Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Minutes of the meeting held on Tuesday 8th May 2018 in Radisson Blu Edwardian, Hampshire Hotel, 31-36 Leicester Square, London WC2H 7LH

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham	
	Ms Jane Case	
	Dr Mark Graham	
	Dr Caroline Harris	
	Dr Sarah Judge	
	Prof Brian Lake	
	Ms Juliet Rix	
	Dr Mireille Toledano	
	Prof Faith Williams	
Food Standards Agency (FSA) Secretariat:	Dr D Gott	FSA Scientific Secretary
	Mr B Maycock	
	Ms Hetty Gbormittah	
	Ms C Mulholland	
	Ms Rufina Acheampong	
	Dr B Doerr	
	Ms F Hill	
	Dr D Hedley	
	Ms C Potter	
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Prof T Gant	PHE
Officials:	Ms Daphne Duval	PHE
Other Invited Experts and Contractors:	Prof P Aggett	SMCN
	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc

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Announcements

1. The Chair welcomed Members and other attendees to the meeting.

2. The Chair welcomed Dr Mireille Toledano to her first meeting as a new Member of the Committee.

3. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda items.

Item 1: Apologies for absence

4. Apologies were received from COT Members Dr Coulson, Dr Crevel, Prof Foster, Prof Harrison, Dr Thompson and Prof Wright. Apologies were also received from HSE Assessor Ms Benton and from Ms Elsom from PHE. Dr Crevel and Prof Foster had provided written comments.

Item 2: Minutes from the meeting held on 20th March

5. The minutes were agreed subject to minor amendments.

Item 3: Matters arising from the meeting held on 20th March 2018

Item 3: Matters arising from previous meetings:

6. Para 6: The statement on the reformulation of 2-chlorobenzylidine malonate (CS) as an irritant spray had now been published.

7. Para 7: The draft statement on potential risks from cadmium in the diet of infants aged 0 to 12 months and children aged 1-5 years was in the process of being finalised and would be published shortly.

8. Para 9: The Committee guidance for submissions of papers for consideration by the COT regarding irritant sprays, and on the information required, had now been published.

9. Para 10: The statement on ochratoxin A in the diet of infants aged 0 to 12 months and children aged 1 to 5 years was cleared by Chair's action and had now been published.

10. Para 11: At the last meeting it had been reported that the draft statement on copper had been sent to the Scientific Advisory Committee on Nutrition (SACN) Subgroup on Child and Maternal Nutrition (SMCN) for comment ahead of being cleared by Chair's action. In fact, it had not been sent to SMCN at that time but subsequently it had been.

11. Para 12: The draft statement on T2-toxin (T2) and HT2-toxin (HT-2) in the diet of infants aged 0 to 12 months and children aged 1-5 years was in the process of being cleared by Chair's action.

12. Para 13: The revised draft statement from a joint committee workshop on the use of epigenetics in chemical risk assessment had been circulated to members of the COT, COT and COM for comment by correspondence.

Item 6: Second draft statement on the potential risks from manganese in the diets of infants aged 0-12 months and children aged 1 to 5 years

13. Para 33: The statement had been finalised by Chair's action. It had not yet been published in anticipation of a publication in the peer-reviewed literature, which was being prepared.

Item 10: reports of the COT-COC Synthesising Epidemiological Evidence Subgroup (SEES)

14. The reports had been sent to the COC for comments and the main report was currently being amended to address comments from both the COT and COC ahead of clearance by the Chairs and publication.

Item 4: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (e-cigarettes)

15. The Chair declared that he was the Chair of the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group (WG) 10 on an "Intense smoking regime"; the WG did not address electronic nicotine delivery systems (ENDS). The Chair also was a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg), which had discussed ENDS. Professor Williams declared a personal non-specific interest in that her brother-in-law was a retired senior manager from British American Tobacco (BAT), one manufacturer of ENDS, and was now in recipient of a pension from BAT. No further interests were declared.

