

DRAFT

MUT/MIN/2011/3

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

Minutes of the meeting held at 10.30 am on Thursday 20th October 2011 in Room 125A Skipton House, Elephant and Castle, London, SE1.

Present:

Chairman: Professor P Farmer

Members: Dr G Clare
Dr D Gatehouse
Professor G Jenkins
Professor D Kirkland (item 4-9)
Dr D Lovell
Dr E Parry
Professor D Phillips

Secretariat: Mr J Battershill (HPA secretariat)
Dr L Hetherington (HPA secretariat)
Ms S Kennedy (HPA administration)
Dr D Benford (FSA secretariat)

Assessors: Ms C Pease (EA)
Dr R Shillaker (HSE CRD)
Dr H Stemplewski (MHRA)

In attendance: Dr C Baskaran (FSA)
Dr K Burnett (HPA – Tox unit, minutes)
Dr E Cemeli (FSA)
Dr P Edwards (HPA)
Dr J Graves (DH for item 6)
Ms C Mulholland (FSA for item 4)
Miss F Pollitt (HPA COC secretary)
Dr O Sepai (HPA)

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ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed Dr C Baskaran (who had recently joined the FSA secretariat), Dr K Burnett (HPA Toxicology unit who was helping with the minutes), Dr E Cemeli (who had recently joined the FSA secretariat), Dr J Graves (DH for item 6), Dr L Hetherington (HPA secretariat introducing item 4), Ms C Mulholland (FSA secretariat introducing item 4), Miss F Pollitt (HPA COC secretary), and Dr O Sepai (HPA).

2. Apologies for absence were received from the members Dr C Allen, Dr B Burlinson, Dr B Elliot Mrs R Glazebrook, Professor A Lynch

3. The Chair informed members that the COM guidance on a strategy for testing chemicals for genotoxicity had been published in early September. He thanked members, the secretariat and in particular Dr Burlinson for their work in finalising the document. He told members he had been reappointed as chair for a final 1 year term ending in October 2013 and that Professor Kirkland had agreed to act as Deputy Chair during this period.

4. Members were reminded of the need to declare any interests before discussion of items.

ITEM 2: MINUTES OF MEETING ON 16th June 2011 (MUT/MIN/2011/2)

5. Members agreed the minutes subject to some minor editorial changes.

ITEM 3: MATTERS ARISING

Item 3.1 Minutes of COM meeting 10th March 2011 (MUT/MIN/2011/1)

6. The Committee noted an error in the minutes of this meeting and agreed a minor alteration.

'Overall members commented that the structure of the consultation document which included testing strategy and mutagenic hazard evaluation had confused several consultees. It was agreed that ~~these two topics should be separated and thus~~ guidance on a strategy for testing chemical substances with no existing data should be the focus of the current COM consideration. it would be necessary to draft a separate document on the mutagenic hazard assessment of chemical substances with inadequate genotoxicity data.'

Item 3.2 Draft Interim guidance on impurities (MUT/2011/15)

7. At the March 2011 meeting COM discussed a strategy paper and concluded that it would be prudent to await the publication of an ICH Step 2 document before finalising any guidance document, but this is not now expected till 2012. The COM reached a number of interim conclusions at the March 2011 meeting

i) Members agreed the TTC was a useful concept in identifying impurities requiring genotoxicity assessment, although reference needed to be made to the classes of concern, e.g. aflatoxin-like, azoxy and N-nitroso compounds.

ii) Members agreed that a combination of Ames and MNvit would optimise the detection of mutagenic hazard of impurities.

iii) Thus, overall, the Committee agreed that impurities should be isolated and tested separately. QSAR data would be helpful, but would be limited in the case of novel structural moieties and in some instances where metabolic activation of pro-mutagens occurred.

