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

USE OF TOXICOGENOMICS DATA IN RISK ASSESSMENT – AN APPROACH TO USING TOXICOGENOMIC DATA IN U.S. EPA HUMAN HEALTH RISK ASSESSMENTS

Issue

1. In 2009 the United States Environmental Protection Agency (U.S. EPA) published a document entitled An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study[1-2]. The majority of that EPA publication can be found in Annex 1 to TOX/2011/22 and is based on literature searches until 2007. Chapter 2 of the publication is published separately, it contains a more up-to-date reference list and is in Annex 2. This paper introduces that publication and Members will be asked their thoughts on the toxicogenomic approaches taken therein.

Background

2. In 2001 the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COT, COM and COC) held a joint symposium on the use of genomics and proteomics in toxicology, which was follow up in 2004 with a joint statement on the use of toxicogenomics in toxicology[3].

3. In 2007 the U.S. National Research Council of the National Academies published its vision for toxicity testing in the 21st century[4]. That vision formed the stimulus for the COT's workshop in 2009 where advances in 'omic approaches were discussed and from which a statement was produced[5]. Members also considered pathway analysis software for the interpretation of complex datasets[6] in 2009.

4. Subsequently in 2010, the Committee considered in detail a discussion paper covering design, analysis and statistical issues associated with the use of toxicogenomics in toxicology[7-8].

5. The COT published a statement on dietary exposure to phthalates, which included a review of the toxicity of dibutyl phthalate (DBP)[9] in 2011. The statement is included in Annex 3. During 2010, Members also considered the presence of DBT in rubber clogs[10].

The EPA risk assessment

6. The approach outlined by the U.S. EPA was intended to be of use to their risk assessors and the wider scientific community. The output of the U.S. EPA is intended to be a systematic approach for evaluating and utilising toxicogenomic data in health risk assessment. The thoughts of the COT on the EPA assessment will feed into future discussions of applications of and roles for toxicogenomics in risk assessment.

Questions asked of the Committee (referring to Annexes 1 and 2)

i. Pages 2-4 to 2-12 and 3-3 to 3-16 summarise areas where toxicogenomics could assist risk assessment. Do members have any comments?

ii. Toxicogenomic studies of DBP utilising different analytical platforms are evaluated through pages 5-1 to 5-46, 6-2 to 6-12 and 6-19 to 6-20. Do members have comments on the summarised design, analysis or statistical aspects of the studies considered?

iii. Pages 6-12 to 6-20 consider whether toxicogenomics could provide insight into the inter-species (rat-to-human) differences in toxicodynamics observed with a DBP mode of action for testicular effects. What are members' views? Did toxicogenomics aid other aspects of DBT risk assessment?

iv. A general approach for the systematic evaluation of toxicogenomic data in risk assessment is outlined in the concluding chapter (7-1 to 7-12). What are Members' views on its general applicability and specifically, to other classes of substances?

v. Pages 5-15 to 5-16 discuss the dose-response data of the study of Lehmann et al. (2004), which was also described in COT paper TOX/2010/36. Alterations in gene expression were reported at the lowest dose of 0.1 mg/kg b.w. per day, whereas the Tolerable Daily Intake for DBP and the risk assessment for DBP in TOX/2010/36 were based on the LOAEL of 1.5 mg/kg bw per day. Should the LOAEL based on gene expression be used in the risk assessment of DBP?.

vi. Recommendations and future considerations are presented over pages 7-16 to 7-20. Does the Committee have comments or suggestions in this regard?

vii. Taking into consideration the evolving view of the Committee3,5-7, do members feel that the toxicogenomic studies reviewed were appraised appropriately? Does the approach taken offer new insights for consideration?

viii. Would Members like to make any further comments?

References

1. U.S. EPA (2009a). An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report) 2009. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/028F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405

2. U.S. EPA (2009b). Chapter 2 to An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report) 2009. Available as a link within this location. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405#Download

3. COT, COM and COC (2004). Joint statement of the use of toxicogenomics in toxicology. Available at: http://cot.food.gov.uk/pdfs/cotstatementtoxicogen0410.pdf

4. U.S. National Research Council of the National Academies (2007). *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Available at: http://books.nap.edu/catalog.php?record_id=11970

5. COT (2009). Statement on the COT workshop on 21st Century toxicology. Available at: http://cot.food.gov.uk/pdfs/cotstatementwkshp200903.pdf

6. COT (2009). Pathway Analysis Software for the Interpretation of Complex Datasets. Available at: http://cot.food.gov.uk/pdfs/tox200935.pdf

7. COT (2010). COT Discussion Paper: Use of Toxicogenomics in Toxicology - Design, Analysis and Statistical Issues. Available at: http://cot.food.gov.uk/pdfs/tox201018.pdf

8. COT (2010). Minutes of the COT's consideration of the paper entitled 'COT Discussion Paper: Use of Toxicogenomics in Toxicology - Design, Analysis and Statistical Issues'. Available at: http://cot.food.gov.uk/pdfs/cotmins22jun2010.pdf

9. COT (2011). COT statement on dietary exposure to phthalates - data from the Total Diet Study. Available at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104

10. COT (2010). TOX/2010/36. Dibutyl phthalate (DBT): Further considerations of Danish EPA review - DBP in rubber clogs. Available at: http://cot.food.gov.uk/pdfs/tox201036.pdf

11. Lehmann, K.P., Phillips, S., Sar M., Foster, P.M.D. and Gaido, K.D. (2004) Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. *Toxicol Sci* 81(1):60−68.

Secretariat

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TOX/2011/22 Annex 1

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

An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report) 2009

This Annex contains the above report, which is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405

Chapter 2 of the report (page numbers starting in “2-”) was published separately and can be found in Annex 2.

TOX/2011/22 Annex 2

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

Chapter 2 of An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report) 2009

This Annex contains chapter 2 the above report, which is available at:

http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405

TOX/2011/22 Annex 3

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

COT statement on dietary exposure to phthalates - data from the Total Diet Study

This Annex contains the above COT Statement, which is available alongside a lay summary at:

http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2011/cot201104