

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

Minutes of the meeting held at 10.30 am on Thursday 26th February 2009 at the Food Standards Agency, Conference Room 5, 4th Floor, Aviation House, London.

Present:

Chairman: Professor P Farmer

Members: Dr C Allen
Dr B Burlinson
Dr G Clare
Dr B Elliot
Dr D Gatehouse
Mrs R Glazebrook
Dr D Lovell
Dr I Mitchell
Dr E Parry
Professor D Phillips

Secretariat: Mr J Battershill (HPA secretariat)
Dr L Hetherington (HPA secretariat)
Dr D Mason (HPA secretariat)
Mr S Robjohns (HPA minutes)
Ms F Pollitt (HPA)
Dr D Renwick (FSA)
Ms S Kennedy (HPA administration)
Mr K Mistry (DH administration)

Assessors: Mr G Evans (VMD)
Dr R Shillaker (PSD)
Dr A Smith (HSE)
Dr H Stemplewski (MHRA)

In attendance: D K Burnett (DH Tox unit)
Dr P Edwards (HPA)
Dr G Jenkins (University of Swansea, item 5)
Professor J Parry (for item 5)
Anne-Sophie Bauer (CEVA Sante Animale France, Item 4)
Fabrice Nessler (External expert for CEVA, Item 4)
Nathalie Petit (CEVA Animal Health UK, Item 4)

Observers:

Dr R Fayokun (DH Tox Unit)
Dr M Parker (FSA)
Mr K Okona-Mensah (DH Tox Unit).

A G E N D A

	Paragraph
Open session	
1. Announcements/Apologies for absence	1
2. Minutes of the meeting on 23 rd October 2008 (MUT/MIN/08/3)	5
3. Matters Arising (not covered by later agenda items)	6
3.1 Acrylamide	
Closed Session	
3.2 Aclonifen	
4. Fumigillin dicyclohexylamine (MUT/09/01)	8-36
Open session	
5. Thresholds for <i>in-vivo</i> mutagens and genotoxic carcinogens	37-45
4.1 Draft discussion paper	
4.2 Presentation by Dr G Jenkins (University of Swansea)	
6. Toxicogenomics: Further discussion paper (MUT/09/03)	46-50
7. Annual report 2008	51
8. Any other business	52
10. Date of next meeting 18 th June 2009	53

ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed Professor J Parry (ACP member and ex COM Chair), Dr D Mason (HPA), Dr L Hetherington (HPA), Mr S Robjohns (HPA), Dr R Fayokun (DH Tox Unit), Dr K Burnett (DH Tox unit), Mr D Parker (FSA), Dr P Edwards (HPA), Dr D Renshaw attending in the place of Dr D Benford (FSA secretariat), Dr G Jenkins (University of Swansea), Mr G Evans (VMD). The Chair also welcomed Anne-Sophie Bauer (CEVA Sante Animal France), Fabrice Nesslany (External expert attending for CEVA) and Nathalie Petit (CEVA Animal Health UK) who would be attending for item 4.
2. Apologies for absence were received from the members Dr J Clements and Professor N Gooderham. Apologies were also received from Dr D Benford (FSA secretariat), the assessors Dr D Dyer (DH), Mr M Hosford (EA) and Mr A Browning (VMD).
3. The Chair thanked three COM members (Dr J Clements, Professor N Gooderham, Dr I Mitchell) who were retiring from the Committee after this meeting. The Chair was particularly grateful for all their hard work and beneficial contributions to the work of the committee. He read out a message from one retiring COM member thanking Members for their support during his term of membership.
4. Members were reminded of the need to declare any interests before discussion of items.