8. The Committee was asked to consider the revised guidance statement Annex 1 to MUT/2011/15.

9. The HSE assessor confirmed that under REACH, "Normally, impurities present in a concentration $\geq 1\%$ should be specified. However, impurities that are relevant for the classification and/or for PBT assessment shall always be specified. As a general rule, the compositional information should be completed up to 100%." (PBT= Persistent ,bioaccumulative and toxic). Members noted there were no data to compare the concentration of impurities in substances with potential exposure to impurities which might help to assess whether such exposures exceeded the Threshold of Toxicological Concern (TTC) for genotoxicants (0.15 $\mu\text{g}/\text{person}/\text{day}$). It was agreed that the correlation between concentration of impurity and potential exposure would be highly variable. One member commented that benzo(a)pyrene concentrations in cola tar creosote of 0.2% had been important in the consideration of regulatory decisions on creosote. Overall there was a preference for using TTC for prioritising impurities for genotoxicity assessment. It was acknowledged that using the TTC to prioritise impurities for genotoxicity evaluation would require information on the structure of the impurity and an estimate of exposure.

10. Members discussed the genotoxicity test package required for impurities and observed that a number of factors could be used to determine genotoxicity test requirements including concentration of impurity, exposure level and duration and potential for bioaccumulation. Members agreed that both the Ames and *in vitro* micronucleus tests should be undertaken when genotoxicity testing of the impurity was needed. The committee confirmed that the results of spiking studies (Cyr MO Mutation Research, 577S, 172, 2005) and an evaluation of the sensitivity of the Ames test (Keynon M et al, Reg, Tox, Pharm, 48, 75-86, 2007) indicated that the most appropriate approach would be to isolate or synthesis impurities for genotoxicity testing. Members also noted the written comment from one member that some classes of chemical are poorly or not detected in the Ames test and thus the need for additional data from *in vitro* micronucleus tests. In addition it was not possible to overrule all QSAR alerts with a negative Ames test alone.

11. Members considered the draft interim guidance document (Annex 1 to MUT/2011/15) and agreed the scope was limited to impurities (unintended

constituent in a substance) and not to additives or contaminants (unintended contamination of a substance). However members agreed that TTC principles would apply equally to impurities, additives and contaminants. Members commented that differing risk/benefit analyses applied to pharmaceuticals and other chemicals (such as pesticides). Thus a risk/benefit assessment is likely to be favourable for target patients treated with pharmaceuticals, but there would be no benefit to be gained from accidental, occupational or environmental exposure to mutagens.

12. Members agreed the written comment from one member that references to QSAR should also include a reference to knowledge-based approaches to SAR. Members also agreed that it would be inappropriate to have complete reliance on QSAR assessment for impurities present in a pharmaceutical substance and requested that reference to this should be deleted from the draft guidance document.

13. Members also noted some minor comments regarding Figure 1. In particular QSAR could be undertaken only if the structure of the impurity was known. Negative QSAR suggested that it was unlikely that the impurity was mutagenic. Some text from the equivocal results in QSAR was missing.

14. Members agreed the overall conclusion should be redrafted as follows. 'The genotoxicity assessment of impurities present in chemical substances is guided by **knowledge of the chemical class and** the application of the TTC concept to select impurities which require evaluation. The testing strategy needs to be derived on a case-by-case basis but should as a minimum include QSAR evaluation of impurities selected for genotoxicity assessment, **coupled with expert judgement and reference to genotoxicity data on similar substances. In the absence of evidence to contrary it should be assumed that ALARP should be applied.** .

ITEM 4: REVIEW OF GENOTOXICITY OF CHLOROPHENOLS (MUT/2011/13)

15. No declarations of interest were made.

16. Chlorophenols are organic chemicals formed from phenol (1-hydroxybenzene) by substitution in the phenol ring with one or more atoms of chlorine. Nineteen congeners are possible, ranging from monochlorophenols to the fully chlorinated pentachlorophenol. Chlorophenols, particularly trichlorophenols, tetrachlorophenols, and pentachlorophenol, are also available as sodium or potassium salts. Low levels of chlorophenols are also found as contaminants in wine. The main source is via contamination of the cork. The Food Standards Agency had asked for advice on the genotoxicity of chlorophenol compounds to assist in developing advice to consumers on the implications of the occurrence of chlorophenol contaminants in wine.

17. The secretariat thanked Professor Kirkland for the additional data on a number of chlorophenols retrieved from the US National Toxicology Program

(NTP) files. Members were told there had been insufficient time to undertake the QSAR analysis of chlorophenols.

