

**COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT****GUIDANCE STATEMENT: THRESHOLDS FOR *IN VIVO* MUTAGENS. (4<sup>TH</sup> DRAFT)****Introduction**

1. Members discussed a second draft guidance statement at the October 2009 meeting and made a number of comments regarding redrafting. Most prominent was the need to clarify the definitions used with regard to thresholds for *in vivo* mutagens and to split the document into two guidance notes; one on thresholds and the second guidance document on some approaches to risk assessment of *in vivo* mutagens.

2. The secretariat circulated revised definitions along with editorial changes to the guidance statement on thresholds (3<sup>rd</sup> draft). There were a considerable number of comments and a fourth draft has been provided for members' consideration (Annex 1). The track changes following changes cited in drafts 2 and 3 have not been included (since there were quite a considerable number of changes) but a short overview of the main changes has been given below.

**Overview of suggested changes in 4<sup>th</sup> draft.***Definitions.*

3. Members asked for definitions to be included in bullet form. After circulating proposals (by e-mail), the text in the 4<sup>th</sup> draft is based on a redraft suggested by one member. It is hoped that first three definitions of threshold (True threshold, Threshold Dose and Practical Threshold Dose) show a logic linking each definition. In order to clarify the rationale underlying biologically meaningful threshold dose, it was considered that a definition of threshold mode of action was required.

4. One member suggested that NOAEL should also be defined. However this term is not used within the context of genotoxicity in the draft guidance statement, thus the clarification of NOAEL is kept to paragraph 11 rather than in the definition section of the paper. The risk assessment of MBC class of pesticides (benomyl, carbendazim and thiophanate-methyl) was based on reproduction NOAELs. Another COM member suggested the use of the term No Observed Genotoxic Effect Level (NOGEL). However the term NOEL is widely used in all toxicological risk assessments and end point specific terms such as 'No Observed Teratogenicity Effect Level' are generally not used, hence the suggested draft retains the use of NOEL.

5. The limitations of NOELs which are dependent upon experimental designs, statistical methods used, dose spacing etc. The determination of a NOEL by the identification of the lack of statistical significance in a comparison with a concurrent control means that real but smaller effects may not be detected because they don't reach statistical significance, (This is a consequence of the low power to detect small but real effects). Therefore the true threshold will be at a **lower** dose level than the NOEL. (The poorer the study, all other things being equal, the higher the NOEL.)

5. One member suggested definitions could be moved to an Annex. Do members agree?

*Introductory paras 4 and 5*

6. These two paras have been expanded and the information now occupies paras 4-6.

7. Members queried the rationale for a sentence on endogenous mutation. The current draft has been altered to explain this more fully. It is hoped the revised information in paras 5 and 6 provides a logic which is clear on the demonstration of a biologically meaningful threshold dose level and that in a number of instances such a dose level has been demonstrated. One member suggested that a reference to the significance of a biologically meaningful threshold dose level for genotoxicity for risk assessment should be noted in this section. It has also been suggested that this is also important to note in the conclusions.

*In vivo mutagens with thresholds*

8. An additional sentence regarding phenol as an example has been included.

*Other aspects of terminology*

9. One member noted a variety of terms were used in the document such as threshold mode of action/activity, threshold of action, potential threshold. The revised document uses a more limited number of terms consistent with the definitions outlined at the beginning of the document.

**COM discussion**

10. Members are asked to comment on the revised draft guidance statement. Can this be agreed by Chairman's action?

**Secretariat January 2010**