ITEM 2: MINUTES OF MEETING ON 23rd October 2008 (MUT/MIN/08/3)

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

ITEM 3: MATTERS ARISING (NOT COVERED BY LATER AGENDA ITEMS)

3.1 Acrylamide

6. The committee was informed that the fourth draft statement on acrylamide had been placed on the COM website. The Polyelectrolyte Producers Group (PPG) had submitted detailed comments on the fourth draft statement. Members were consulted on the comments and a response had been sent to PPG. A number of amendments had been made to the draft statement in light of received comments which had been finalised by the Chair. A copy of the response sent to PPG would be circulated to members for information. The Chair thanked the secretariat and members for their hard work on acrylamide.

3.2 Aclonifen

7. Members were informed that the Advisory Committee on Pesticides (ACP) had accepted the advice from COM on aclonifen regarding the suggestion for further metabolism to investigate the formation of the postulated metabolites hydroquinone and phenol. Members queried whether

the committee should consider the mutagenicity of presumed metabolites. The secretariat suggested that this should be considered on a case-by-case basis.

Closed session

ITEM 4: FUMIGILLIN DICYCLOHEXYLAMINE (MUT/09/01)

8. Dr Burlinson noted that some genotoxicity studies on fumgallin dicyclohexylamine (fumagillin DCHA) had been undertaken in his department some 20 years prior to his employment. The Chair considered that this declaration did not affect his participation in the COM consideration of fumagillin DCHA.

9. The Committee on Mutagenicity (COM) had been asked by the Veterinary Medicines Directorate (VMD) for an opinion on the genotoxicity of fumagillin DCHA and in particular the interpretation of studies undertaken by the Stanimirovic group. Fumagillin DCHA is an antibiotic authorised for use in honey bees for the prevention of infections caused by the *Nosema apis* parasite present in the gut of infected bees. Infections caused by *Nosema* parasites might be associated with bee Colony Collapse Disorder. The commercial formulation of fumagillin DCHA is a stabilised water-soluble preparation, Fumidil-B (CEVA Animal Health). Fumagillin DCHA currently has no maximum residue level (MRL) status because the Committee on Veterinary Medicinal Products (CVMP) were unable to make a recommendation when the substance was evaluated in 1999. One of the main reasons given was that no conclusions could be reached on the genotoxicity or carcinogenic potential of fumagillin.

10. Recently, reports of genotoxic effects of fumagillin DCHA in cytogenetic tests both *in vitro* and *in vivo* were published by the Stanimirovic group. Based on these published data, VMD recommended immediate suspension of the marketing approval for Fumidil-B due to a potential risk to consumer safety. Subsequently, the marketing approval holder (MAH), CEVA Animal Health, provided VMD with reports of additional regulatory genotoxicity studies, conducted by Nesslany between 2004 and 2007. The MAH was invited to make a presentation to the Committee and Mr Fabrice Nesslany attended as the MAH's expert.

11. Fumagillin DCHA can undergo thermal and photo degradation under varying conditions to produce a number of degradation products, the toxicity of which is currently unknown. The Stanimirovic group investigations did not follow recognised regulatory OECD guidelines, the GLP status of the studies was unknown, and the material used, Fumidil-ET, is not authorised in the UK and its specification is not fully known. The contact for the Stanimirovic group was emailed twice by the Secretariat prior to finalising the draft discussion paper with a request for further information on their studies but to date no response has been received.

12. With regard to the mutagenicity studies, there appeared to be a good degree of concordance between the *in-vitro* studies of Nesslany and the

Stanimirovic group. All three bacterial gene mutation studies gave negative results; all three chromosome aberration studies in human lymphocytes and the sister chromatid exchange assay gave positive results. Overall, the *in-vitro* results indicate that fumagillin DCHA is clastogenic but the mode of action has not been investigated. The *in-vivo* UDS and comet assay results of Nesslany (2004, 2006) do not indicate a potential for *in-vivo* DNA damage but the interpretation of assays of chromosomal effects are more problematic. Thus, the Chinese hamster bone marrow assay by Molinier (1992) was considered invalid and excluded by CVMP. The mouse bone marrow chromosome aberration and micronucleus studies (Kiss, 1989, Stanimirovic et al 2007) were positive and suggested an *in-vivo* clastogenic effect. However, the micronucleus test in rat bone marrow was negative (Nesslany, 2006) although plasma concentrations in this study 24 hours after the final dose were below those reported to induce clastogenicity *in-vitro* and no data on tissue concentrations were available.

