

This is a draft paper for discussion. It should not be quoted, cited or reproduced. The Text does not represent an agreed view of COM.

**DRAFT DISCUSSION PAPER**

**MUT/2010/09**

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

**2<sup>ND</sup> DRAFT DISCUSSION PAPER: GUIDANCE ON A STRATEGY FOR TESTING OF CHEMICALS FOR GENOTOXICITY.**

**Introduction**

1. The COM considered a draft discussion paper (Annex 1 to MUT/2010/01) at the March 2010 meeting. Members suggested a number of revisions which are outlined below. A 2<sup>nd</sup> draft discussion document is appended as Annex 1 to MUT/2010/09. A proposal for generating a glossary for the finalised COM guidance is also outlined below.

**Comments from COM members**

2. Corrections and amendments suggested by members are outlined as track changes in Annex 1. An overview of the most substantive changes is outlined below;

a) An overview of the health significance of mutation is provided (paragraph 10).

b) A section on additional considerations for genotoxicity testing of chemicals with limited or inadequate genotoxicity data has been added (paragraph 20).

c) Pre-screening is now termed Stage 0

d) Revised simplified flow diagrams have been appended. There is still a need to clearly note core tests are presented in the diagrams whilst non core tests are not included.

e) The QSAR section has been extended to include information on publicly available databases.

f) Reference to both three and two test approaches to Stage1 has been included.

g) Data on sensitivity and specificity have been included to the first decimal place (as per publications). (throughout text) In addition sensitivity data from Kirkland and colleagues has been quoted without the inclusion of equivocal data which is suggested to be a better comparator to the Matthews publication (where it is not know how equivocal data was handled).

h) The default is to not require independent confirmatory tests for mammalian cell tests provided a number of criteria are fulfilled.

This is a draft paper for discussion. It should not be quoted, cited or reproduced. The Text does not represent an agreed view of COM.

- i) The strategy refers to core tests within Stages 1 and 2, which have a higher value than other tests cited in the text. One proposal is the IVCA and MLA are removed from the core list for Stage 1.
- j) Stage 2 now refers to approaches which can reduce the number of animals required (paragraph 56).
- k) The introduction to Stage 2 has been subdivided to make more explicit reference to germ cell testing and the supplementary Stage 2 strategy.

### **Development of a Glossary.**

3. It is proposed to use the current COT glossary which defines most of the terms cited in the draft COM guidance and to build internet links where appropriate. A copy of the current COT glossary is appended as Annex 2. A number of other terms (DNA stand breaks, polypoidy, recombination ) could be taken from ICH guidance. A further number of terms could be taken from the 1989 COM guidance glossary (prokaryotic, eukaryotic) and a further small number of terms would require definitions to be derived, (*in silico*, pre-screening assay, historical negative control, sensitivity, specificity). One possible suggestion is to incorporate further terms into the COT glossary and place this on the COT, COC and COM internet sites.

4. Draft proposed definitions are given at the end of the revised 2<sup>nd</sup> draft strategy document.

### **Appended recently retrieved publications**

5. A copy of the recent publication by Pfuhler S and colleagues reporting on the COLIPA analysis of genotoxicity testing for cosmetics has been appended for information. The third recommended test in the *in vitro* genotoxicity testing package is required to comply with a legislative requirement rather than on a scientific basis. The weight of evidence evaluation approach has components which are similar to those proposed in the 2<sup>nd</sup> draft strategy for chemicals with limited or inadequate genotoxicity data with the exception that exposure factors have, at request of COM, been removed from the revised draft strategy paper.

6. A copy of a review on germ cel genotoxicants published by Bishop JB in 2003 is appended. What are members views regarding the correlations between the different germ cell genotoxicity endpoints considered?

### **COM Discussion**

7. Members are asked to consider the revised 2<sup>nd</sup> draft strategy document, particularly in the light of the presentation from Professor Kirkland on 'Which mammalian cell tests best complement the Ames test in terms of detecting rodent carcinogens and in vivo genotoxins?' (MUT/2010/08) and the

This is a draft paper for discussion. It should not be quoted, cited or reproduced. The Text does not represent an agreed view of COM.

further pre-publication information on the utility of the mouse lymphoma assay (MUT/2010/12).

8. Further discussion of the content of the COM consultation document is presented in MUT/2010/10.

**Secretariat May 2010.**

- A further reference reporting a poor correlation between polyploidy and aneuploidy was retrieved after the 2<sup>nd</sup> draft strategy was completed. (Muehlbauer PA, Env-Mol, Mut, 49, 318-327,2008.