9th October 2017 – Joint COC, COM, COT Workshop

Paper 2

COMMITTEES ON CARCINOGENICITY, MUTAGENICITY AND TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC, COM and COT)

Joint COC, COM and COT Horizon Scanning

1. The Committees Terms of Reference indicate that the primary role of the Committees is to advise on the mutagenic, carcinogenic and toxic risk of s
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4. ubstances to humans at the request of Government departments and agencies. However, the Code of Practice for Scientific Advisory Committees (Office of Science and Technology, December 2001), specifies that:

> *"Committees should ensure that they have mechanisms in place that allow them to consider on a regular basis whether new issues in their particular areas of responsibility are likely to emerge for which scientific advice or research might be needed".*

5. The Committees have undertaken a regular Horizon Scanning exercises in which the Secretariat, Members and/or Assessors have suggested areas/topics that may need consideration in the light of new and emerging evidence relating to chemical risk assessment.

6. Due to overlapping interests in horizon scanning items, and a recommendation from the latest COM triennial review[1] for flexible and coordinated approaches to work of intersecting interest, it is considered timely for the Committees to have a joint horizon scanning session.

COT current topics on horizon scanning list

7. The following horizon scanning items were identified by COT at their annual horizon scanning session in February. Due to a combination of resource issues and workload related to the infant and young child feeding work, not all work arising from the discussions has not been completed or scheduled at this time.

- Endocrine disruptors - Endocrine disruptors are of continuing interest to COT and have previously been the subject of a COT workshop. It was agreed that this should continue and that the COT should consider responding to the

[1] https://www.gov.uk/government/consultations/committee-on-mutagenicity-triennial-review (accessed 27/09/2017)

European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA) joint guidance that was currently being prepared.

- RISK21 - Members agreed that they would like a presentation on the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century (RISK21) approach. This was scheduled for September or October, but has been delayed due to the cancellation of the October COT meeting.

- The Microbiome - The COT agreed that the application of knowledge of the microbiome in risk assessment would be of interest. Members agreed that the COT should consider this topic and could produce a position note. A workshop on this topic has been scheduled for February 2018.

- Adverse Outcome Pathways - Members agreed that it would be useful to explore the issues around adverse outcome pathways (AOPs) and how they could be used in chemical risk assessment.

COM current topics on horizon scanning list

8. Below are the outstanding topics from the COM horizon scan with the numbered items in order of priority while those in bullet points are yet to be prioritised:

i. Updates from OECD Test Guidelines [*this is a standing agenda item*]

ii. Review current practices of incorporating genotoxicity testing into existing toxicity tests for example, integration of the micronucleus test and the comet assay into repeat dose toxicity testing to reduce the overall numbers of animals tested and the use of transgenic animals in 28 day toxicity studies to evaluate transgenic mutations.

iii. How high the maximum tested dose should be and what constituted a biologically significant response, for example a fold increase above background.

iv. Watching brief on how nanoparticle will be addressed in OECD Genotoxicity test methods.

- Ames II or Ames MPF [*subject of a new OECD project*]

- Expanded simple tandem repeat (ESTR) mutation induction in male germline

- Review of current methods in QSAR and implication for the COM Guidance.

COC current topics on horizon scanning list

9. Below are the outstanding topics agreed at the COC horizon scan in 2016, though in no specific order of priority:

- Applicability of Margins of Exposure for exposure of young children
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- Epigenetics
- *In vitro* systems - to be undertaken when resource allows
- Immunological and stromal cell modulations relevant to cancer risk
- Nanomaterials
- E-cigarettes and novel tobacco products, and effect of early life exposure to cigarettes

New topic suggestions

10. Members, Assessors and the Secretariat have been approached to consider new topic areas, and the following suggestions have been made.

Publication of data

Study quality, regulatory decisions and publication bias

11. It is noted that some regulatory decisions (particularly in Europe) are giving more weight to published positive (i.e. genotoxic) findings, sometimes using non-standard test systems and non-recommended routes of administration, than to negative findings from OECD guideline compliant studies conducted according to GLP. There is also overlap with discussions around reproducibility of experimental data.

12. This topic cuts across the three committees. It could be addressed by getting a joint view on the issues for regulatory science around the relative weight of peer-reviewed academic research and OECD-type protocol studies.