13. At a meeting with the Secretariat, the MAH was requested to submit additional data including thermal and degradation studies with fumagillin DCHA, genotoxicity studies with fumagillin acid and dicyclohexylamine alone, a critical analysis of the regulatory studies undertaken by Nesslany and those published by the Stanimirovic group.

14. Significant degradation of fumagillin solid as supplied by the MAH was seen at varying temperatures and time periods up to 12 months. Analysis by HPLC showed that, batch-to-batch, the total level of impurities was around 10% and the impurity profile remained stable. Overall the published *in-vitro* mutagenicity data on dicyclohexylamine were too sparse to draw any definite conclusions. The MAH did not perform original genotoxicity studies with dicyclohexylamine and considers that the evaluations of cyclamate, cyclohexylamine and dicyclohexylamine by the EU Scientific Committee on Food and the authorisation of such products in foodstuffs to be sufficient evidence for the exclusion of the role of dicyclohexylamine in the *in-vitro* mutagenic potential of fumagillin DCHA. The Secretariat evaluated the regulatory studies on fumagillin acid. An oral bone marrow micronucleus test in the mouse was negative but exposure of bone marrow could not be assessed. An oral bone marrow micronucleus test in the rat was negative following dosing of up to 2000 mg/kg bw on 2 successive days and plasma concentrations measured 2 hours after the first treatment were up to 6 µg/ml (Molinier 2000).

15. The expert for the MAH considered that recent publications, using chemical genetic approaches, strongly support the hypothesis that the mode of action of fumagillin acid results from specific and high affinity irreversible inhibition of methionine aminopeptidase II.

16. Advice was requested from COM on the interpretation of the available data, and an opinion on the Stanimirovic data and the potential for fumagillin DCHA as a mutagen and an *in-vivo* clastogen.

17. The Chair noted that the referral to COM did not include advice on consumer risk assessment. He suggested that questions for the MAH could be divided into four areas, namely the manufacture and impurity profile of fumagillin, the stability of fumagillin DCHA, the genotoxicity of fumagillin DCHA, fumagillin acid and dicyclohexylamine, and the strategy used by the MAH.

18. Members noted that under certain culture conditions, *Aspergillus sp* could produce toxins. In addition, there were many methodological differences between the *in-vivo* genotoxicity tests undertaken by Stanimirovic and Nessler including species of rodent used, differences in source and purity of test material used, use of different dosing vehicles to administer fumagillin that made it difficult to compare these studies. Members commented on the uncertainty of the test material identity used in the Stanimirovic studies and noted the purity of the test material used in the regulatory studies by Nessler had varied between the submitted studies. Members considered the MAH should be asked to comment on whether the effects reported by Stanimirovic were due to impurities and whether the MAH had a plausible suggestion for the *in-vivo* mutagenic effects reported by Stanimirovic.

19. Members agreed to ask the MAH whether there were any data that the genotoxicity of fumagillin varied depending on light/dark conditions and temperature of test material dosing solutions and temperature of culture available.

20. The Chair noted one possible reason for the different results obtained by the Stanimirovic and Nessler groups was that studies had been undertaken by these groups in mice and rats respectively. The COM agreed to ask whether differing amounts of metabolism by epoxide hydrolase in mice and rats was one potential explanation for the results of *in-vivo* genotoxicity tests reported by these groups.

21. Members commented that it was possible that the systemic absorption of the dicyclohexylamine salt of fumagillin was higher than the free fumagillin acid and agreed this should be raised with the MAH. The limited genotoxicity data on dicyclohexylamine was noted and Members agreed to raise this aspect with the MAH.

