted to non-smokers)?

... how was it determined that four quantiles are sufficient to derive a reliable NOAEL? Has EFSA considered organising the data in **deciles**?

Critical effect and epi studies

Other

... While theoretically possible, the interpretation of the results as causally related to dioxin exposure is **not consistent with the results of the Seveso studies** reporting an effect of roughly the same extent but at about 10-fold higher dose levels.

... due to shortcomings and limitations the critical study does **not provide an appropriate basis** for a casually related dioxin effect to be used for the derivation of a HBGV.

Critical effect and epi studies

Presentation on:

Studies in humans: Russian Children's Study and others

TEF scheme

... can EFSA further elaborate on the **uncertainty of the existing TEF** scheme?

... what is the **impact of the uncertainty in the potency of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF** on the observed associations, in comparison to PCB-126.

... most studies on which TEF values are set, do not include critical endpoints like sperm production and pubertal onset following exposure of the mother (...) there is considerable uncertainty related to the sensitivity of humans compared to animals. This is of particular importance given the large contribution of PCB-126 to Total TEQ exposure.

Presentation on:

Uncertainties linked to the TEF scheme

Toxicokinetic modelling

... the model **overestimated the real life accumulation** of PCDD/Fs and PCBs from human milk and from the diet.

... Extrapolating the general decreasing trend from 2010 to 2018 with declined decrease rate of 6% (...) at least 90% of country mothers in Total-TEQ terms **are below the 5.9 pg/g fat** level.

... What is the basis for taking a **duration of 12 months of breastfeeding?** (typically 6 months or shorter)

... a daily **intake of 800 mL of breast milk appears conservative**.

... how did the model **take into account declining levels**?

... the model output appears to be based on **worst case scenario assumptions**, it is **highly conservative**, and **possibly unlikely**.

Toxicokinetic modelling

... **assumptions** were made on several parameters. How is concentration, age (or weight), constant milk supply, daily intake, and lipid content dependent incorporated in the model?

... for the boys, an oral exposure of twice that of the mother is assumed. **What other assumptions** have been considered on the exposure of the sons?

... what is the uncertainty of not taking into account the properties of the **other congeners in the model calculations**?

... how will the **TWI be affected if variation in the parameters included in the model** is addressed?

... can EFSA **provide uncertainty and uncertainty levels** when addressing the variation of the various parameters in the model calculations?

Interpretation of the TWI

... should an indication be given to the **TWI that it is only protective when not breastfeeding for longer than 12 months**?

... Leaving out the DL-PCBs altogether results in an overly conservative TWI. **Could the TWI also be derived including the DL-PCBs**?

... the TWI is only intended to protect the children of mothers-to-be (...) Can EFSA explain **why exposure of breast-fed children should be interpreted on a different basis than exposure of infant-formulae fed children**, and how this should be done (i.e., to what should the exposure of breast-fed infants be compared)?

... does EFSA mean that **for Toddlers and other children actually a twice higher TWI should be applied**?

... has EFSA considered deriving HBGVs for **effects that are not mediated by exposure of the mother**?

Interpretation of the TWI

... is there a **difference between boys and girls** in terms of tolerable intake?

... if the observed effect is caused solely by PCDD/F, it might be **more correct to designate the TWI for PCDD/F-TEQ** and leave the DL-PCBs out

... The effects on semen quality of exposure during puberty are only linked to TCDD and PCDD (...) any suggestion of the modification of **TWI should refer specifically to PCDD/F**.

... The effects concerns a very narrow age window (pre-puberty and puberty) (...) **the TWI should refer only to the specific category at risk**.

Presentation on:

Trends in exposure and levels in human milk

Presentation on:

Toxicokinetic modelling, derivation of the HBGV

Uncertainties

... Table 56 combines the uncertainty of the exposure via food and feed. Would EFSA consider **separating uncertainties** to make clear they refer to different assessments?

... given the interdependence of uncertainties within the model, which are difficult to follow, and the concerns about the suitability of the pivotal study, it is **difficult to understand the overall level of uncertainty associated with the HBGV**, which raises the question if it is fit for purpose with regard to protecting human health.

uncertainties

Presentation on:

Uncertainties and Recommendations

Thank you…

… for being here

… for your comments and sharing your views with EFSA

… for contributing to the work of EFSA