CC/MIN/2016/02

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

Minutes of the meeting held at 10.30am on Thursday 21st July 2016 at Department of Health, Skipton House, 80 London Road, Elephant and Castle, London, SE1 6LH.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr P Greaves	
	Professor R Kemp	
	Dr D Lovell	
	Professor J Peto	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
Secretariat:	Dr D Benford	FSA Scientific Secretary
	Miss B Gadeberg	PHE
	Dr H Garavini	Toxicology Unit, Imperial College
	Dr K Vassaux	Toxicology Unit, Imperial College
Assessors:	Mr N O'Brien	VMD (Items 1-5)
	Dr O Sepai	PHE
	Dr V Swain	HSE
Officials:	Dr M Jacobs	PHE

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ITEM 1: Apologies for absence and announcements

1. Professor David Harrison introduced himself to the Committee as its new Chair and welcomed the Members, Assessors and Officials to the meeting. This was followed by a round of introductions from those present.

2. Apologies were received from Professors N Pearce and S Warnakulasuriya, and Dr J Doe, who was attending a memorial service for Professor Iain Purchase, a former COC member. One member had provided written comments. Dr H McGarry (Health and Safety Executive assessor) sent apologies and was represented by Dr V Swain, as did Mr S Fletcher (Veterinary Medicines Directorate assessor) who was represented by Mr N O'Brien. Apologies were also received from Dr H Stemplewski (Medicines and Healthcare products Regulatory Agency).

3. Members were reminded to declare any interests they may have in an item before its discussion.

ITEM 2: Minutes of meeting held on 17th March 2016 (CC/MIN/2016/01)

4. The minutes were agreed subject to editorial amendments as necessary.

ITEM 3: Matters arising

Items 3 &9: Matters arising and any other business – BTS presentations

5. The Committee were informed that both the presentations to BTS on COC work had gone well. The oral communications session on the alcohol work had received good feedback and the poster presentation on the COC guidance statement had resulted in some discussions, but no gaps in the coverage of the statements had been highlighted.

Item 4: Possible carcinogenic hazard to consumers from insulin-like growth factor -1 (IGF-I) in the diet. Part 3

6. During the discussion at the last meeting, it had been queried whether the book "Your life in your hands" (Plant, 2007) in which claims were presented about the health effects of IGF-I, had been updated. No further editions had been published though Professor Jane Plant had continued to write and contribute to other books on cancer. The Committee was informed that Professor Plant had died in March 2016.

ITEM 4: COC Guidance Statements – an overview (CC/2016/06)

7. This paper presented an overview of the guidance statements series indicating publication status and date, or progress towards publication.

8. The Committee noted that the coverage of the series was complete despite being undertaken on a document by document basis. It was suggested that a preface or introductory document to the guidance statements would be helpful to explain in lay terms the purpose before going to the more technical individual statements.

9. In terms of additional topics, it was queried whether epigenetics should be covered in the series. A presentation and paper had been presented to the last COM meeting on epigenetics and it had been suggested that a joint COM, COC and COT

meeting be held to discuss the topic further as many aspects hold mutual interest. The Committee could then decide after that how the topic should be addressed in the guidance statement series.

10. The guidance statement on “Interpretation of evidence of carcinogenicity in humans: epidemiology and case reports” (G02) was awaiting the report of the joint COT/COC Synthesising Epidemiological Evidence Subgroup. Progress on this had been delayed and it was suggested that the COC members involved could offer support to progress this work. It was recognised that while the report would not necessarily cover the whole of the aspects required for the guidance statement, it would be prudent to wait for a draft report before identifying other aspects to cover.

11. The nanomaterials statement (G10) had been published over 10 years ago and was a joint statement by COM, COT and COC. COT had issued an update a couple of years later, though the COC and COM had not felt anything further could be added on carcinogenicity or mutagenicity at that time. In the meantime there had been various activities elsewhere and COT considered it not appropriate to consider the topic further at this time. A presentation on nanomaterials and the inhalation aspects being researched by PHE by Rachel Smith had been arranged for a future COC meeting, and it was agreed that further consideration of G10 could be made at that time.

12. It was agreed that the guidance statements should be dated against the version numbers and a check be made especially of the older statements so they could be brought up to date as required. It was suggested that a regular cycle of checking each statement every 2-3 years should be established, to ensure the documents remained relevant and were perceived to be in date.