22. The COM considered the genotoxicity testing strategy used for the second tissue *in-vivo* assay and queried whether *in-vivo* rat liver comet assay was the most appropriate second tissue assay. It was noted a site of contact assay would have been preferable. Members agreed to raise this topic with the MAH.

Presentation by MAH

23. The Chair welcomed attendees representing the MAH and invited them to make a presentation on the genotoxicity of fumagillin DCHA.

24. The MAH provided background information on the use of fumagillin DCHA (Fumidil-B) to prevent and treat *Nosema apis* in honey bees. It was noted that the mode of action was not fully known although there were data to demonstrate irreversible inhibition of an enzyme involved in endothelial cell proliferation. A description of the submerged culture manufacture of fumagillin DCHA using cultures of *Aspergillus fumigatus* was presented. The MAH noted it was very difficult to obtain, in industrial scale, a significantly better purity than approximately 90%. The impurity profile was stable from batch to batch, the main structures had been identified. Stability data for storage under three different conditions up to 12 months were available. Batches used for toxicological testing were representative of commercial batches. The EMEA had accepted data on manufacture. The MAH recommended that fumagillin DCHA was stored at 4°C to guarantee quality.

25. An overview of all the available genotoxicity data on fumagillin DCHA was presented. A comparison between the studies conducted and results obtained by Nesslany (using commercial batches of fumagillin DCHA) and the studies reported by the Stanimirovic group (using fumagillin DCHA not sourced from the MAH) was presented. For *in-vitro* studies information on purity, storage of test material, solvent and results were presented. Both research groups had found that fumagillin DCHA is an *in-vitro* clastogen using the *in-vitro* chromosomal aberration test in human lymphocytes. The level of cytotoxicity was clearly different between the two groups but the NOEL for clastogenicity was similar. The difference could be attributed to a difference in purity and/or a degradation product linked to preservation conditions of the test compound. The MAH showed a number of tables demonstrating slight differences in the presentation of results by the Stanimirovic group in two separate publications for essentially identical *in-vitro* chromosome aberration tests in peripheral blood lymphocytes, although this was complicated further by the reported differences in test material.

26. A comparison of the *in-vivo* genotoxicity tests undertaken by the Stanimirovic and Nesslany groups was presented. Information on purity, source and storage of the respective test materials was given together with a description of the different test systems used by the Stanimirovic group (mouse bone marrow chromosome aberration and MN assays) and Nesslany group (rat bone marrow chromosome aberration assay). Information on the control of concentrations in dosing formulations was available for the Nesslany study. Information on the dosing solutions for both groups were available. An overview of results was presented and it was noted that plasma concentration data for the Nesslany study proved exposure of the bone marrow to the test substance. An overview of the conduct and results for two additional studies (rat liver UDS and comet assays) undertaken by the MAH was also presented.

27. The MAH suggested the conclusion from the Stanimirovic group was of clastogenic effects in the mouse with seven daily oral treatments (cumulative 525 mg/kg bw) in male and female mice. The equivalent Nesslany GLP compliant study indicated no genotoxic potential following two oral treatments of up to 1000 mg/kg bw in male and 640 mg/kg bw in female rats. Two further

in-vivo GLP compliant studies performed with fumagillin DCHA were negative (oral rat liver UDS assay (up to 250 mg/kg bw with two sampling times), and oral rat liver comet assay (up to 800 mg/kg bw with two sampling times)).

28. The MAH briefly reported on genotoxicity studies performed with fumagillin acid. Negative results were available for *in-vitro* (bacterial and mouse lymphoma) assays. Negative results were obtained in oral MN tests in mice and rats.

29. The MAH suggested the discrepancy between the published studies from the Stanimirovic group and GLP complaint studies performed by the MAH were due to a difference in fumagillin DCHA quality and/or preservation conditions.

COM Questions for MAH

30. The Chair thanked the MAH for the presentation to COM. He asked members to raise questions.

31. In answer to a question on impurity profile, the MAH reported that the profile of impurities had a relatively stable batch to batch variation, but genotoxicity data on impurities were not available.