18. The Chair asked for any general comments on the genotoxicity test data on chlorophenols. Members commented that the majority of cytogenetic tests had been conducted to old protocols and the data were of limited use. It was agreed that the publication from Armstrong MJ et al (Mutation Research, 303, 101-108, 1993) had been adequately undertaken. Overall though, the genotoxicity data for most chlorophenols was very limited and in particular there was a paucity of *in vivo* genotoxicity data. Members agreed the further data from the NTP program was helpful. Members noted that many of the mammalian cell tests had been conducted using V79 cells which highly sensitive to free radical induced clastogenicity. It was felt that the positive clastogenicity of trichlorophenols was due to metabolism of these chemicals to quinone/semiquinone metabolites with resultant generation of free radicals. One member suggested that a number of chlorophenol metabolites could potentially undergo auto-oxidation in the culture media.

19. Members commented that further clarification of the source of contamination of cork was needed but agreed dietary intakes were very low and were between 0.87-1.75 µg total chlorophenols/week.

20. The Committee discussed whether chlorophenols could be considered as a common mechanism group. There was discussion as to whether three groups could be considered; i) mono and di-chlorophenols, ii) trichlorophenols, iii) tetrachlorophenols on the basis of the available genotoxicity data. It was agreed that there was some limited evidence to suggest that trichlorophenols could be considered as a common mechanism group based on evidence of quinone/semiquinone formation and free radical induced clastogenicity. Other possible mechanisms of genotoxicity of chlorophenols included auto-oxidation (which was more likely for chlorophenol metabolites with adjacent hydroxyls) and enzyme-induced auto-oxidation (which was more likely when hydroxyl groups on the phenol ring were more separated). However, overall, it was concluded that the data on genotoxicity and mode of genotoxic action for chlorophenols were too sparse to derive conclusions on a common mechanism group.

21. The Committee agreed that no definite conclusions could be reached on whether there was a threshold for chlorophenol-induced genotoxicity.

22. The Committee discussed the genotoxicity data submitted in MUT/2011/13. A number of generic comments were made with regard to specific references. Thus COM agreed that there were significant limitations in the studies undertaken by Strobel K and Grummt T, Tox Env Chem, 14, 279-284, 1987 and no weight of evidence could be placed on the results reported. The CHO/HGPRT gene mutation results reported by Tegethoff K et al Mutat Res, 470, 161-7, 2000 were of limited value as it was likely that an insufficient number of cells had been exposed. The Committee agreed that results of DNA strand breakage in the *E.coli* prophage induction assay could be used as supportive evidence in the assessment of clastogenicity in mammalian cells. The Committee agreed that the studies undertaken by Galloway S et al Env

Mol Mut, 10, 1-175, 1987 provided adequate data for genotoxicity assessment.

23. The conclusions reached with regard to the individual chlorophenols are given below:

2-Chlorophenol

24. 2-CP is not-mutagenic in bacterial cells. The available evidence suggests 2-CP may be an *in vitro* aneugen in mammalian cells. There are insufficient data to draw conclusions with regard to mutagenicity *in vivo*.

3-Chlorophenol

25. The weight of evidence suggests that 3-CP is not mutagenic in bacterial cells. There are insufficient data to assess *in vitro* mutagenicity in mammalian cells or *in vivo* mutagenicity.

4-Chlorophenol

26. 4-CP is not mutagenic in bacterial cells. The available evidence suggests 3-CP is clastogenic effects in mammalian cells with chromosome aberrations being reported in SHE cells. The same cells were negative for UDS and cell transformation and the comet assay was negative in mouse lymphoma cells and human fibroblasts. There are insufficient data to draw conclusions with regard to mutagenicity *in vivo*.

2,3-dichlorophenol

27. 2,3-DCP is not mutagenic in bacterial cells. There are insufficient data to assess genotoxicity in mammalian cells or to assess mutagenicity *in vivo*.

2,4-dichlorophenol

28. 2,4-DCP is not mutagenic in bacterial cells. The available evidence suggests that 2,4-DCP has clastogenic effects in some mammalian cells *in vitro*; the results are contradictory depending on the cell line used. 2,4-DCP may also be aneugenic in mammalian cells *in vitro*. There are insufficient data to assess mutagenicity *in vivo*.

2,5-dichlorophenol

29. 2,5-DCP is not mutagenic in bacterial or mammalian cells *in vitro* and gave negative results in an *in vivo* mouse micronucleus test.