Predatory journals

13. Issues around predatory journals has been covered in a number of recent papers (Beall, 2017; Cobey, 2017; Shamseer et al, 2017). A regulatory agency from one country has taken the decision that its scientists should not submit manuscripts to journals or publishers suggested to be predatory.

Methodologies

COM guidance

14. It has been suggested that the COM guidance on a strategy for genotoxicity testing of chemical substances could be updated. Annex A provides an outline paper on areas where revision could be undertaken numbered according to the current documents[2].

Use of epidemiology data for risk assessment

15. This topic was raised with note for the need to consider biological plausibility and adverse outcome pathways (already on the COT horizon scan list), and exposure assessment. There is a joint EFSA/EBTC scientific colloquium on evidence integration in risk assessment in October 2017[3], which may provide relevant information to this topic, and it should also be considered alongside the draft report from the COT-COC synthesising epidemiological evidence subgroup (SEES)[4].

Threshold of Toxicological Concern

16. The Threshold of Toxicological Concern (TTC) was raised by a COT Member. An update on work on the TTC by EFSA and WHO, as well as elsewhere, is due to be presented to the COC in November to inform the COC guidance statement series. The discussion paper could be presented to the COT and COM, as desired, subsequent to the COC meeting.

Quantitative risk assessment and defining uncertainty

17. A session on the proposals from EFSA on quantitative risk assessment and defining uncertainty was requested, noting in particular what is required from toxicokinetics to support these. The Secretariat proposes that a presentation on this is given to the Committee(s) depending on interest. There is also work being undertaken by the FSA Science Council which can be presented.

Health effects of chemicals

Contribution of environmental chemicals to neurodegenerative disease,

18. This topic could include gene-environment interactions and influence of the microbiome. A review of environmental chemicals and neurological diseases in particular Parkinson's disease and Alzheimer's disease was carried out by the

[2] https://www.gov.uk/government/publications/a-strategy-for-testing-of-chemicals-for-genotoxicity (accessed 27/09/2017)
[3] https://www.efsa.europa.eu/en/events/event/171025-0 (accessed 27/09/2017)
[4] TOX/2017/13 available from: https://cot.food.gov.uk/cot-meetings/cotmeets/cot-meeting-28-march-2017 (accessed 27/09/2017)

Health Protection Agency (now PHE) in 2007[5], which could be a helpful starting point to a review.

Developmental neurotoxicity following exposure to environmental chemicals

19. Areas of interest for this topic could be autism, ADHD and IQ deficit, and considering *in utero* and infant exposures. It is noted that effects of infant exposure should be covered by the work programme in infant feeding undertaken by the COT over the last few years. The topic area was considered by COT in 2009, as outlined in the 2009 Joint Annual Report[6].

Effects of exposure to by-products of water treatment

20. Effects of chlorination disinfection by-products of water treatment have been considered previously by all three Committees, with COM and COC considering trihalomethanes in 1994 and 1995[7], and COT considering the risk of adverse reproductive outcomes and congenital anomalies[8]. Water treatment by ozonation is associated with bromate formation, but this is monitored for in treated water. Other treatment technologies also exist which may be associated with other by-products.

21. Water companies are required to disinfect all water before supplying it, though by-products of water treatment should be kept as low as possible, while not compromising the effectiveness of disinfection[9].

Safety of natural food supplements e.g. botanicals

22. There is a lack of regulation of natural food supplements and a number of issues which affect the risk assessment of these products. EFSA are producing a compendium on botanicals which may be informative, but it could also become an important area as the UK leaves the EU.

Nanoparticles and nanomaterials

23. This is of interest to all the Committees with a number of aspects currently in progress. EFSA is updating its guidance and this can be presented when it goes for public consultation. In addition, Defra is actively involved in working with ECHA on the REACH requirements for nanomaterials.

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5 http://webarchive.nationalarchives.gov.uk/20140722174900/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947320712 (accessed 27/09/2017)

6 https://cot.food.gov.uk/cotreports/cotcomcocrep2009 (accessed 27/09/2017)

7 https://cot.food.gov.uk/cotreports/cotcomcocrep1994 (accessed 27/09/2017) and https://cot.food.gov.uk/cotreports/cotcomcocrep1995 (accessed 27/09/2017)

8 https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cotdbp200802 (accessed 27/09/2017)

9 The Water Supply (Water Quality) Regulations 2016 Part 8, 26 – Disinfection and other treatment arrangements: http://www.legislation.gov.uk/uksi/2016/614/contents/made (accessed 27/09/2017)

Exposures to chemicals

Extrapolation from lifetime animal studies to young humans with less than lifetime exposure

24. This was raised by a COT member. The COC has been considering less than lifetime exposure on a number of occasions in recent years, and a further discussion paper is planned for the November COC meeting. This paper will also consider the applicability of the margin of exposure to children, which is on the list of current COC topics. If there is wider interest and a broader remit, the approach to this topic could be reconsidered.