32. In answer to a question on stability of test materials used in genotoxicity studies, the MAH suggested that differences between the Stanimirovic and Nessler groups regarding storage of test materials was one possible explanation. The MAH noted there were no relevant genotoxicity studies of MAH derived test material conducted in light and dark conditions available.

33. Members commented that the *in-vitro* genotoxicity data from the Stanimirovic and Nessler groups were very similar which might suggest that light/dark storage might affect cytotoxicity but not mutagenicity. One possible explanation was that fumagillin was storage sensitive but a genotoxic impurity was not storage sensitive.

COM Discussion and Conclusions

34. The COM agreed that the Stanimirovic data were limited and no definite conclusions could be reached. There were several possible explanations for the differences between the results obtained for *in-vivo* genotoxicity studies undertaken the Stanimirovic group and the MAH. These included possible differences in absorption, metabolism of the administered test material, differences in stability of the test materials including storage, and different impurity profiles between test materials used by the research groups. The COM agreed that the data on fumagillin acid and dicyclohexylamine tested separately did not provide sufficient information to draw conclusions on the role of these substances in the potential mutagenicity of fumagillin DCHA. The COM agreed that a repeat of the Stanimirovic study in mice (using the same test protocol and evaluation for MN and chromosome aberrations) with

test material sourced by the MAH should be undertaken with appropriate measures of systemic absorption. The COM considered that a second *in-vivo* tissue evaluation should be undertaken and suggested a site of contact MN formation in the gastrointestinal tract. Negative data from appropriately conducted tests (according to the Stanimirovic protocol) using two tissues in mice would be sufficient to refute Stanimirovic data. Equivocal or positive data from such tests would confirm that fumagillin DCHA should be considered an *in-vivo* mutagen. The Committee also commented if any genotoxicity was observed with fumagillin DCHA, more genotoxicity data (*in-vitro* chromosomal aberration test in human lymphocytes) should be provided on dicyclohexylamine to evaluate its potential role. The COM considered that the differences in statistical reporting in the Stanimirovic group publications as highlighted by the MAH were not necessarily founded.

35. Members agreed that further additional data on the influence of light/dark conditions on the genotoxicity of fumagillin DCHA were not necessary. Members agreed that the data on potential fungicidal mode of action submitted were not relevant to the potential genotoxicity mode of action of fumagillin DCHA.

36. The Chair asked the Secretariat to prepare a draft statement for circulation to Members that could be submitted to the MAH for comment.

Open session

ITEM 5: THRESHOLDS FOR *IN-VIVO* MUTAGENS AND GENOTOXIC CARCINOGENS

37. The committee was reminded of the COM statement on the risk assessment of *in-vivo* mutagens published in 2001 (COM/01/S3). The conclusions stated that it was prudent to assume that there is no threshold for *in-vivo* mutagens, but when a potential for a threshold related mechanism had been identified, appropriate data could be generated on a case-by-case basis. It had been agreed that two mechanisms had been identified for a threshold for a genotoxic response; aneugenicity induction by tubulin inhibitors (specifically the methyl benzimidazoles carbendazim and benomyl) and the rapid detoxification of hydroquinone and phenol via the oral route. Members were informed that it was proposed to revise the COM statement in the light of new evidence and publish new guidance in the form of a guidance note to be published on the COM internet site.

4.1 Draft discussion paper (MUT/09/02)

38. A draft discussion paper by the DH Toxicology Unit, on studies on thresholds in mutagenicity published since the COM 2001 statement, was provided to members for information. This paper was intended to provide some background on the subject of genotoxicity threshold mechanisms prior to the presentation by Dr Gareth Jenkins.