2,6-dichlorophenol

30. 2,6-DCP is not mutagenic in bacterial cells. There are insufficient data to assess mutagenicity in mammalian cells *in vitro* or to assess *in vivo* mutagenicity.

3,4-dichlorophenol

31. 3,4-DCP is not mutagenic in bacteria cells. There were no genotoxicity tests in mammalian cells *in vitro* or *in vivo* genotoxicity studies retrieved.

3,5-dichlorophenol

32. 3,5-DCP is not mutagenic in bacterial cells. There are insufficient data to assess mutagenicity in mammalian cells *in vitro* or to assess *in vivo* mutagenicity.

2,3,4-trichlorophenol

33. 2,3,4 TCP was not mutagenic in bacterial cells on the basis of the data available but it has not been adequately tested. There were no genotoxicity tests in mammalian cells *in vitro* or *in vivo* genotoxicity studies retrieved.

2,3,5-trichlorophenol

34. 2,3,5-TCP was not mutagenic in bacterial cells; though the data are not adequate. There were no genotoxicity tests in mammalian cells *in vitro* or *in vivo* genotoxicity studies retrieved.

2,3,6-Trichlorophenol

35. 2,3,6-TCP is not mutagenic in bacterial cells. There was evidence of clastogenicity in mammalian cells *in vitro*. There were no *in vivo* genotoxicity studies retrieved

2,4,5-Trichlorophenol

36. 2,4,5-TCP is not mutagenic in bacterial cells. There is some evidence of clastogenicity in mammalian cells *in vitro* but there are insufficient data to assess *in vivo* mutagenicity.

2,4,6-Trichlorophenol

37. 2,4,6-TCP is not mutagenic in bacterial cells but there is evidence for clastogenicity and aneugenicity in mammalian cells. There is some limited evidence for *in vivo* mutagenicity (from a mouse spot test). 2,4,6-TCP may also be carcinogenic, though it is unclear whether this effect may be attributable to contamination.

3,4,5-Trichlorophenol

38. 3,4,5-TCP is not mutagenic in bacterial cells. It is aneugenic and positive for chromosome aberrations in mammalian cells *in vitro*. There were no *in vivo* genotoxicity studies retrieved

2,3,4,5-Tetrachlorophenol

39. 2,3,4,5-TeCP was not mutagenic in bacterial cells. There were no genotoxicity tests in mammalian cells *in vitro* or *in vivo* genotoxicity studies retrieved .

2,3,4,6-Tetrachlorophenol

40. 2,3,4,6-TeCP is not mutagenic in bacterial cells 2,3,4,6-TeCP produces chromosome aberrations in mammalian cells *in vitro*. There are insufficient data to assess *in vivo* mutagenicity

2,3,5,6-Tetrachlorophenol

41. 2,3,5,6-TeCP was not mutagenic in limited data in bacteria. There were no genotoxicity tests in mammalian cells *in vitro* or *in vivo* genotoxicity studies retrieved .

Pentachlorophenol

42. PCP is not mutagenic in bacterial cells. There is contradictory data on genotoxicity in mammalian cells *in vitro* and *in vivo* genotoxicity. Overall there are insufficient data to assess genotoxicity in mammalian cells or to draw conclusions with regard to mutagenicity *in vivo*.

Pentachloroanisole summary/conclusion

43. There is equivocal evidence that pentachloroanisole has mutagenic effects in bacterial and mammalian cells *in vitro*. There are no data to assess *in vivo* genotoxicity.

ITEM 5: GUIDANCE ON A STRATEGY FOR GENOTOXICITY TESTING AND MUTAGENIC HAZARD ASSESSMENT OF CHEMICALS WITH EXISTING INADEQUATE DATA (MUT/2011/11)

44. This guidance statement has been drafted for consideration at this meeting. A postal circulation had taken place. The COM had previously agreed that the strategy for chemicals with existing inadequate data should be separated from the testing strategy for chemicals where no genotoxicity data exist.