Balance of environmental exposure and food intake in exposure to chemicals

25. For some chemicals environmental exposure outweighs exposure that could occur through food where the chemicals are present as contaminants, while for other chemicals the opposite could be the case. If this topic is of interest to take forward, it would be helpful to specify any chemicals or specific sources of interest.

Technologies for food production

Biological control agents for crop diseases

26. It has been queried whether the human safety regulations are adequate for biological control agents for crop diseases such as RNAi, pheromones, semiochemicals, and viruses. This topic would be more appropriate for referral to the Expert Committee on Pesticides (ECP) if this is considered a concern.

Gene editing of crops

27. It was queried whether there is a human safety concern for gene editing of crops. This would sit within the remit of the Advisory Committee on Novel Foods and Processes (ACNFP), but might require input from COT, COC or COM depending on the result of gene editing. The potential for work on animals is also noted.

Increases in natural toxins and allergens of crops and vegetables due to native trait breeding

28. Native trait breeding is not currently regulated, unlike use of GMO crops and vegetables, but has potential to increase the presence of allergens and natural toxins. The available literature tends to focus on GMOs, but native breeding is outside the remit of ACNFP

29. It could be considered whether the last two aspects in this section could be covered together in terms of effects of changes in the genome on crops, but consideration would need to be made on other Committees or Groups with interest in the area.

Questions for the Committees

30. Members are invited to comment on each of the topic areas above and in particular:

i. Consider areas of overlap between the Committees and how these would best be addressed

ii. For topics of interest, provide a view on the scope and priority, and if appropriate

Secretariat
September 2017

References

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Cobey K (2017) Illegitimate journals scam even senior scientists. Nature 549(7670) World View, 7

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9th October 2017 – Joint COC, COM, COT Workshop

Paper 1 – Annex A

COMMITTEES ON CARCINOGENICITY, MUTAGENICITY AND TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC, COM and COT)

Joint COC, COM and COT Horizon Scanning

Scoping paper for update to COM guidance on a strategy for genotoxicity testing of chemical substances

Document is numbered according to the current guidance available here: https://www.gov.uk/government/publications/a-strategy-for-testing-of-chemicals-for-genotoxicity (accessed 27/09/2017)

Secretariat
September 2017

COM Guidance Update

Outline scoping paper – what's new and potentially impacting on COM Guidance

II Introduction

- Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines 2015 – interestingly they quote COM Guidance 2000 but not our 2011 version or EFSA Guidance. The document provides a comprehensive table of GL's – those that have been updated, deleted etc
    - includes details of combining and integrating tests for 3R's, dose level selection, use of one or both sexes , statistical considerations , importance of historical control databases , use of positive controls
- General discussion papers on strategy eg Dearfield et al 2017; Kirkland et al 2014a,b; Zeiger et al 2015
- Since the guidance the comet assay TG has been published OECD TG489
- Many OECD GLs updated

III Significance of chemical-induced mutation for human health

- Add link to the piece which was published after we published the Guidance
- https://www.gov.uk/government/publications/the-significance-of-chemical-induced-mutation-for-human-health
    - Do Members feel any changes to this are required?

IV General principles of genotoxicity testing strategies

- EFSA (2012) – updated guidance in line with our recommendations
- ICH guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use Step 5 June 2012. EMA/CHMP/ICH/126642/2008. Recommendations are an Ames test and a mammalian test and state 'The *in vitro* metaphase chromosome aberration assay, the *in vitro* micronucleus assay and the mouse lymphoma L5178Y cell *Tk* (thymidine kinase) gene mutation assay (MLA). These three assays are currently considered equally appropriate and therefore interchangeable for measurement of chromosomal damage when used together with other genotoxicity tests in a standard battery' Two options provided: 1) two in vitro tests plus a in vivo bone marrow micronucleus (BMMN), 2) Ames plus in vivo evaluation in two tissues (which may mean a BMMN and a second in vivo assay) This is a significant departure from previous recommendations and more in line with COM Guidance (as far as the two in vitro tests go)
- Section on follow up tests for positive tumour findings – is this something that COM could/should also provide guidance on?