4.2 Presentation by Dr Gareth Jenkins (University of Swansea)

39. Dr G Jenkins provided an interesting presentation to the committee on thresholds for *in-vivo* mutagens and genotoxic carcinogens. He outlined the existing COM statement on in-vivo mutagens and showed that there were many stages in mutagenesis which might potentially have a threshold. It was pointed out that terminology regarding thresholds varied between different research groups. For example, it was important to note that the demonstration of a practical threshold did not necessarily imply the presence of an absolute threshold. Studies designed to investigate whether direct acting genotoxins display thresholds for genotoxicity needed high quality protocols involving multiple dose levels to assess the shape of response and increased sensitivity by screening large numbers of cells to distinguish between a threshold and a biphasic dose-response. In addition specific statistical packages needed to be developed to perform appropriate dose-response modelling for the determination of thresholds. Dr Jenkins outlined the theory underlying hormesis but noted this was a controversial area.

40. Dr Jenkins gave an overview of the DNA adduct profiles for alkylating agents (MMS, EMS, MNU, ENU) and reported on the dose response for micronucleus formation and Hprt mutagenicity in AHH-1 lymphoblastoid cells. These data showed that there were potentially two different endpoint thresholds due to two different adducts. Thus MMS preferentially formed N-7-Guanine adducts leading to clastogenicity whilst MNU preferentially formed O⁶-Guanine adducts leading to mutations. The available DNA adduct data for MMS in AHH-1 lymphoblastoid cells showed no evidence for a threshold but there was an experimentally demonstrable threshold for Hprt mutations (Swenberg et al Chem Res Tox, 21, 253-265, 2008) These data inferred DNA repair was one potential mechanism for a threshold for MMS mutagenicity. Subsequent studies had shown elevated induction of O⁶-methylguanine-DNA-methyltransferase (MGMT) at low doses of MMS and other alkylating agents. (Doak et al, Mutat Res, 648, 9-14.) Dr Jenkins noted that genotoxic thresholds demonstrated *in vitro* might well be exaggerated *in vivo* due to other protective mechanisms (e.g. bioavailability and detoxication). He reported on recent studies undertaken by Roche to investigate the potential threshold for EMS and to assess the risk of exposure of patients exposed to Viracept containing low levels of EMS. This included evidence for a threshold dose of EMS *in-vivo* and a linear dose-response for the formation of ethyl valine haemoglobin adducts. Presentation of EMS MN formation expressed as a function of ethylvaline adducts showed clear evidence for a threshold. Additional MutaMouse liver data for EMS indicating evidence for a threshold was reported.

41. Dr Jenkins concluded that some genotoxins have demonstrated a threshold for mutagenicity both *in-vitro* and *in-vivo*. However, it is not possible to generalise to other chemicals that have not been tested to the same extent. There is a need to consider chemicals on a case-by-case basis and to have confidence in the mechanism for a threshold and the dataset. To date the evidence is most convincing for EMS. Mutation frequencies and DNA repair

can vary over orders of magnitude over the genome (which could potentially limit the value of Hprt data). Important caveats regarding thresholds for mutagenicity included; that the data are based on available test systems, mechanistic data are required, genetic variability in the human population might indicate the need to assess thresholds in specific animal/cell models, exposures to mixtures have not been considered, and that the evidence is not currently available for cancer relevant genes such as P53 and kras.

42. Dr Jenkins suggested that thresholds might be important for weak mutagens where these might lie in human exposure ranges, although exposure to potent mutagens should be avoided even if a threshold could be identified. More data were required before extrapolation between closely related chemicals was possible. It was suggested that the COM statement regarding thresholds for genotoxicity would need to be updated in light of these conclusions, but the case-by-case approach should be retained.