Item 4a: Paper 3: Toxicological review of the main constituents, propylene glycol (PG) and vegetable glycerine (VG, glycerol) – TOX/2018/19

16. A series of papers on electronic nicotine (and non-nicotine) delivery systems (E(N)NDS) was being discussed by the Committee. The present paper (TOX/2018/19) was a toxicological review of propylene glycol (PG) and vegetable glycerine (VG, glycerol) which are the main constituents in the e-liquid that is used in these devices.

17. The Committee discussed PG and noted that the systemic half-life indicated that accumulation would not occur. There were a few summaries of papers that Members requested be checked for accuracy. The effect of PG as a skin irritant was discussed, as while this had been noted by the Health Council for the Netherlands,

neither the OECD Screening Information Data Set (SIDS) document on PG nor REACH registrations noted such effects. The Committee also concluded that if it is a skin sensitizer it is only likely to be in a very small percentage of the population.

18. Members discussed VG and noted that the risk assessment was based on the LOAEL in rats and requested information as to whether the authors had commented on the mild squamous metaplasia observed. It was also noted that the amount of VG present in one puff was similar to the concentration of 662 mg/m^3 producing local irritant effects (mild metaplasia) in the 13-week study in rats, although it is difficult to compare these concentrations directly.

19. In response to the questions asked of the Committee it was noted that the 13-week inhalation study for PG could be looked at in more detail to determine whether an inhalation health-based guidance value (HBGV) could be established. For VG, in order to establish an HBGV for inhalation the repeat dose study in rats could be looked at in more detail. Information would also need to be provided on the concentration that an end-user would be exposed to from use of ENDS. The Committee was also interested to know how the UK workplace exposure limits were derived.

Item 4b: Follow up to paper 2: Additional information on reports describing the presence of silicon/silicates in the aerosol of E(N)NDS (TOX/2018/20)

20. The Committee noted that silica fragments had been found in e-cigarette vapour, which appeared to derive from the sheath and wick, following the work of Williams *et al.* (2013, 2017), but that apart from these two papers, no other data had been found. Moreover, no data were available on whether some e-cigarette brands released more silicates than others.

21. Members were concerned that the electron micrograph of a spherical amorphous silicate bead in the paper by Williams *et al.* (2013) may not be representative of the majority of the siliceous material present in the aerosol because the toxicity of silica particles is very dependent on their physical form. Microcrystalline silica is appreciably more toxic than amorphous silica when inhaled.

22. The Committee stated that, in order to risk assess e-cigarettes for their silicon/silicate content, they would require further information on background exposure to inhaled silicates, the form of the released material (amorphous vs microcrystalline) and whether there were current engineering solutions that could minimise silicate release.

Information on yellow card system

23. The committee was informed about the available yellow card system reports for E(N)NDS. The system reported a total of 110 reactions, for example cardiac effects, gastrointestinal, immune effects, general disorders, injuries and respiratory

effects. The 110 reactions came from 41 reports, with generally only 1 to 2 reports per effect.

24. It was queried whether the effects were reported by type of e-cigarette. It was noted that the yellow card system gathers data on this, where reported, and the Committee enquired if MHRA had, or had plans to, evaluate the data, which the Secretariat would follow up with the MHRA.

25. It was noted that the information provided by the system was not very sensitive and that background levels of reporting for the different reactions would be needed to interpret the reported effects accurately. It was further noted that additional background information, such as age, medical history etc are available, should the Committee wish to consider this, though it would also be useful to know the extent to which this information is provided for each report.

Item 5: A presentation by Professor Boobis on the Risk Assessment in the 21st Century (RISK21) approach

26. During horizon scanning discussions the Committee had expressed interest in the Risk Assessment in the 21st Century (RISK21) approach developed by the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) and it had been agreed that they would receive a presentation from the Chair, Professor Boobis, who had co-chaired the HESI RISK21 project.

