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**DRAFT**

**MUT/07/16**

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)**

**REVIEW OF GENOTOXICITY OF ACRYLAMIDE**

**SUBMISSION FROM THE POLYELECTROLYTE PRODUCERS GROUP (PPG)**

**[This discussion document has been drafted to aid members in their consideration of acrylamide. It does not represent a formal view of COM]**

### **Referral to COM on acrylamide**

1. The HSE requested a further evaluation from the COM regarding the information cited by the PPG in its letter to the chair of COM (dated 8 May 2007) (Annex 2 to this draft discussion paper). The Food Standards Agency have also requested that a consideration be given to all available genotoxicity data on acrylamide by COM. The COM agreed that the ESR review completed by HSE (EU Risk Assessment report 2002) could be used as a basis for the review.

### **Background to COM review of acrylamide**

2. HSE asked for an opinion on the evidence regarding germ cell mutagenicity of acrylamide and the evidence regarding a threshold for germ cell mutagenicity with this chemical in January 2007. A response to HSE was published in February 2007 (<http://www.advisorybodies.doh.gov.uk/com/acryla.htm> (Annex 1 to this draft discussion paper). The COM was made aware of a response from the Polyelectrolyte Producers Group (PPG) to the chair (dated 8 May 2007) at the COM meeting of the 17 May 2007 and agreed to a further evaluation of the genotoxicity data on acrylamide.

### **Introduction to COM review**

3. Discussion paper MUT/07/16 presents an overview of the submission from PPG. Discussion paper MUT/07/17 presents an overview of the EU risk assessment report and the strategy being used by the secretariat to complete the review of the genotoxicity of acrylamide.

### **Advice requested from COM**

4. The COM is asked to consider the PPG submission and to raise any questions with the PPG group. The chair has agreed that PPG can make a 30 minute presentation to support the submission as this will be made by an internationally recognised expert on mutagenicity evaluation.

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## Introduction to review of PPG submission

### Secretariat meeting with PPG 20 June 2007

5. A copy of the minutes of this meeting are appended as Annex 3 to this draft discussion paper. The objective of the meeting had been to supply PPG with a copy of the referral statement, terms of reference of COM and information on the code of practice for COT/COC/COM. The COM secretariat gave attendees from PPG a copy of the COM statement on risk assessment of *in vivo* mutagens (and genotoxic carcinogens) COM/01/S3 June 2001 <http://www.advisorybodies.doh.gov.uk/com/comivm.htm> . The secretariat outlined that the provisions in this statement formed the basis upon which COM evaluated whether the *in vivo* mutagenicity of compounds had a threshold. The COM secretariat also gave PPG attendees a copy of the COM discussion on the paper by Jenkins et al (Mutagenesis, 20, (6), 389-398, 2005). Of particular note was paragraph 29 of these minutes where COM had agreed that that the information in the Jenkins 2005 paper did not indicate a need to change the COM's current view that for *in vivo* mutagens and genotoxic carcinogens it is prudent to assume there is no threshold for mutagenicity. It might be possible to identify a possible threshold when appropriate data on DNA adduction, mutation mechanisms, DNA repair were available. However such data needed to be generated on a chemical-by-chemical basis.

6. PPG made a short presentation to the secretariat which is summarised in paragraphs 8-14 of Annex 3 to this draft discussion paper. The main points raised in the presentation to the COM secretariat are included in the current submission (Annex4). The objective of the presentation was to help focus the main submission on the key areas for consideration with regard to acrylamide. PPG cited a number of papers during the presentation. This included Abramasson-Zetterberg flow cytometry of micronuclei in mice given intraperitoneal doses of acrylamide (Mutation Research, 535, (2), 215-22, 2003.) PPG indicated considerable difficulties in the statistical evaluation of the shape of the dose-response curve from this study. The COM secretariat noted that COM had seen this paper (as a general information paper) and COM had noted the flow cytometry approach might improve the precision of a NOEL determination but would not necessarily improve sensitivity due to natural variance between animals and possible experimental variation resulting from the flow cytometry procedure.

7. The COM secretariat noted at the meeting of the 20 June 2007, that the review of genotoxicity of acrylamide was a large review and it was unlikely that the COM could evaluate all of the data in one sitting.