Questions for Dr Jenkins

43. Members discussed the presentation and agreed that the terminology regarding thresholds would be an important topic in any COM guidance document. The COM queried whether it was possible to extrapolate between cell lines and tissues regarding experimental data for a threshold of genotoxic response. Dr Jenkins considered that the Muta™ mouse data for EMS demonstrated evidence for a threshold in three tissues with varying background rates of cell division. Members noted the dose-response for induction of MGMT mRNA and protein levels was dose-related and maximal at 1.0 µg/ml but was not evident at 1.5 µg/ml and asked what rationale could explain these results. Dr Jenkins reported that induction of P53 could suppress MGMT induction. Members commented on the interpretation on dose-related increases in mutagenicity which was apparent in the historical background range. Dr Jenkins considered that such data would indicate a concern for treatment-related induction of genotoxicity. One potential approach to data evaluation included subtraction of the control mutation frequency from results generated using test materials.

44. The Chair thanked Dr Jenkins for his presentation and asked Members to consider the letter from the ACP chair on the evaluation.

45. The committee was informed of a letter from Professor J Ayres the Chair of the ACP. Essentially, the COM was asked for their view on whether exposure to a mutagen below a demonstrated threshold should be considered as negligible? Members agreed that the reply should report on the classification of mutagens and the category 2 mutagens where COM had advised on thresholds. It was important to note that the COM review of the approach to evaluation of potential thresholds for *in-vivo* mutagens had just started and a future publication of a Guidance document would be forthcoming.

ITEM 6: TOXICOGENOMICS: FURTHER UPDATE DISCUSSION PAPER (MUT/09/03)

46. Professor D Phillips declared an interest as he had written a scientific paper in this area.

47. The COT/COC/COM intended to update their joint statement on toxicogenomics published in 2004. To contribute to this process a literature search had been conducted and studies most relevant to the COM (MUT/08/14) had been considered at the October 2008 COM meeting.

48. It had not been possible to obtain the results of the International Life Sciences Institute/Health and Environmental Sciences Institute (ILSI/HESI) trial of inter-laboratory variation in transcriptomic studies for genotoxicity. Dr J Aubrecht from ILSI/HESI had written to the committee regarding the current position of the ILSI/HESI work and had asked whether any COM members would be willing to liaise with ILSI/HESI regarding their inter-laboratory trial. One member agreed to liaise with ILSI/HESI.

49. A further update paper was provided to members (MUT/09/03), which summarised a number of studies that for the first time had made comparisons between transcriptomics and proteomics for the same mutagen using identical culture conditions except that transcriptomics was measured 4h post exposure and proteomics 12h post exposure. The additional identified studies included investigations (DNA microarray and proteomic approaches) of the alkylating agent N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and anti-benzo(a)pyrene-7,8-dihydrodiol-9,10 epoxide (BPDE) in human Amniotic FL cells.

50. Members noted that although there was some comparability between the two toxicogenomic approaches for both MNNG and BPDE regarding overall functions affected by treatment, there was very little comparability at the individual gene level. Overall, members considered that there was no evidence from these studies for a good correlation between transcriptomics and proteomic approaches. It was also noted that changes seen at the mRNA level did not necessarily mean there would be a change at the protein level and vice versa.

51. It was hoped that the ILSI/HESI data could be brought back to the committee as soon as possible to allow the completion of the current COM review of toxicogenomics.

ITEM 7: ANNUAL REPORT 2008 (MUT/09/04)

52. The committee was asked to provide any comments on the draft COM annual report to the secretariat within two weeks.

ITEM 8: ANY OTHER BUSINESS

53. There was no other business.

ITEM 9: DATE OF NEXT MEETING

54. 18th June 2009.

Item	Actions	Responsibility
4. Fumigillin dicyclohexylamine.	Prepare a statement and advise VMD for a repeat of the Stanimirovic study in mice using test material from CEVA and an additional site-of-contact genotoxicity test.	Secretariat
5. Threshold for <i>in-vivo</i> mutagens and genotoxic carcinogens.	Bring back to the committee, draft statement and provide a response to the ACP.	Secretariat/Chair
6. Toxicogenomics	Bring back to the committee with the ILSI/HESI data and draft statement.	Secretariat
7. Annual Report 2008	Members to provide any comments within two weeks.	Secretariat/Chair