45. There had been some confusion over the wording of the March 2011 minutes, as shown below. It was not intended that testing and hazard assessment should be separated. The Committee noted the change agreed for the March 2011 COM minutes (paragraph)

46. Members were asked to consider the revised document. A key addition was a table of core and non core tests along with the affirmation that tests not included in the COM testing strategy should be attributed little or no weight of evidence. In addition a review of published COM opinions was undertaken to consider if there were any generic conclusions on approaches to the testing and evaluation of chemicals with inadequate genotoxicity that could be reached.

47. Members noted the written comments from COM members not present were generally supportive of the document. The Committee confirmed that the if there were no data available for a chemical then the first preferred option would be to test in accordance with the COM strategy and in particular completing the Stage 1 recommended tests (Ames and *in vitro* Micronucleus tests). If this were not possible then weight of evidence conclusions should be reached on the available data.

48. The FSA secretariat expressed reservations concerning the layout of the document and considered that in practise a hazard assessment stage

preceded consideration of testing. The Chair noted that paragraph 7 of the submitted draft text went some way to answering the concerns raised by FSA 'where no genotoxicity data are available, initial assessment of potential genotoxicity can be based on publicly available QSAR models.' One member suggested a separate document to cover hazard assessment of chemicals with no data. The Chair asked the secretariat to reconsider the structure of the document and circulate an amended version for Members' consideration.

ITEM 6. GENOTOXICITY ASSESSMENT OF NANOMATERIALS AND EXPERIMENTAL CONSIDERATIONS **MUT/2011/12**

49. No interests were declared.

50. Validated genotoxicity assays have been standardised for single chemical compounds and the assessment of nanomaterials using the same test methods has been questioned. Due to their specific physico-chemical properties, nanomaterials tend to have high reactivity and may interact with experimental components of assays with the consequent generation of misleading data. Assay compatibility, therefore, is an important consideration. This discussion paper presented some discrepancies in nanomaterial genotoxicity data for related substances, different particle sizes, and results for the same material in different tests. In addition, evidence was presented for a number of potential confounding factors in existing standard assays used for the assessment of nanomaterials. Also, a broad overview of evidence for DNA-mediated genotoxicity and indirect DNA damage in the presence of nanomaterials was provided.

51. Members were asked to consider the literature and answer the following questions:

1. Do standard genotoxicity tests offer a practical and pragmatic approach to the genotoxicity testing of nanomaterials given that they may have properties which make them different from the same basic material with larger particle size? What additional considerations, if any, would the Committee recommend with regard to the application of these tests to nanomaterials and the interpretation of test results?
2. Does the evidence for direct DNA interaction of a number of nanomaterials suggest potential generic mechanisms? What further studies on mode of genotoxic action should be considered?
3. Can the Committee recommend particular areas for investigation to improve genotoxicity testing of nanomaterials.
4. What approaches to risk assessment of genotoxicity would the COM advocate for nanomaterials?

52. Members heard that a special edition of Mutation Research on nanomaterials genotoxicity testing was in preparation. This edition would

publish a series of papers most of which were presented at EMS and EEMS workshops and symposia on nanomaterials during 2010. In addition, a European Joint Action research programme involving 16 research centres was due to finish towards the end of 2012. The Royal Commission had published reports on nanomaterials in 2004 and 2008. Members were also told that the OECD general introduction to genotoxicity testing was to be redrafted to include information on nanomaterials. EFSA had also recently published guidance on the risk assessment of the application of nanoscience and nanotechnologies in food and the feed chain. EFSA had recommended a *in vitro* genotoxicity of mammalian cell gene mutation test and an *in vitro* micronucleus test.

53. Members noted that many of the studies in the published literature were of questionable quality and in particular, the materials tested had not been fully characterised or exposure accurately measured. Most reputable journals now required a minimum set of physico-chemical data and characterisation of the test material. The physico-chemical behaviour of nanomaterials in test system media was complex and investigation of this aspect was time consuming. It was considered unlikely that a single protocol applicable to all nanomaterials could be derived for genotoxicity tests.

54. Members commented on specific aspects on the draft discussion document. It was agreed that the Ames test was unsuitable for testing nanomaterials since such materials were unlikely to pass through bacterial cell walls. For mammalian cell tests definitive proof of uptake was required using microscopical approaches. There were comparatively few *in vivo* studies and the available data from such tests was inconsistent.