### Overview of PPG submission

8. The PPG submission is included as Annex 4 to this draft discussion paper. PPG submitted a document in July which was revised following a number of questions from the secretariat in August 2007. The evidence

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presented in the submission is subdivided into ten sections each of which is entitled by an overall summary comment of the evaluation of that section. The ten sections lead to an overall conclusion that ‘... acrylamide is a murine aneugens and clastogen causing chromosome damage in bone marrow and sperm cell damage in rodents. It is extremely weak, albeit consistently active. The genetic effects appear to be more dependent on its protein reactivity than on its DNA reactivity.’ A number of comments raised by the secretariat on the first document submitted are noted below along with a procedural comment on the conclusion from PPG. In order to assist members in considering the submission. Copies of the references provided by PPG are appended as Annex 5 to this draft discussion paper. In some instances the full reference lists of papers, protocols etc have not been included to reduce the bulk of this particular Annex. The Committee is not being asked to review these individual papers in detail at this stage. The references have been included to help COM members assess the PG submission. The secretariat note that these studies will also be included in the overview evaluation document which is currently being drafted. (see MUT/07/17 for outline of strategy).

Table 1: Overview of PPG submission to COM July 2007.

1. <i>Acrylamide adducts to haemoglobin and the 7-position in guanine in mammalian cells.</i> The secretariat suggest that there will be additional data on DNA adducts identified in the overview review which is currently being undertaken for COM. It is noted the Swenburg reference cited in the submission focuses on alkylating agents (e.g methylating, ethylating agents). The Secretariat asked for further evaluation of the significance of this reference citation. Further information on the thermodynamic stability of acrylamide DNA adducts and repair of acrylamide DNA adducts was provided.
2.. <i>DNA Breaks are unrelated to sites of alkylation and rapidly repaired.</i> Members are asked to comment on the suggestion that oxidative stress is responsible for DNA breaks in a range of tissues.
3. <i>Prokaryotic cells are not mutated by acrylamide.</i> The data appear consistent with information identified by the secretariat to date. What are members views of the study undertaken by Emmert et al 2006. Does this contribute to acrylamide hazard assessment?
4. <i>Induction only of chromosome aberrations in mammalian cells in culture;</i> The data are generally consistent with information identified by the secretariat to date, although it is noted that Bessaratinia A et al (2004) J Natl Cancer Inst, 96, 1023-1029 reports on formation of DNA adducts <i>in vitro</i> in Big Blue mouse embryonic fibroblasts following exposure to acrylamide and glycidamide and evidence for <i>cll</i> mutations with glycidamide. Thus this aspect will be considered in more detail in the overview paper being drafted by the secretariat. (It is noted that this study is cited in section 6 of the PPG document submitted in August 2007 )
5. <i>Acrylamide inhibits kinesin and causes oxidative stress in-vivo;</i> Members are asked whether the effects on kinesins and oxidative stress explain the <i>in vivo</i> mutagenicity of acrylamide.
6 <i>The Big Blue Mouse data confirm that frameshifts, rather than base-</i>

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*pair substitutions, are the major component of increased mutagenic response.* The study published by Manjanatha et al (2006) Environ Mol Mutagen, 47, 6-17, 2006 would appear to be important with regard to the evaluation of spectrum of *in vivo* mutagenic activity of acrylamide and glycidamide. Members are asked to comment on this study. Are mutations in HGPRT solely due to deletions and/or chromosomal effects as noted in the PPG submission? The secretariat asked for more detailed reporting of the PPG evaluation of this study.

7. *The data reveal a threshold in the micronucleus test in vivo;* PPG have submitted information from a new dose-response study for MN PCEs/NCEs formation in rats dosed orally with acrylamide. Members are asked to comment on this study and the presentation of the results in the PPG submission in terms of MN NCE compared to glycidamide adducts formed. The secretariat asked for more detail regarding the statistical analysis of the results of this study. PPG note that data on PCEs should be available in time for the COM meeting on 4 October 2007.

8. *Acrylamide binds to proteamines in vivo;* The data presented are generally consistent with that identified by COM secretariat to date. It is noted that a linear transformed relationship was documented for adducts formed with sperm proteamine and DNA, although DNA binding was substantively less than proteamine binding. PPG note a minute amount of protein contamination of DNA would affect the interpretation of this study. Members are asked to comment on this aspect and in particular the study by Xie et al (2005) Toxicol Lett, 163, 101-8. Members are asked to comment on the chronological association between alkylation of proteamines and induction of dominant lethal effects in rodents. The secretariat note that additional dominant lethal data should be presented in the overview discussion paper currently being drafted.

9. *The induction of heritable translocations is non linear.* What are members views of the dose-response analysis based on the Adler et al (1994) study (Mutation Research, 309, 285-291.)

