

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**DRAFT GUIDANCE PAPER: GUIDANCE SERIES: RISK ASSESSMENT OF *IN-VIVO* MUTAGENS.****Introduction**

1. The COM have provided advice to Government Departments on the risk assessment of *in-vivo* mutagens. A copy of the COM statement COM/01/S1 is appended for members information as Annex 1.

Revision of COM guidance

2. The COM agreed to update its generic guidance previously published in the form of statements and a guidance document on strategy for testing for mutagenicity in the form of a new 'Guidance series' of documents. A draft guidance document on risk assessment of *in-vivo* mutagens is appended as Annex 2. This document includes additional information from the 2004 discussion of DNA repair mechanisms, the COM discussions in 2006 relating to a paper by Dr G Jenkins and colleagues (Jenkins G *et al.* Do dose response thresholds exist for genotoxic alkylating agents? *Mutagenesis* 2005; **20**: 389-98), and the recent presentation to COM by Dr Jenkins.
3. Information concerning potential thresholds for genotoxicity of MBC compounds (e.g. benomyl and carbendazim), phenol and hydroquinone have been previously considered by COM and conclusions reached.
4. An important part of the consideration of potential threshold doses for genotoxicity concerns dose-response modelling and the statistical analysis of data. A key reference by Dr Lovell is included as Annex 3 to this draft discussion paper.
5. Additional information on topoisomerases has been appended as Annex 4. The COM is asked for advice on the approach taken and whether the data is sufficient to conclude on potential for a threshold related mechanism and the derivation of appropriate NOELs.
6. Additional information on small molecular weight alkylating compounds has been cited in the draft guidance note and additional papers appended as Annex 5. The COM is asked for advice on the approach taken and whether the data is sufficient to conclude on potential for a threshold related mechanism and the derivation of appropriate NOELs.

7. Information on acrylamide has been abstracted from the recently agreed COM statement on this compound. Acrylamide is an example where some, but not all, of the relevant genotoxicity mechanisms have been shown to exhibit a threshold for genotoxicity.

Approaches to risk assessment

8. The following conclusions have been proposed in the draft guidance document. The COM is asked whether it is possible to define a minimum amount of data on a group of chemicals (e.g. MBCs) where it is possible to conclude that new chemicals could be added to the group on less than full mechanistic data?
 - i) The COM reaffirmed that for *in-vivo* mutagens, it is prudent to assume that there is no threshold for mutagenicity.
 - ii) It is necessary to investigate the potential for a threshold mechanism for all genotoxic effects seen with a particular chemical.
 - iii) An appropriate strategy should be devised for each chemical under consideration to identify NOELs for potential thresholded mechanisms of genotoxicity which may include either *in-vitro* or *in-vivo* studies.
 - iv) The regulatory approach to chemicals where all mechanisms of genotoxicity have been shown to have a potential threshold can then be based on the critical NOEL and use of appropriate uncertainty factors.
9. An approach to risk assessment of mutagenicity due to EMS contamination of Viracept is outlined in MUT/09/08. The COM is asked whether any generic conclusions can be reached on the acceptability of such an approach for other *in-vivo* mutagens. A draft proposed conclusion for the draft guidance paper on risk assessment of *in-vivo* mutagens is outlined in para 11 of Annex 2 to this draft discussion paper.
10. The COC has recently agreed a Margins of Exposure as a pragmatic method for ranking and presenting information concerning risks of genotoxic carcinogens.
11. The COC committee broadly accepted the banding approach and thought that the banding approach, described in CC/07/08, could be adapted so that the bands were termed: "May be a concern", "Unlikely to be a concern", and "Highly unlikely to be a concern" as

outlined overleaf. This provides a useful tool for managing and communicating information on risks. The COM is asked whether such an approach based on NOEL or BMD(10) for *in-vivo* mutagenicity could be adopted for *in-vivo* mutagens where there are no appropriate carcinogenicity data.

MOE Band	Interpretation
<10,000	May be a concern
10,000-1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be a concern

12.

13. The COM is asked whether such an approach could be extended to *in-vivo* mutagens where there are no carcinogenicity data and the default is to assume no threshold.?

Secretariat May 2009