ITEM 5: G07 – Alternatives to the 2-year Bioassay, Part d) Alternative testing strategies incorporating results from short-term tests (CC/2016/07)

13. This paper presented an overview of alternative testing strategies that incorporate results from short-term tests and/or *in silico* data. It followed from the scoping paper discussed at the March 2016 meeting.

14. In terms of structure of the complete guidance statement “Alternatives to the 2-year bioassay” (G07), it was noted that parts a) *in vivo* assays, and b) cell transformation assays, were complete and published. Some of the contents of the discussion paper presented at this meeting could be more relevant to part c) developing methodologies, than d) alternative testing strategies incorporating results from short-term tests, and this would be considered in the preparation of the first draft of part d).

15. The discussion focussed on the likely Committee conclusions on the topic, with recognition of the need to move forward from the use of the 2 year bioassay as the gold standard test. However the data available did not give a clear indication of the direction of progress in replacement.

16. There was concern that while 3 month animal studies might provide indication that a chemical was potentially carcinogenic, they would be unlikely to provide a basis for estimation of tumour risk. Often the signals in a 3 month study to indicate

potential carcinogenicity were identified in different tissues to those in which tumours were identified in longer term studies. In addition, the signals could be hypertrophy or hyperplasia which are not of themselves pre-neoplastic effects. Historically the one year study had been found to be a good means of predicting the result of a two year study, but this study was no longer undertaken to reduce animal use.

17. The possibility of a negative prediction was of interest, but there were concerns over whether human metabolism was suitably accounted for in the test system, whether *in vivo*, *in vitro*, or *in silico*. While the pharmaceutical industry generally has good data available on toxicokinetics and metabolism, this is not necessarily the case for other chemicals.

18. It was agreed that an alternative strategy would need to be focused on predicting potential human carcinogenicity, rather than rodent carcinogenicity. To this end, it was considered important that emphasis be moved away from development of further rodent studies. It was suggested that metabonomic approaches could be used to extrapolate from animal *in vivo* and *in vitro* experiments through human *in vitro* experiments to likely outcomes for humans. It was also noted that biomarkers would be useful, and while a lot of information had been generated in that area, a better understanding of the key markers was required before this could progress.

19. The differences in approach between testing of pharmaceuticals compared to other chemicals was noted, with pharmaceuticals generally being tested in animals at a maximum dose equivalent to a large multiple of human exposure, while other chemical sectors tend to use the maximum tolerated dose. Pharmaceuticals are also in themselves associated with a pharmacological effect in humans, whereas other chemicals either have only a technical purpose in the media they are in (e.g. food additives), or are tested to ensure they do not show adverse effects in non-target species (e.g. pesticides). The Committee considered it important to bear in mind the differences in approaches, and recognise that alternatives may not address the requirements of all the different sectors, but to maintain the collaborative approach across the sectors.

20. With the developments in REACH, where the drive is away from testing in animals, some chemicals have very little information on toxicity. The Committee noted the need to provide a sound basis on which to determine whether adverse effects would occur in humans. One method often being used and which is well accepted is quantitative structure activity relationships (QSARs), however these require good working knowledge of the underpinning evidence and correct interpretation of the results, and there was concern that this was not always the case.

21. For pharmaceuticals it was suggested that a post market assessment could be made of prescriptions for each product and the cancer rates in the people prescribed the drug by linkage of relevant national databases. This could then be assessed against the 2 year bioassay data, e.g. tumour sites, to determine whether any effects observed from the pharmaceutical in use could be detected in the animal studies.

22. Overall, the Committee agreed that it was important for alternative means of assessing health risks from chemicals to be developed with the good interaction

between different sectors continuing. The challenge for such alternative strategies would be to not miss crucial adverse effects while not over predicting issues of concern.

Item 5a) Presentation on IATA for Non-Genotoxic Carcinogens

23. Dr Miriam Jacobs (PHE) gave a presentation on the ongoing work for the Organisation for Economic Co-operation and Development (OECD) to develop an Integrated Approach to Testing and Assessment (IATA) for non-genotoxic carcinogens.

24. The presentation outlined the requirements for such an IATA, with the move away from animal testing where possible, and also the concern over whether testing was adequate to detect carcinogens not acting via genotoxic mechanisms. An outline of the work programme was given, and progress since acceptance of the published paper circulated with CC/2016/07[a]. Members were invited to join the expert group either to undertake the work, or to review the work once complete.

ITEM 6: Recent developments in the Mode of Action and Human Relevance Framework (CC/2016/08)

25. This paper presented an update on recent developments in the Mode of Action and Human Relevance Framework since the Committee had last considered the topic in 2008. A presentation had been given at the 2013 horizon scanning session and it was agreed then, and again in November 2015, that the Committee should be updated in more detail on the use of the framework.

