

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT****REVISION OF COM GUIDANCE****DISCUSSION PAPER: OVERVIEW OF STRATEGY FOR TESTING OF CHEMICALS FOR GENOTOXICITY****[PREVIOUS DOCUMENTS MUT/08/03, MUT/08/11]****Introduction**

1. The COM discussed the review of its strategy for testing of chemicals for mutagenicity at two meetings in 2008. Copies of the relevant papers (MUT/08/03 and 08/11) are available on the COM internet site (<http://www.iacom.org.uk/>) A copy of the proposed structure for guidance statements is appended as Annex 1. This incorporates a subdivision of genotoxicity assessment into discrete areas of assessment which can be drafted as separate documents and be independently updated as the science which underpins each of these statements advances. The advantage of this approach is that all of the areas previously considered for inclusion in COM guidance in MUT/08/11 are included in the draft guidance statements but need not be drafted and agreed simultaneously.
2. The objective of this draft discussion paper is to provide sufficient information to initiate discussion of the content for the overall strategy for testing, *in vitro* testing, *in vivo* testing and germ cell testing guidance statements. It is hoped to develop a consensus based text(s) for consideration at a future meeting. This could include a separate full publication of the guidance and individual statements along the line suggested in Annex 1.

**Principles of previous COM guidance**

3. The draft previous guidance used a number of principles which included; only refer to selected tests which the COM agreed on, use a simple rationale which is explained in the text and in easy to read flow diagrams. The strategy should be scientifically defensible and agreed by the whole COM. The Committee did not need to incorporate the strategies published by other groups in order to reach a consensus view, and did not cite specific chemicals as examples supporting a particular strategy.

## **Principles applied to current 2010 1<sup>st</sup> draft of guidance**

4. In order to draft the appended draft discussion paper, it was necessary to retain the principles previously agreed and to derive a rationale from first principles using the available published literature (which has expanded considerably since 2000). It became necessary to develop a rationale where genotoxicity tests were used to answer a range of questions (including screening for *in vivo* mutagenic potential, cancer target organ genotoxicity, germ cell genotoxicity, identification of mutagenic end points affected). In addition the substantially increased literature on QSAR and pre-screening needed to be taken into account. However it wasn't possible to include genotoxicity tests which have never been reviewed or seen by the COM such as *Pig-A* and expanded simple tandem repeats where there appears to be limited information in the published scientific literature.

## **Internal peer review**

5. The draft guidance was reviewed by a member of the COM secretariat and a scientist in the DH Toxicology Unit (based at Imperial College London) and a number of comments were discussed.
6. The title has been altered to strategy for testing of chemicals for genotoxicity. This takes a wide view of the types of tests that can be included. However COM conclusions usually relate to mutagenic hazard, thus requiring the results of genotoxicity tests to be interpreted with regard to mutagenic hazard.
7. Overall the balance of the document was thought to be sufficient for a general guidance strategy document. One suggestion was to further develop general guidance on interpretation of QSAR, pre-screening tests those genotoxicity assays recommended by the COM for inclusion and in addition for those assays considered to be inadequate for inclusions (e.g SCEs, cell transformation).
8. A further comment was whether the proposals would be seen by industrial based and/or contract genotoxicologists as practical, and thus there was a balance to be obtained between what is scientifically feasible compared to what is scientifically practical.
9. The term 'Mode-of Action' is also widely used in carcinogen risk assessment where some scientists see mutagenesis as 'a potential key event in disease aetiology' rather than a MOA for carcinogenesis. However, the term MOA as applied in the COM guidance document is consistent with the usage of the term in genotoxicology literature where it refers to the MOA of genotoxicity not carcinogenicity. Would the COM need to invent a new term, e.g 'Mode of Mutagenic Action' (MOMA)? Specific guidance on

developing an approach to MOA investigations has not been included in the current draft discussion document.

10. There were a number of areas in the guidance which would need specific advice, for example, the need for independent repeat tests with all mammalian cell mutation tests, and the view expressed that mammalian cell tests can use concentrations higher than 1 mM (on the basis that the evidence to restrict to below 10 mM is not sufficient good enough for all categories of chemicals). Thus the COM will need to go over all aspects of the guidance document, which might take several meetings.
11. Estimates of sensitivity and specificity for prediction of rodent carcinogenesis are included in the document, mainly to help members with assessment of the relative merits of particular assays and the strategy for Stage 1. These estimates are dependent on the datasets used for prediction of assay performance. In addition the purpose of genotoxicity testing is also to predict potential *in vivo* mutagenicity which may identify a risk of heritable diseases.
12. The emphasis has been placed on the use of negative historical control data. It may also be appropriate to include a statement on the value of positive historical control data.
13. Some aspects of the proposed strategy have been drafted with the intention of stimulating a debate. Thus it is proposed that toxicokinetic data should be normally provided for the interpretation of oral bone marrow MN tests.
14. The Flow diagrams (figures 1 and 2) retain a relatively simple decision logic, but the text in the boxes may be too detailed and will probably need to be reduced in content.
15. The previous COM guidance published in 2000 was subject to a limited consultation with professionals working in genotoxicology. The COC guidance published in 2004 was subject to a more formalised consultation procedure lasting 3 months. The secretariat hopes to advise on procedures at the COM meeting of 4 March 2010.

#### **Overview of 1<sup>st</sup> draft 2010 strategy.**

16. The resulting draft discussion document (Annex 2) presents a two stage strategy:
17. In Stage 1; *in vitro* mutagenic potential is assessed using a similar strategy to that agreed in 2000, although the available evidence suggests the *in vitro* MN test can replace all aspects of the *in vitro* mammalian cell metaphase analysis. There is a need to carefully consider the conduct and interpretation of data to avoid misleading

false positive results. Stage 1 of the strategy also needs to include the assessment of chemicals which, for regulatory reasons, cannot be subject to an *in vivo* genotoxicity testing strategy.

18. One new principle which COM members will need to consider is whether IWGT guidance can essentially be used as a standard for advice on the conduct of studies in situations where no appropriate OECD agreement for a test guideline exists.
19. Stage 2 is split into an initial *in vivo* genotoxicity testing strategy whereby one or more tests are used to answer the specific questions (as outlined in paragraph 4 above) and the first test is likely to be chosen on the basis of the end-point(s) identified in stage 1 which need to be examined *in vivo*. It is possible that definitive answers to the testing questions under consideration can be achieved in the initial *in vivo* testing phase. A supplementary *in vivo* testing phase is undertaken to resolve equivocal results, or to investigate aspects (such as MOA or assessment of mutagenic end points) not fully resolved during the initial phase.
20. Unlike the 2000 COM guidance, it is suggested that an initial assessment of germ cell genotoxicity can be undertaken during the initial *in vivo* genotoxicity testing. This might require quite specific protocols to be developed. However the argument proposed is that *in-vivo* genotoxicity testing is a case-by-case approach, rather than use of specified tests.
21. The recently updated IPCS guidance is appended as Annex 3 as a comparator document. In addition an extract (page 984) from Custer LL and Sweder KS *from Curr Drug Metab, 9, page 978-985, 2008* is included as an example of a proposed strategy based solely on high throughput genotoxicity screening tests which might be considered in the future.

### **COM Discussion**

22. The COM is asked to consider;
  - i) Approaches to disseminating the COM guidance; a) as identified in the draft structure for guidance documents (Annex 1), and/or b) as a hard copy publication for the COM strategy for genotoxicity testing.
  - ii) The draft strategy outlined in Annex 2.
  - iii) Proposals for taking the project through to finalisation.
  - iv) Procedures for consultation with the scientific community.

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