10. *Acrylamide is only a weak clastogen in vivo;* The secretariat note that Allen B et al (2005) Regul Toxicol Pharmacol, 41, 6-27. had been included in the focused review undertaken in February 2007. Members are asked for their interpretation of this paper.

*Secretariat Comment on conclusion reached by PPG*

9. The referral from HSE to COM covers aspects of mutagen hazard assessment and dose-response raised in the PPG letter of the 8 May 2007 and the referral from FSA covers a full genotoxicity evaluation of acrylamide. This includes reaching conclusions on the *in vitro* and *in vivo* genotoxicity and mutagenicity data. The default assumption is that *in vivo* mutagenic effects are not threshold related unless there is specific chemical data to show otherwise.

10. The PPG conclusion on page 16 of Annex 4 to this draft discussion paper (and summary on page 2) considers mutagenic hazard and also

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considers the setting of reference doses (BMD) and use of margin of exposure to indicate mutagenic risk. There is no agreed generic position of COM on these latter two aspects, although COM has discussed some principles regarding setting potency reference doses at the February and May 2007 meetings. Members will be aware that COC has agreed a generic approach to MOE statements on carcinogens but no equivalent discussion of mutagenicity has taken place.

### Overview of Annexed papers

10. A copy of all the papers submitted by PPG is appended for members use at Annex 5. These papers have been ordered in alphabetical sequence to facilitate access to papers. The secretariat note that a full evaluation of these studies and other identified by the secretariat is in preparation. The objective of submitting these papers is to help members in evaluating the PPG submission. There is no proposal to go over the appended papers sequentially and that the focus of the present discussion is the interpretation of data advanced by PPG.

### COM Discussion and Questions

11. The secretariat suggest the COM can meet the referrals by producing a comprehensive statement on the genotoxicity of acrylamide (including data on its metabolite glycidamide) according to existing published COM guidance. The evaluation of reference dose data and MOE would be the responsibility of the referring regulatory agencies taking into account the advice from COM on genotoxicity. There is no referral for evaluation of carcinogenicity data on acrylamide. Members are asked to consider the following questions

i) Is COM content that all aspects of the PPG submission have been fully considered.

ii) Do members wish to comment on any aspects of the genotoxicity evaluation of acrylamide and glycidamide which the secretariat should consider in the overview currently under preparation.

iii) Is the COM content with the proposal to produce a full statement on the genotoxicity of acrylamide.

**Secretariat August 2007**

### **Annexes**

Annex 1: Statement on acrylamide, COM/07/S2 - February 2007, Rrequest for advice on germ cell mutagenicity of acrylamide. Text of letter from COM chair to HSE.

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Annex 2: Letter from Dr P Ungeheuer, Secretary General, Polyelectrolyte Producers Group, 8 May, 2007.

Annex 3: Minutes of Secretariat meeting with PPG 20 June 2007.

Annex 4: An analysis of Acrylamide Genotoxicity. Submitted to the Committee on Mutagenicity by the Polyelectrolyte Producers Group (PPG), August 2007.

Annex 5: References submitted by PPG (in alphabetical order)

## **Annex 5 to MUT/07/16:**

### **References submitted by Polyelectrolyte Producers Group.**

(Note this is for members information only. Details of referencing cited in papers and protocols may be omitted.)

#### 5.1 A-D

Abramsson-Zetterberg L (2003) Mutation Research, 535, 215-222.

Adler ID et al (2000) Mutagenesis, 15, 133-136

Adler ID et al, (1994) Mutation Research, 309, 285-291.

Atay Z et al, (2005) THEOCHEM, 728, 2489-251.

Baum M et al, (2005) Mutation Research, 580, 61-69.

Allen B et al (2005). Regulatory Toxicology and Pharmacology, 41, 6-27.

Besaratinia A and Pfeifer GP (2003). J Natl Cancer Inst, 95, 889-96.

Besaratinia A and Pfeifer GP (2004) J Natl Cancer Inst, 96, 1023-29.

Blaisiak J et al (2004) Chem Biol Interact, 149, 137-149.

Bolt HM, Toxicol Lett, 140-141, 43-51.

#### 5.2 C-J

Davies DR et al (2007). ILS Report C155-01.

Doerge DR et al (2005). Mutation Research, 580, 131-141.

Emmert B et al, (2006) Toxicology, 228, 66-76.

Fennell TR et al (2005). Toxicological Sciences, 85, 447-59.

Fennell TR et al (2007) unpublished results.

