TOX/2021/41

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

Impact of updated BMD modelling methods on perchlorate and chlorate assessments of human health hazard – Haber et al. 2021

1. A recent publication by Haber et al (2021) on “Impact of updated BMD modelling methods on perchlorate and chlorate assessments of human health hazard” has been brought to the Secretariats attention by HSE (informally) via a Member of the Expert Committee on Pesticide Residues in Food (PRiF). The paper is attached at Annex A.

2. The following summary paragraphs, comments and thoughts have kindly been provided by two COT Members in advance of the meeting.

3. Exposure limits for perchlorate and chlorate are derived from a human study of radioactive iodide uptake (RAIU) by the thyroid (Greer et al, 2002). The analyses are based upon Bayesian hierarchical modelling which, the authors argue, allows dose-response modelling to take into considerations repeated measures using hierarchical modelling.

4. Beta distribution was used for the modelling to reflect bounding of RAIU values between 0 and 1. The implication of this constraint for the model result suggests to be close to zero. However, the authors did not evaluate the implications of each assumption which differs from those used in previous modelling.

5. The benchmark response (BMR) was determined to be a point value of 8% RAIU (not a change in RAIU), based on the interpretation of medical literature that RAIU values lower than this are considered abnormal. The definition of the BMR was based on the assumption that the mean response would correspond to about 50% of the population with a response below the BMR at the benchmark dose.

6. This study uses a hybrid definition of the BMR (Crump, 1995), based on the extra risk of having an RAIU in the abnormal range. Crump's “hybrid approach” is where "the modelling is on the continuous scale, but expresses the metric of risk in terms of a probability of response". The authors noted that "This approach allows us to define a BMD at which it was estimated that there would be a 10% extra risk in the population of having RAIU of 8% or lower."

7. The applied version of BMD modelling was developed because the standard BMD modelling packages such as the BMDS and PROAST versions (RIVM and EFSA platforms) of programs/software are unable to handle repeated measures (and the associated correlations), Proast/BMDS model-types - Exponential and Hill models -were adapted for the Bayesian approach. The modelling was carried out using STAN. STAN is described as a "…a C++ library for Bayesian modelling and inference that primarily uses the No-U-Turn sampler (NUTS) (Hoffman and Gelman 2011; 2012) to obtain posterior simulations given a user-specified model and data.

8. The authors derive a tolerable daily intake (TDI) of 0.008 mg/kg per day for perchlorate from a BMDL (and POD) of 0.03 mg/kg which adds to a set of divergent estimates from various other papers and organizations (c.f. JECFA 0.11 and EFSA 0.0012). Consistent with the approach of EFSA (2015), the authors concluded that the chlorate TDI could be calculated as 10x the perchlorate TDI. The resulting chlorate TDI would be 0.08 mg/kg per day. However, the authors did note, that an "alternative approach would be to conduct model averaging of the five models; such an approach would result in a higher POD."

9. Overall, the authors seemed to be critical of current BMD modelling approaches stating that “This particular case does emphasize that risk assessors need to ensure that all modelling assumptions are scrutinized and verified to be appropriate for the data under consideration. Standard packages are not designed to correctly handle every situation that might arise and for which one might need dose-response modelling; thus, appropriate risk assessment practice should avoid over-reliance on such packages.” While this raises an important point, the authors themselves made several assumptions, e.g. on the model distribution, but no model diagnostics are reported.

10. Applying a binary outcome measure (being below 8%) in a study that only contains 37 individuals is statistically more unstable than using the raw (continuous outcome measured). Hence the original study by Geer et al. (2002) may not be appropriate for this type of repeated-measure modelling; measurements taken at different time points are applied as repeated measure within each dose group and the same person has been counted repeatedly if RAIU is below 8%). Hence, trying to account for repeated measure with a binary outcome that is based on so few individuals may not be very robust.

11. The statistical methods and computational approaches used in the paper are complex, unfamiliar to most toxicologists and validation and checking, for instance, of the assumptions made is not straightforward. This would require the assistance of someone with specific expertise in Bayesian modelling approaches and, probably, practical experience of the STAN software.

12. Modelling the raw data using a BMR of 5% the authors results approximately in the POD as EFSAs. The authors state that this is “fortuitous“ without providing any arguments to support that statement. It appears that since a similar POD is derived

by Haber et al. the Bayesian repeated measure approach does not contribute much new. The reason for the ~30 fold higher POD derived by Haber et al. (compared to EFSA) most likely lies in the definition of the BMR -> RAIU < 8%.

Questions to the Committee

i. Considering the implications of using alternative models, does the Committee think it useful to have a more in depth evaluation of the paper by Haber et al.?

ii. Does the Committee have any comments on the specific methodology and/or BMDs and TDIs derived?

iii. Do Members have any other comments?

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References

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Hoffman, M.D. and Gelman A. (2011). The No-U-Turn Sampler: Adaptively Setting Path Lengths in Hamiltonian Monte Carlo. http://arxiv.org/abs/1111.4246.

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Annex a to TOX/2021/41

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