26. It was noted that while the concepts of key events and adverse outcomes were well accepted, it was important to recognise that adaptive and physiological responses also occur. The distinction between adaptive and adverse outcomes was considered to be a grey area and thus it was important to consider the dose response of a chemical to determine whether an adverse effect would be likely to occur.

27. The Committee noted an interest in the Halifax project, organised by Getting to Know Cancer, and in particular the suggestion that the low levels of exposure to multiple chemicals which individually are not carcinogenic, may cause cancer. It was agreed that this should be checked further to consider whether it was being appropriately addressed in the overarching guidance statement (G01) and the guidance statement on mixtures (G08). Other recent developments at EFSA on mixture assessment were also highlighted to be checked.

28. Overall, the Committee found the update useful and it was agreed that a comment on adaptive or physiological responses be added in the overarching guidance statement (G01) and appropriate referencing is given to the up to date papers when the framework is mentioned.

[a] Jacobs et al (2016) ALTEX Online first, published 27th April 2016. http://dx.doi.org/10.14573/altex.1601201

ITEM 7: G09 Assessing the risks of less-than-lifetime exposure to carcinogens (CC/2016/09)

29. This paper presented a second draft statement on assessing the risk of less-than-lifetime exposure to carcinogens, which had been revised following discussion at the March 2016 meeting.

30. There was concern that the approach outlined in the paper would be used as a means to justify planned higher exposures, which would not be appropriate for genotoxic carcinogens. It was also noted that even for non-genotoxic carcinogens, exposure to sufficiently high doses could be expected to have an effect, even on a short-term basis.

31. It was noted that occupational exposures would only occur over part of a lifetime, but a number of chemicals for which exposure occurs in the workplace are also present in the environment, and therefore occupational exposure occurs above an ongoing background concentration. Similarly where exceedances of regulatory limits in food or water occur, this results in a peak above prolonged low level exposure.

32. It was noted that for some carcinogens short-term exposures are of less concern than long-term exposure, e.g. radon and smoking, however for others the opposite is the case, e.g. short-term high level exposure of children to UV. In most instances an approach of assessing cumulative dose is generally considered to be conservative.

33. A key aspect to consider in undertaking an assessment is the mode of action of the chemical in question, which supports the need for a case-by-case consideration of less-than-lifetime exposure rather than generic advice based on Haber's Law.

34. Overall the Committee agreed that the challenges of risk assessment of less-than-lifetime exposure should be discussed as a Committee statement, but as no guidance will be offered on approaches to be used, this would not form part of the guidance statement series.

ITEM 8: Frailty and Cancer (CC/2016/10)

35. This paper presented a commentary paper which had been raised under Horizon Scanning in 2015 and the associated review, other commentary papers and author's response on frailty and cancer. There was also interest in whether the several hundred/thousand SNPs which influence cancer risk suggest there is a continuum of disease rather than that suggested by the multistage model.

36. Use of uncertainty factors as a means of addressing known unknowns is well established, but the concept of frailty was interesting from a mechanistic perspective especially considering the mixture of exposures experienced and the diseases acquired through life. It was noted that frailty also covers individual differences in response, whereas uncertainty factors are applied on a population basis. The large variation in individual susceptibility was not always appropriately covered but raised questions about using this kind of information to adopt a more personalised approach, though it was acknowledged that there were a large number of

environmental factors, diet and affluence which all affect cancer risk. The link with epigenetics, both in terms of signatures for potential susceptibility and the influence of environmental factors on the epigenome, was noted and frailty could be borne in mind for the joint meeting on epigenetics.

ITEM 9: Any other business

37. It was queried whether the Committee should consider the issue of shift work and breast cancer, but it was noted that the International Agency for Research on Cancer was considering revisiting the topic. It was agreed to keep a watching brief on the IARC work for the time being.

38. One Member asked if comment could be made on how the UK's involvement with EU bodies would be influenced by the recent UK referendum vote to leave the EU. From an industry perspective, it was noted that to benefit from trade there would still need to be compliance with EU legislation, e.g. REACH. Involvement with EU scientific committees could still continue, as experts are appointed on their own merit rather than as representatives of their country. It was also noted that the outputs from EU scientific committees and EU bodies would still be useful resources for UK Government Departments and Agencies.

ITEM 10: Date of next meeting

39. The date of the next meeting was 17th November 2016.