Fennell TR et al (2006). Toxicological Science, 93, 256-267.

Foth H et al Arh ig Rada Toksikol, 56, 167-175.

Gamboa da Costa et al (2003). Chem Res Toxicol, 16, 1328-37.

Hashimoto K and Tanii H (1985). Mutation Research, 158, 129-133.

Haseman J (2007) Summary of statistical analysis related to acrylamide genotoxicity project (unpublished. To follow)

Hoorn AJ, et al (1993) Mutagenesis, 8, 7-10.

Jenkins GJ et al (2005). Mutagenesis, 20, 389-398.

#### 5.3 K-M

Klaunig JE and Kamendulis LM (2005). Adv Exp Med Biol, 561, 49-62.

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Koyama N et al (2006) Mutation Research, 603, 151-8.  
Krebs O and Favor J (1997). Mutation Research, 388, 239-48.  
Maniere I et al (2005) Mutation Research, 580, 119-129.  
Manjanatha MG et al (2006) Environ Mol Mutagen, 47, 6-17.  
Moore MM et al (1987). Mutagenesis, 9, 261-267.

#### 5.4 N-Z

NTP Center for Evaluation of Risks to Human Reproduction (2004) NTP-CERHR –Acrylamide 04 (conclusion; genetic toxicology)  
NTP (2007) Database search. In-vitro mutagenicity data.  
Sega GA et al (1989) Mutation Research, 216, 221-30.  
Sickles DW et al (1995) J Tox Env Health, 44, 73-86.  
Sickles DW et al (2007) Tox Appl Pharm, 222, 111-121.  
Sumner S et al (1999) Chem Res Toxicol, 12, 1110-1116.  
Swenburg JA et al (1985), Env Health Perspectives, 62, 177-1873.  
Xie Q et al (2005). Toxicology Letters, 163, 101-8.  
Yousef MI and EL-Demerdash FM (2006). Toxicology, 219, 133-141.  
Zeiger E et al (1987). Environ Mutagen, 9 (suppl 9), 1-109.

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**Annex 3 to MUT/07/16**

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

**REVIEW OF ACRYLAMIDE: MEETING WITH POLYELECTROLYTE PRODUCERS GROUP (PPG): 20 JUNE 2007**

**Present**

Dr D Marroni	President PPG
Dr M Friedman	Consultant
Dr W Matthews	FSA
Mrs N Webber	FSA
Mr J Battershill	HPA COM Secretariat.
Dr D Mason	FSA COM Secretariat.
Mr K Mistry	DH Administrative support for COM secretariat.

**Item 1: Introduction**

1. The COM Secretariat thanked attendees for coming to the meeting and asked everyone to give a short introduction to their work. For PPG, Dr Marroni noted he was head of regulatory affairs for SNF (a major producer of acrylamide) and also was president of PPG and the North American Polyelectrolyte Producers Association (NAPPA). Dr Friedman outlined his considerable experience as a bench toxicologist dealing with acrylamide and was acting as a consultant for PPG. The officials attending introduced their work.

**Item 2: COM referral and procedures**

2. The COM secretariat gave attendees from PPG a copy of the referral statement which had been previously supplied as an e-mail. Thus HSE had asked the COM to consider the new data referred to in the letter dated 8 May 2007 from Dr P Ungeheuer (Secretary General PPG) to Professor Farmer (COM chair). In addition the FSA had asked the COM to undertake a full review of the mutagenicity data on acrylamide. This had been interpreted by the secretariat as meaning both genotoxicity and mutagenicity data.

3. The COM secretariat gave attendees from PPG a copy of the terms of reference of the COM, a copy of Annex 1 from the 2005 Joint COT/COC/COM Annual report outlining the code of practice for COM, the seven principles of public life followed by members of the COM and the procedure for declarations of interest. It was noted that the COT/COC/COM were independent advisory committees reporting to the Chief Medical Officer for England (Professor Sir Liam Donaldson) and the Chair of the Food Standards

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Agency (Dame Deirdre Hutton). The secretariat was formed jointly from the Health Protection Agency (HPA) and the Food Standards Agency (FSA), with the HPA leading for COM/COC and FSA leading for COT. There was considerable inter agency working regarding the COT/COC/COM.

