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

DRAFT DISCUSSION PAPER: GUIDANCE SERIES: RISK ASSESSMENT OF *IN VIVO* MUTAGENS.

Introduction.

1. The COM discussed a first draft guidance note on risk assessment of in vivo mutagens at the 18 June 2009 meeting. A revised 2nd draft discussion paper is appended as Annex 1 with track changes included.

2. Members asked for a number of topics to be further considered including

   Nomenclature, def
   Further examples (e.g paracetamol, methotrexate) of genotoxins with evidence for threshold mechanisms,
   Information on EMS as discussed at the February 2009 meeting.
   Stratification of examples into non-DNA target and protective mechanisms,
   Information on appropriate examples where threshold genotoxicity data have been used in risk assessment.
   Further information on an approach to investigating potential thresholds including more information on dose-response analysis.

3. The secretariat has added information from the COM statement on assessment of high dose positive mutagens (.http://www.iacom.org.uk/statements/COM03S5.htm). This fulfils the COMs' request to combine generic guidance where possible during the drafting of guidance documents. The current statements on risk assessment of *in vivo* mutagens (COM/01/S3) and high dose mutagens (COM/03/S5) are often used together.

Possible approaches to ranking in-vivo mutagens.

4. A possible approach to ranking exposure (TTC for oral exposures) and ranking potential mutagenic oral potency (LED) for in vivo mutagens where no threshold has been derived are outlined below. Neither approach would affect the overarching policy of ALARP.

TTC

5. MUT/09/09 outlined the COC approach to developing MOEs for genotoxic carcinogen contaminants. The COM was asked whether a pragmatic ranking of exposure to *in vivo* mutagens for risk management purposes could be developed. Members suggested further consideration of the Threshold of Toxicological Concern (TTC). A copy of the draft EU SCHER, SCCP, SCENIHR preliminary report on the use of the TTC for the safety assessment

of chemical substances is appended as Annex 2. In brief the default TTC intake of 1.5 µg/person/day was established originally for food contact materials as a *de minimis* risk value where the level of the compound is so negligible as to present no concern even if subsequently shown to be a carcinogen (i.e less than 1 in 10^6 lifetime risk of cancer). Five classes of chemical were identified were an intake of 0.15 µg/person/day was identified as being of potential risk and thus concern (which included three classes of genotoxic carcinogens, aflatoxin-like, azoxy- and N-nitroso-compounds). The TTC is useful as a pragmatic tool to aid in prioritising oral exposures and has been adapted for use with genotoxic impurities in pharmaceuticals. The SCHER/SCCP/SCENIHR report notes that in principle TTC could be applied to any substance but overall there was a need for further research on the development of the databases used to support the derivation of the TTC to include more chemicals and development of data on a variety of exposure scenarios.

6. The COC agreed in its guidelines that the TTC could not be used as a generic approach for carcinogens. The COC agreed that it could be used for carcinogens along with hazard identification and characterisation data, for prioritisation of chemicals, particularly for chemicals that are not subject to regulatory approval scheme.

7. Given the limitations noted above, it is suggested that no generic use of TTC could be made for prioritising exposure to *in-vivo* mutagens. The COM agreed the pragmatic prioritisation of pharmaceutical impurities when this was discussed at the June 2008 meeting. The COM did not concur with the proposal to scale up the TTC value for short duration of exposure to genotoxic pharmaceutical impurities.

<u>Comparison of carcinogenicity and mutagenicity potency estimates</u>

8. A copy of the paper by Sanner T and Dybing E (*Basic and Clin Pharmacol & Toxicol*, 96, 131-139, 2005) is appended as Annex 3. Theses authors propose that the LED (oral) could be used as a potency estimator for *in vivo* mutagens. Previous consideration of potency estimates for carcinogenicity by COC has indicated that rough correlations such as the numerical correlation between LED and T25 of 5-10 are acceptable if the intention is to produce broad categories of potency.

9. One further aspect is that if a potency indicator for *in vivo* mutagens could be agreed then it would be possible to develop MOEs similar to those agreed by COC.

COM Discussion

10. Members are asked to consider the revised draft guidance document on risk Assessment of *in vivo* mutagens.

11. Members are asked to consider the application of TTC to *in vivo* mutagens.

12. Members are asked to consider the application of LED as a potency indicator for *in vivo* mutagens.

Secretariat July 2009