55. The COM considered the review of discrepancies in genotoxicity data. Thus, the same or related material gave different results in the same genotoxicity tests. Six *in vitro* studies had compared the genotoxicity of nanosized and corresponding larger sized materials. The results showed that nanosized materials were genotoxic whereas micron sized particles were either not genotoxic or had less genotoxic activity in the test systems used.

56. The COM discussed the factors which influenced genotoxicity studies which included, size and morphology of nanomaterials, impurities, surface characteristics, dosimetry, culture media components, agglomeration of particles, exposure time and use of cytochalasin B treatment, the potential for artifacts (including reactions between nanomaterials and reagents) and experimental controls.

57. It was recommended that data on impurities should be included in manuscripts submitted for publication. Transmission electron microscopy could be linked to X-ray dispersion spectra to assess potential impurities in nanomaterials. Nanomaterial particles could be seen to have a corona of adsorbed material which was dependent on the media in which the particle was suspended and this affected potential biological interactions and agglomeration. Members noted there was no standard agreed way of reporting dose in genotoxicity studies. Overall particle number, the use of

surface area of the dose (particularly for nanotubes) combined with investigations of uptake into cells were preferred for genotoxicity studies.

58. Members reviewed a comparison of test protocols for *in vitro* micronucleus tests. The majority of tests reporting positive results required exposures of at least 24 hours. Cytochalasin B inhibited endocytosis and hence uptake of nanomaterials. One study had shown that simultaneous exposure to a nanomaterials and cytochalasin B was not genotoxic whereas sequential exposure was genotoxic. The serum content in cell culture medium affected nanomaterials uptake which was both cell type and nanomaterials dependent.

59. Members agreed there was evidence for nanomaterial uptake into the nucleus and hence potential for DNA interaction. However, most evidence available at this time suggested indirect effects mediated through oxidative DNA damage.

60. The COM considered the specific questions outlined in the draft discussion document (and reproduced in paragraph 51 of the minutes).

1) The COM agreed that standard protocols as used in genotoxicity testing of chemicals were not appropriate for nanomaterials which needed a case-by-case approach. The COM considered the most appropriate *in vitro* package was gene mutation in mammalian cells and the *in vitro* micronucleus test. However each test would require physico-chemical characterisation of the nanomaterials in the test medium and direct evidence for uptake into cells.

2) The COM agreed there was currently no convincing evidence for direct DNA-mediated genotoxic effects of nanomaterials. There was a need for more investigations of mode of genotoxic action.

3) The most important areas for further research was to obtain more information on nanomaterials uptake and persistence in cells.

4) The COM agreed that no recommendation could be reached, at the present time, regarding risk assessment of the genotoxicity of nanomaterials. There was still considerable uncertainty regarding the nature of genotoxic hazards identified in the available studies. The most appropriate approach to hazard characterisation had not been resolved.

ITEM 7:HORIZON SCANNING 2011(MUT/2011/14)

61. There was insufficient time to consider this paper which was deferred to the March 2012 COM meeting.

ITEM 8. ANY OTHER BUSINESS

62. One member provided an update of the current revision of OECD test guidelines. There were two major topics where agreement still needed to be

reached. These were whether a recommendation to use p53-competent human cells for mammalian cell tests could be made, and the consideration of lowering the top concentration for use in mammalian cell genotoxicity tests. Data sets for chromosome aberration assays, and mouse lymphoma assay had been reanalysed, but did not help clarify thinking on the top concentration. It was hoped to discuss these topics further at the next OECD guidelines meeting in Paris at the end of January.

63. Members were informed of the procedures for reappointment of the Committee. The March 2012 meeting would be the last meeting of the present Committee.

ITEM 9: DATE OF NEXT MEETING

64. 8 March 2012

Item	Actions	Responsibility
Item 3: Testing of impurities	Revise and submit to March 2012 COM meeting.	Secretariat
Item 4: Chlorophenols	Draft statement and circulate to Members	Secretariat
Item 5: strategy for genotoxicity testing and mutagenic hazards assessment of chemicals with inadequate data	Finalise guidance document with one further postal circulation	Secretariat
Item 6: Genotoxicity of nanomaterials	Draft statement for March 2012 meeting	Secretariat
Item 7: Horizon scan	Resubmit paper to March 2012 COM meeting	Secretariat