4. In answer to questions from PPG, the COM secretariat reported that this was a large referral for COM to consider. It was intended to consider the presentation from industry at the 4 October 2007 meeting and the secretariat hoped to complete as much, if not all, the additional mutagenicity evaluation by this time. The secretariat noted that for major submissions approximately 3h of committee time was the maximum spent on any one item at a single COM meeting. PPG reported that a large dose-response study of micronuclei in mice with investigation of internal dose of acrylamide and glycidamide measured as haemoglobin and DNA adducts had been completed. Some initial results would be presented during the meeting with the secretariat. The COM secretariat indicated that the submission from PPG should be a succinct summary of all the data relevant to the evaluation of mutagenicity of acrylamide supported with reports as indicated in the letter to the chair dated 8 May 2007. The submission should reach the secretariat by the third or fourth week in July 2007. The Secretariat would complete a literature search based on studies published after the 1995 cut off used for the EU risk assessment report. PPG indicated that they had submitted two searches and relevant published papers dated September 2006 and June 2007 which covered between 1995 and approximately May 2007.

5. The COM secretariat reported that the default position would be to assume an open discussion of papers published on the COM internet site. It was agreed that there might be some prepublication papers submitted by PPG which could not be published on the COM internet site and would be made available to members on an in confidence basis, but the discussion of these data would be held in open session.

### **Item 3: COM statements of relevance.**

6. The COM secretariat gave attendees from PPG a copy of the COM statement on risk assessment of *in vivo* mutagens (and genotoxic carcinogens) COM/01/S3 June 2001 <http://www.advisorybodies.doh.gov.uk/com/comivm.htm> . The secretariat outlined that the provisions in this statement formed the basis upon which COM evaluated whether the *in vivo* mutagenicity of compounds had a threshold. The COM secretariat also gave PPG attendees a copy of the COM discussion on the paper by Jenkins et al (Mutagenesis, 20, (6), 389-398, 2005). Of particular note was paragraph 29 of these minutes where COM had agreed that the information in the Jenkins 2005 paper did not indicate a need to change the COM's current view that for *in vivo* mutagens and genotoxic carcinogens it is prudent to assume there is no threshold for mutagenicity. It might be possible to identify a possible threshold when appropriate data on DNA adduction, mutation mechanisms, DNA repair were available. However such data needed to be generated on a chemical-by-chemical basis.

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7. PPG raised the interpretation of the Abramsson Zetterberg flow cytometry of micronuclei in mice given intraperitoneal doses of acrylamide (Mutation Research, 535, (2), 215-22, 2003.) PPG indicated considerable difficulties in the statistical evaluation of the shape of the dose-response curve from this study. The COM secretariat noted that COM had seen this paper (as a general information paper) and had noted the flow cytometry approach might improve the precision of a NOEL determination but would not necessarily improve sensitivity due to natural variance between animals and possible experimental variation resulting from the flow cytometry procedure. PPG indicated that they had asked several independent experts on mutagenicity to evaluate this and other relevant papers for the assessment of acrylamide and a peer reviewed publication was in the process of being finalised for submission.

### **Item 4: Presentation on acrylamide**

8. PPG gave an introduction to the history of the risk assessment of acrylamide. HSE had drafted the EU risk assessment review in the mid 1990s but the evaluation had been halted following investigations into an industrial accident relating to acrylamide in Sweden. In the intervening period before the risk assessment process had been started, again the consensus view of member states on acrylamide had reached a conclusion that there was a need for risk reduction measures. At this time industry had started research on the mode of action for acrylamide end points identified in the hazard assessment (e.g. carcinogenicity, mutagenicity and risk of heritable mutations). Some of this work had included a re-evaluation of the histopathology from long term studies in rodents which had led to the reclassification of acrylamide induced testicular tumours in rats as tunica vaginalis mesothelioma of the testes. The COM secretariat noted that there was no referral to look at carcinogenicity data. PPG reported subsequent meetings with HSE where the Abramsson-Zetterberg paper (see para 6 above for reference) had been discussed and the subject of a threshold for the heritable mutagenicity seen in rodents identified as a key area for further consideration. PPG had subsequently identified the letter from the chair of COM following the postal consideration of data supplied by HSE which had concluded that the mechanism for acrylamide induced germ cell mutagenicity was not fully understood and therefore it was not possible to identify a threshold for this effect. PPG considered that the COM evaluation had been limited and had requested a full in-depth review of all the mutagenicity data on acrylamide. The COM secretariat noted that this was the request from FSA.