27. The RISK21 project was initiated in recognition of recommendations by the US National Academy of Sciences, and others, to move away from reliance on the current extensive traditional toxicology testing in animals for chemical risk assessment and transition to the use of non-animal methods (i.e. computational and *in vitro*). The objective of the project was to develop a scheme whereby the most relevant and resource appropriate approaches could best be applied to chemical risk assessment. The approach developed comprises 4 steps or tiers for both exposure and hazard, lower tiers being more conservative but less resource-demanding. The accuracy of the information required depends on the estimated exposure. For example, where exposure is very low, it might be possible to provide reasonable assurance of lack of harm using the threshold of toxicological concern, an approach that requires no toxicological information on the substance itself.

28. The 4 tiers for exposure comprise: Tier 0 – minimal information on exposure; Tier 1 – deterministic estimates; Tier 2 – probabilistic estimates; Tier 3 – biomonitoring data. Those for toxicity are: Tier 0 - structure-activity relationships and existing databases such as the Threshold of Toxicological concern (TTC) approach; Tier 1 - predictive *in vitro* assays and extrapolation; Tier 2 - apical endpoints from *in vivo* assays; Tier 3 - biologically-based dose-response models, based on the mode of action. Working through these tiers provides increasing confidence in the risk estimates. Whilst the expectation is that increasing use will be made of information from non-animal methods, advice on chemical risks will continue to depend, to a greater or lesser extent, on the results of conventional animal toxicology and hence RISK21 was designed to enable integration of different data sources. Underpinning many of the non-animal methods is the concept of an adverse outcome pathway (or

mode of action), comprising a series of necessary key events. If the causal pathways involved are known, predictions can be made on how chemicals may affect human health, based on effects on the key events determined *in vitro* or modelled *in silico*. However, given that there are currently very few OECD approved *in vitro* toxicity tests, there are some substantial challenges to overcome in the use of such data for risk assessment. One of these is to be able to predict the dose of the chemical at the site of action. The RISK21 project has also developed an online, free-to-use, matrix tool that can be used to compare the exposure/toxicity profiles of several chemicals, exposure scenarios or risk mitigation measures, to provide an "at a glance" figure of their relative risks. The matrix can be used for either external dose (e.g. mg/kg bw) or internal dose (e.g. μg/ml). More information and the RISK21 tool can be found on the Risk 21 website at www.risk21.org

29. Members were interested in this approach but noted that there were still large knowledge gaps limiting the ability to incorporate non-animal data. The importance of physiologically-based pharmacokinetics (PBPK) was observed. It was agreed that the use of the RISK21 matrix should be trialled in a couple of COT Statements over the next few months.

Item 6: A presentation by David Gott on risk assessment of regulated products. (Reserved Business)

30. Following the discussion at the December meeting on the risk assessment of regulated products following EU exit, David Gott gave a short presentation on developments and current thinking. Due to the sensitivity of this topic, this item was discussed as reserved business.

Item 7: Second draft statement on potential risks from methylmercury in the diet of infants age 0 to 12 months and children aged 1 to 5 years (TOX/2018/21)

31. No interests were declared.

32. The COT had been asked to review the risks of toxicity from chemicals in the diet of infants and young children age 1-5 years, in support of the review by the SACN of Government recommendations on complementary and young child feeding. Methylmercury was being considered as part of the review.

33. At the February COT meeting, a discussion paper (TOX/2017/03) was presented to the Committee, which contained details on the establishment of Health-Based Guidance Values on methylmercury by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2004 and the European Food Safety Authority (EFSA) in 2012. Exposure calculations for methylmercury in the diet of infant and young children were presented along with a risk assessment and conclusions. A first draft Statement was then presented to the Committee in March (TOX/2018/13). Following the discussion of the draft Statement, the text was revised to reflect Members' comments.

34. Members were asked to consider the second draft statement. A number of comments were made on the structure and content of the statement and editorial changes requested. It was agreed that the revised Statement could be cleared by Chair's action.

Item 8: FSA Scientific Advisory Committees (SACs) update – TOX/2018/09

35. This paper was provided for information.

Item 9: Any other Business

36. The Chair noted that two draft guidance documents on the risk assessment of the toxicity of mixtures would be published shortly, one by EFSA and the other by the OECD.

Date of next meeting

37. The next meeting would be held on Tuesday 3rd July 2018 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.