

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Draft manuscript on developmental toxicity and the uncertainty factor for interspecies extrapolation

Introduction

1. The COT considered papers on this topic at its December 2013 and May 2014 meetings. The Committee concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity was not always adequate, and having considered data on effects other than in utero developmental toxicity, extended this conclusion to non-developmental outcomes also. The Committee agreed that a paper should be written for publication in a peer-reviewed journal. A short COT statement could then be produced, based on the paper.
2. The Secretariat approached a potential co-author for the paper. They wished to see a draft manuscript before deciding whether to be added as a co-author. A manuscript was drafted focussing on the developmental toxicity data.
3. The possible co-author has now provided comments on a draft manuscript and declined to be included as a co-author. This paper includes the comments provided and seeks the Committee's view on the way forward.

Nature of comments received and implications for the draft manuscript and the COT's review of uncertainty factors.

4. Comments on the draft manuscript are in Annex A, with separate comments added to the draft manuscript in Annex B.
5. Comments received relate to:
 - *Justifications for substances being included as human developmental toxicants.* These comments could be addressed by including more explanation that all types of developmental toxicity were considered, not only teratogenesis (e.g. the draft manuscript was not intending to imply that propranolol and aspirin are teratogens); and of the approach to including substances as human developmental toxicants. For substances for which the 10-fold uncertainty factor does not appear to be adequate,

further discussion of the strength of evidence for the substance being a human developmental toxicant could be included.

- *Justifications of selected LOAELs.* The bases of the selected LOAELs for all substances could be added.
- *The selection of LOAELs from studies in which only one dose level was tested.* Such LOAELs were selected over multiple papers in most cases. These comments could be addressed by summarising the basis of each LOAEL in the paper and highlighting in the table where a substance was selected from a study which tested only one dose. For substances for which the 10-fold uncertainty factor does not appear to be adequate, further discussion of the robustness of the estimate of the human LOAEL and the robustness of the LOAELs in rats and rabbits could be included.
- *The comparison of LOAELs for different types of developmental effect.* One comment indicates that only LOAELs for the same type of developmental effect should be compared. This is not the approach taken in the COT papers and the draft manuscript since the type of developmental toxicity observed in laboratory animals is not always the same as that occurring in humans and the aim was to assess the validity of the uncertainty factor in identifying a level of human intake without appreciable risk of any form of developmental toxicity.
- *The use of data from case reports to identify human LOAELs.* These comments are critical to the approach taken in the COT papers and the draft manuscript since case reports were often the only source of quantitative dose-response data for humans. Such data might be considered more reliable where the nature of the developmental effect were an infrequent effect in the population such as a specific type of malformation, or a specific type of effect for which there was also supporting epidemiological evidence.

Questions on which the views of the Committee are sought

6. Members are invited to consider the comments attached and advise on the way forward. In particular:

- i). What are the Committee's views on the use of data from case reports to identify human LOAELs?
- ii). What are the Committee's views on the suggested approaches to addressing the other comments, as indicated in paragraph 5, above?

Secretariat
January 2015

**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**Draft manuscript on developmental toxicity and the
uncertainty factor for interspecies extrapolation**

Comments on the draft manuscript.

Note: This Annex contains confidential comments from a peer reviewer and is not included in the published version on the COT website.

**Secretariat
January 2015**

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**Draft manuscript on developmental toxicity and the
uncertainty factor for interspecies extrapolation**

Draft manuscript with attached comments.

Note: This annex is not included in the published version on the COT website as it is reserved pending publication of the manuscript in a peer-reviewed journal.

**Secretariat
January 2015**