- REACH guidance was updated (December 2016 and/or July 2017) but their strategy differs from updated ICH, COM and EFSA guidance = still require mammalian cell mutagenicity as standard if negative results are obtained in the Ames and in vitro MN – however this can be by-passed if reliable negative in vivo gene mutation tests are available. Chapter R.7.7-1
- VICH GL23: Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing October 2015 EMA/CVMP/VICH/526/2000. This adopts the same strategy as in Option 1 for human pharmaceuticals (ie Ames plus in vitro cyto including the tk assay, plus in vivo cyto). Potentially genotoxic impurities (veterinary medicines)

Do Members want to comment on the different strategies used for different regulatory settings?

V Genotoxicity Testing Strategy

Stage 0: Preliminary Considerations

- Structure Activity Relationships: Update on SAR methods for genotoxicity evaluation (DEREK etc - could be updated based on the outcome of the discussions of the scoping paper to be presented February 2018)
- Screening tests: would Members like to see updates on
    - mini-Ames,
    - GreenScreen/BlueScreen,
    - ToxTracker,
    - any other new tests?

Stage 1: In vitro genotoxicity

- Updated OECD Test Guideline (TG 476) for the mouse lymphoma and the new *in vitro* mammalian cell gene mutation test new (TK, HPRT, and XPRT assays)
- Also, in vitro SHE transformation assay guidance document (not a guideline) – do we need to update our evaluation of this assay?
- Any need to revisit the sensitivity and specificity data reviewed for the guidance

Stage 2: in vivo genotoxicity tests

- Mammalian Erythrocyte Micronucleus Test OECD GL 474 – updated 2016 - does the guidance need changing to reflect this?
- Mammalian Bone Marrow Chromosomal Aberration Test OECD Test No. 475: updated 2014

- Transgenic mutation assay – given that this has become an accepted test with an OECD GL, there is very little information published in the public domain. The best information on its general utility and robustness will probably be available from CRO's – do Members think an evaluation on its performance is required? If so how can this be done?
- In vivo comet assay: Since the guidance there have been significant developments in the use and acceptance of this assay.
    - EFSA 2012 EFSA Journal 2012;10(11):2977 Minimum Criteria for the acceptance of *in vivo* alkaline Comet Assay Reports – published in lieu of finalisation of the OECD guideline
    - Guideline OECD 489 – In Vivo Mammalian Alkaline Comet Assay June 2016
    - JacVAM trial (Uno et al 2015)
    - IWGT (Speit et al 2015)
    - Numerous other publications on comet eg Burlinson 2012
- <u>Does the comet assay need a more in depth review now?</u>
- UDS – what do Members think about this now?

Other topics for consideration; (Possible future developments section)

- Germ Cell genotoxicity
    - Two revised *in vivo* germ cell genotoxicity OECD Test Guidelines had been agreed, namely the Rodent Dominant Lethal Test (TG 478) and the Mammalian Spermatogonial Chromosome Aberration Test (TG 483). A clause would be included in each to say that they are intended as supplemental and not primary tests (i.e. as both use a relatively large number of animals, which is not encouraged under the 3Rs principles).
    - There's a proposal to remove and archive the Test Guideline 478 for the dominant lethal assay within the next two years. (therefore remove from list of assays)
- Pig A: For the *in vivo* PIG A assay, a Standard Project Submission Form (SPSF) had been accepted into the OECD work plan.
    - COM have reviewed this on several occasions – there has been significant use of this assay in vitro, in vivo, including germ cells and some applications in humans – is it worth reviewing it again or simply commenting in the guidance?
- Update on incorporation of genotoxicity studies into 28 day rodent studies
- Introduction of guideline for nanomaterials - lots of recent information on this topic (eg Pfuler et al 2016) and COM have reviewed since the guidance was published

- The use of genotoxicity evaluations in human biomonitoring? (eg Collins et al 2014; Bonnassi et al 2016, There are many examples does the committee think there is value in reviewing this topic?
- Toxicogenomics to identify genotoxicity?
- Adverse outcome pathway approaches (should reference be made to these? – eg the germ cell AOPCOM reviewed previously)

Sample references:

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