TOX/2020/49

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

Discussion paper on the approach for the review of the dioxin tolerable daily intake (TDI)

Background

1. At the September meeting, the COT reviewed the basis and implications of the new EFSA Tolerable Weekly Intake (TWI) for dioxins and considered that there were uncertainties over the derivation of the TWI and possible inconsistencies between the animal and human data. The Committee noted that the published opinion was insufficiently transparent on the rationales for the choices of key studies which made it difficult to evaluate the strength of the evidence. These concerns meant that they were unable to endorse the opinion.

2. The revised TWI would have significant risk management implications in a number of areas and therefore it is important that the data underpinning it are robust.

3. The COT recommended that a review of the evidential base and derivation of a health-based guidance value (HBGV) based upon this should be undertaken. The COT noted that their 2001 Tolerable Daily Intake (TDI) was derived in a similar manner due to differences between the SCF and WHO reviews at that time. However, COT acknowledged that a full systematic review of the dioxins database was neither feasible nor practicable.

4. The Committee noted that there was a need to examine both the epidemiological data and the animal data to determine the synergies and divergencies within the database. The Committee considered that the work of the SETE subgroup might provide a suitable framework for this.

5. Following these discussions, the Secretariat has drawn up a scope of work and proposed action plan and is seeking the Committee’s views on this approach The likely approaches and timescale are set out and the COT’s views on whether this is the appropriate way to proceed is sought. The approach is derived from the commonly accepted assumption that a HBGV based on the most sensitive endpoint in a vulnerable subpopulation will be protective of the whole population and for other endpoints.

6. The Secretariat proposes to systematically review evidence for the critical endpoint identified by EFSA namely effects on the reproductive system, focussing on

changes in the male reproductive system parameters. There will be a need to confirm the COC's previously expressed views that the carcinogenicity observed with dioxins does not involve direct genotoxicity and that a threshold approach to dioxin effects is still appropriate. In view of the recent IARC evaluation as class 2A, it will need to be confirmed that cancer is not the most sensitive endpoint in the database. A narrative review to confirm that other effects are less sensitive than the critical endpoint chosen for systematic review would be necessary and would serve as a basis for identifying dose response relationships that may be necessary for any risk benefit (the benefit deriving from other parts of the diet e.g. oily fish) analyses in other populations that are considered necessary.

7. There are several areas that need to be considered before embarking on applying the SETE approach.

8. The basis of the current COT TDI (COT, 2001)was the reports of Faqi et al., (1998) and Mably et al., (1992) describing effects in the male offspring of exposed dams and body burdens in dams respectively. There have subsequently been further studies to investigate these findings. The Secretariat proposes that a literature review of reproductive effects published since 2001 should be commissioned and this literature evaluated together with the studies used in 2001.

9. A literature review of epidemiological evidence in humans would be commissioned in parallel and Members views are sought on the appropriateness of starting literature searching from three months prior to the cut-off date used by EFSA and reviewing any new data together with that in the EFSA opinion. A narrative review of the entire database would identify all the endpoints reported in the epidemiological studies and the available dose response data. A subsequent systematic evaluation of the studies on the most sensitive endpoint will take place.

In 2001 the human data were not used as the basis for the TDI because:

- the exposure data were rough estimations and did not include all the dioxins and dioxin-like substances of concern
- the studies did not adequately consider other possible causes of the observed effects
- in all apart from the Dutch developmental studies, the patterns of exposure included periods of high-level exposure rather than continual low-level exposure from food
- in the occupational studies, exposed workers were mostly male and therefore the wrong population for the critical effect seen in animal studies (effects on the foetus)

10. The Secretariat proposes that a mode of action analysis of the consistency between the animal and human data should be undertaken together with application of the interim guidance from the SETE subgroup on the outcomes of the reviews of experimental and human data. This would permit the establishment of a HBGV

based upon the entirety of the available data and identify the uncertainties with this value and their potential significance.

The Committee views are sought on the following:

- The Committee is asked to advise on whether this review should be narrative or systematic and whether inclusion and exclusion criteria can be defined.
- Members views are sought on the appropriateness of starting literature searching from three months prior to the cut-off date used by EFSA and reviewing any new data together with that in the EFSA opinion.

- Members are asked to consider how different exposure patterns should be dealt with in the human studies. Whilst using the body burden approach permits the use of chemical specific adjustment factors and removes the need for a toxicokinetic adjustment factor for extrapolation from animals to humans, there will still be a need to correct for differences between individuals.

- Members are asked to consider the extent to which the available toxicokinetic models should be reviewed to improve body burden extrapolation in both the experimental and human data.

- Members views are sought on how to account for periods of higher acute exposure and its effect on fluctuations in the short-term body burden and the differences in toxicodynamic behaviour of dioxins including identifying possible windows of vulnerability to acute rather than chronic dioxin exposure.

- Members are asked to comment and, if appropriate agree the proposed plan for the work as outlined in the provisional timetable below.

The proposed schedule is:

- October 2020 COT agree scope and proposed workplan
- December 2020 Secretariat commissions literature searches and systematic reviews on human epidemiology, reproductive effects in animals and carcinogenicity
- Quarter 1 2021 Draft interim guidance from SETE
- Quarter 2/3 2021 drafts of systematic reviews discussed by COT and COC, following discussion mode of action framework drawn up whilst reviews are finalised
- Quarter 3 2021 need for additional work clarified and if necessary commissioned
- Quarter 4 2021synthesis of toxicological and epidemiological evidence around framework and dose response modelling
- Quarter 1 2022 Draft COT statement discussed and basis for HBGV agreed, uncertainty analysis conducted and incorporated
- Quarter 2 2022 statement finalised

11. Members are asked to recognise that due to the potential resource implications of EU exit for the Secretariat given the scale of the task, the specialist skills required and the time pressures combined with the need to incorporate external work, this is a provisional outline and may take longer than estimated here.

Secretariat

October 2020

REFERENCES

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