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

COT symposium discussion: Potential implications of obesity on the kinetics of persistent organic pollutants and possible ramifications for the risk assessment process.

Introduction

1. In October 2014 the COT agreed that a symposium would be held on the 18th March 2015 to discuss the effects of obesity on toxicokinetics. The aim would be to provide a basis for interpreting Food Standards Agency (FSA)-funded research on biomonitoring of persistent organic pollutants in obese subjects, and to consider more generic implications for the risk assessment process. Members were provided with a list of possible topics for presentations and speakers, and were asked for their opinions on the proposals. They agreed that such a symposium was timely, and suggested a number of modifications to the planned programme.

2. In February 2015 the COT Horizon Scanning paper included modelling kinetics. “New publications had become available stemming from a European-wide cooperative initiative on physiologically-based toxicokinetic modelling. The Committee agreed that it would be useful to keep abreast of developments in this area, particularly as it might be asked in the future to advise on risk assessments using such models, and that possible future COT activities in this area should be discussed further after the COT symposium on the implications of obesity on the kinetics of persistent organic pollutants.”

Objectives of the symposium

3. Prior to the symposium pre-reading material was sent out to all attendees. The references sent out are listed in Annex A

4. The symposium was divided into two sessions; a morning session which consisted of a number of presentations and an afternoon session comprising two discussions with summaries and a closing summary. The presentations in the morning, delivered by invited experts, were designed to provide relevant information to inform the discussions.

5. The discussions that took place in the afternoon were set up to answer a number of specific questions to assist in interpretation of the FSA-funded research. The discussion groups split the invited experts, Members of the COT and other

attendees to try and ensure consistent expertise in both groups. The final symposium programme is included in the symposium booklet in Annex B.

6. A brief summary of each of the presentations has been provided in Annex C and the slides containing an overview of the FSA-funded research, and the preliminary results are presented in Annex D.

7. The discussion session in the afternoon comprised two discussion groups and two discussion sessions. Each group answered the questions from both discussion sessions. The questions that were asked in each discussion and the rapporteur summaries from each of the discussions are presented in Annex E. The notes of the discussions are presented in Annex F.

8. The aim of the first discussion was to consider the tissue distribution data of persistent organic pollutants (POPs) measured in obese and non-obese patients in a FSA research project. The FSA was seeking discussion on available options and determine the optimum modelling solution for analysis of this data set. Some of the key points from these discussions were:

- Different modelling options, such as PBPK or simpler models, available for data analyses. Discussion was also had around the modelling that may be used for the analysis of the different subsets of data in this study.
- There are currently follow-up data from five individuals which have shown substantial heterogeneity in the results and there was discussion around how representative these results would be. Samples from four additional individuals were awaiting analysis.
- The need to consider other POPs/chemicals because dioxins are a historical problem whereas levels of other POPs, for example, BFRs have increased in recent years.
- Added value of comparing data in this study to other data concerning POPs, obese individuals and POP levels in tissues. There are also reviews on the influence of bariatric surgery on certain pharmaceuticals which may provide useful information for POPs.
- Discussion around whether anything could have been done differently and whether further studies should be considered.
- Current models do not predict the initial results. Possible factors that could explain this were discussed including CYP1A2 binding. There are a number of physiologic changes that take place subsequent to bariatric surgery and/or weight loss which could impact the kinetics of dioxins/POPs. Certain medications (lipid lowering drugs and statins) could play a role in disturbing the kinetics of these chemicals. It was highlighted that the data was likely to be congener specific.

9. The second discussion was around whether the current risk assessment process is adequate for/protective of the obese population. The discussions concerned the lack of 1:1 ratio of the concentration of the same POPs in blood lipid:visceral fat. If the ratio isn't 1:1 there may be an impact on the risk assessment.

There was also concern regarding the data which suggested that steady state is not being reached. If this is the case the current risk assessment may need to be revisited. Current risk assessments for dioxins were discussed, including the derivation of the COT tolerable daily intake (TDI) and the US EPA reference dose (RfD). It was felt that certain population groups (cyclical dieters and young people) may require further consideration, once the data analysis has been completed. Consideration was also given to other POPs and whether there are adequate risk assessments in place.

10. Following the discussions there was a closing summary in which the Chair of the symposium highlighted interesting points which came from the discussions and the data:

a. The lack of a 1:1 relationship between the concentrations of POPs in blood lipid and the concentration of the same POPs in visceral fat.

b. The large differences in behaviour and physiology between individuals and between individual congeners

11. The impact on risk assessment was also considered in the closing summary. It was considered that it was unlikely that the default uncertainty factors would not be sufficient for dioxins. However this would need to be reassessed and confirmed once the data analysis had been completed.

Questions on which the views of the Committee are sought

i. Would Members like to see the discussion from the symposium summarised as a COT statement

ii. If so, do they have recommendations for the format and content?

iii. Do Members have recommendations for further research in the light of the discussions?

iv. Do Members have recommendations for further COT activity in relation to toxicokinetic modelling, in the light of the symposium discussions?

Secretariat

June 2015

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

Discussion from the COT symposium: Potential implications of obesity on the kinetics of persistent organic pollutants and possible ramifications for the risk assessment process.

Below are links to the pre-reading material sent to all symposium attendees:

The Interdepartmental Group on Health Risks from Chemicals (IGHRC). (2003). Uncertainty factors: Their use in human health risk assessment by UK Government. Available at: http://ieh.cranfield.ac.uk/ighrc/pdf/cr%20reports/cr9[1].pdf

World Health Organization (WHO). (2010). Characterization and application of physiologically based pharmacokinetic models in risk assessment. Available at: http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf?ua=1

La Merrill M *et al.* (2013). Toxicological function of adipose tissue: Focus on persistent organic pollutants. *Environ. Health Perspect.* 121: 162-169. Available at: http://ehp.niehs.nih.gov/wp-content/uploads/121/2/ehp.1205485.pdf

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

Annex B: COT Symposium booklet

Annex C: Summaries of the presentations given at the COT symposium in the morning to inform the afternoon discussion sessions

Annex D: pre-publication data presented at the COT symposium

Annex E: Summary from the rapporteurs for each discussion group

Annex F: Report back from the discussion groups

These annexes contain preliminary discussion of unpublished data. The data will be published when the research is completed