9. Dr Friedman outlined the presentation. PPG considered the most important question was whether acrylamide was a human genotoxin. In answering this question it was necessary to consider whether there was a threshold for genotoxicity. This required two approaches i.e phenomenological (i.e description of effect) and mechanistically. The difficulty was that the size of study using volunteers would be prescriptive. Dr Friedman gave an overview of the *in vitro* and *in vivo* mutagenicity of acrylamide. PPG had

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developed BMD estimates for the in-vivo genotoxicity endpoints for acrylamide which ranged from 40-110 mg/kg bw (given parenterally). Potency was much lower when administered orally. The most sensitive end effect was micronuclei induction in mice given by intraperitoneal injection. Rats had a much lower sensitivity. PPG noted that potency and toxicological effects of acrylamide were not solely described by the extent of metabolism to glycidamide.

10. Thus a 28 day mouse micronucleus study had been undertaken using oral dosing at the MTD. Exposure had been assessed by haemoglobin adduct formation. Micronuclei formation in normochromatic erythrocytes had been assessed in  $10^6$  NCEs/animal at 11 acrylamide doses of 0.125-24 mg/kg bw/day at 24 hours after the last dose. The COM secretariat asked if this was the optimum sampling time and whether exposure of the bone marrow to acrylamide and glycidamide had been assessed. PPG indicated the full report would answer these points. The results showed a relatively weak dose-response but with a clear threshold in the assay. This had been estimated to be 1-2 mg/kg bw/day. Dose-response fitting suggested a quadratic model was the most appropriate. Results for haemoglobin and DNA adducts were to follow.

11. PPG reviewed the potential mechanisms by which acrylamide might induce micronuclei

a) Glycidamide alkylation at the 7 position in guanine and the 3 position in adenine. It was noted that 7 guanine alkylation predominated with adenine alkylation approximately 1/100<sup>th</sup> less prevalent. The biological significance of these adducts was uncertain.

b) Kinesin inhibition thus inhibiting segregation of DNA. This was considered to be the most sensitive effect of acrylamide.

c) Proteamine binding thus affecting DNA replication.

d) Oxidative stress resulting in DNA damage.

12. Overall PPG suggested a combination of these effects was relevant to micronuclei induction in mice but it was likely that kinesin inhibition predominated. There was discussion of the various approaches which could be used to evaluate the threshold for DNA alkylation with acrylamide. PPG noted the recent publication of an AMS study with acrylamide. (Xie Q et al Toxicol Lett, 163 (2), 101-8, 2006) It was noted protein binding exceeded potential interaction with DNA. PPG indicated that some AMS work with acrylamide was to be initiated in the USA. The COM secretariat noted that the COM had used data from AMS during its evaluation of 2-phenyl phenol (<http://www.advisorybodies.doh.gov.uk/com/phenylphenol.htm>).

13. PPG reported on some calculations which had attempted to estimate the systemic dose of acrylamide which would result in a level of DNA adducts

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equivalent to the overall estimated threshold for micronuclei induction. This had been estimated to be approximately 325 g/person, which was unlikely to ever be achieved, leading to the conclusion that acrylamide was not a human genotoxin.

14. The secretariat noted the publication of a number of *in vivo* transgenic mutation assays (Majanatha MG et al Environ Mol Mut, 47, 6-17, 2006, and Krebs O and Favor J Mutation Research, 384, 239-248, 1997.) These assays could be interpreted as indicating *in vivo* gene mutation activity of acrylamide presumably from metabolism to glycidamide. PPG indicated they had a number of independent reviews of these studies which could be forwarded to the COM if requested. The COM secretariat considered this might be important data for the evaluation of acrylamide and hence should be considered fully in the submission.

### **Item 5: Discussion**

15. PPG indicated that the representation at COM on the 4 October would include some internationally recognised independent experts on mutagenicity. PPG asked whether they would be able to make a presentation to the COM. The secretariat agreed to raise this with the COM chair. In answer to a question from PPG the COM secretariat suggested that all communications should go through the secretariat and that PPG should not attempt to contact the COM chair directly. The COM secretariat also noted that the submission from PPG should consider the results from studies of CYP2E1 knockout mice which helped with the evaluation of the role of glycidamide formation as a mechanism for acrylamide induce *in vivo* mutagenicity. PPG asked what outcome FSA was interested in. FSA responded that the Agency wanted a full evaluation of all the literature on acrylamide.

16. PPG asked what were the likely outcomes of the COM review. The COM secretariat indicated that this could not be predicted. In answer to a question from PPG the COM secretariat confirmed that setting data requirements was one possible outcome of COM evaluations of chemicals.

17. The COM secretariat thanked PPG for attending the meeting and looked forward to receiving the submission towards the end of July 2007.

J.Battershill  
For COM secretariat