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DRAFT

MUT/08/11

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

SCOPE OF REVISION OF COM GUIDANCE

[PREVIOUS DOCUMENT MUT/08/03]

Introduction

1. MUT/08/03 (appended for ease of reference as Annex 1 to MUT/08/11) provided the background to the proposed review of the COM guidance document. At the February 2008 COM meeting, members held an initial discussion on scope for the review. (A copy of the draft minutes is appended for ease of reference at Annex 2 to this covering paper.) The chair asked for a summary discussion paper to be circulated prior to the June 2008 COM meeting to help members further consider scope of the review.
2. The secretariat have also enclosed the contents pages for the current COM and COC guidance documents to help members consider the proposal outlined below (Annex 3).

Outline scope of proposed revision of COM guidance document

3. A tabulation showing a proposed contents structure for the revised COM guidance document along with comments on the current COM guidance document and comments on possible approaches which could be used is given below. The text of the COM guidance documents represented the agreed collective views of members. References cited in the COM guidance were those which were considered important to support the document but did not represent a full systematic citation of the literature. The background documents provided during the previous review to help inform members on various aspects (e.g. SAR) were not full systematic reviews of the literature.

TABLE 1 Possible Areas for Revised COM guidance

Contents	Current guidance document	Comment on possible approach to revised document
Title	Guidance on a Strategy for testing of Chemical for mutagenicity	Guidance on a strategy for risk assessment of chemical for genotoxicity
Preface	Role of COM	Largely unchanged for review <i>Comment from COM Members; Differences between separate guidelines should be put into context e.g REACH dealing with large number of chemicals about which little is known. ICH dealing with small numbers of chemicals for specific purposes where a</i>

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		<i>large amount of data is available.</i>
Introduction	Introduction to strategy for mutagenicity testing of single chemicals. Information to be provided on gene mutation clastogenicity and aneugenicity. No single validated test that provides information on all three end points. Definition of genotoxicity provided.	Similar scope but also expanded to include comment on need to consider risk assessment of mutagens and approaches to evaluation of evidence for threshold mechanisms of mutagenicity.
General Principles of testing strategy	Introduction to three stages of testing. Brief comments on SAR (Comment that commercial packages no better than inspecting structure and using expert judgement). Clear statement that negative in three in-vitro mutagenicity tests can offset need for animal tests. Comment on physico-chem properties affecting testing, toxicity and kinetics affecting route of admin in-vivo tests and dose selection for in-vivo tests. No consideration of mixtures in guidance.	<p>Similar scope but expanded to note developing gene screens, and developments regarding SAR. Need to consider where biomonitoring might be cited in this section. What further comment on 3Rs can be made?</p> <p>COM has considered mixtures and a short paper on impurities is being drafted. Should these be included in scope?</p> <p><i>Comment</i> Member's views were divergent on the amount of information on mixtures/impurities which should be included.</p>
Stage 1 In-vitro tests	Flow diagram and outline comments on the tests. Comment on use of FISH approaches. Comment MN test adequately validated (reference to development of OCED guideline). Use of kinetochore stains for aneugenicity in MN test outlined, COM reaffirmed they gene mutation in bacteria and chromosomal aberration may miss some mutations and hence need for third mammalian cell test (MLA specified). Discussion regarding colony sizing. Short note on artifactual positives. Note that in line with good scientific practice in-vitro tests should be repeated, but outline rationale for avoiding this for mammalian cell tests given. COM did not recommend SCE or tests with fungi.	<p>Similar scope but are new sections on gene screens, SAR required?</p> <p>Debate required on what in-vitro tests, how many, what end points, under what conditions should any be omitted, need for repeat assays, need for positive controls.</p> <p><i>Comment</i> i) Include key tests and any limitations. Key protocol features governing acceptance/interpretation, need for positive controls, conflicting data, status of data from unusual/unvalidated tests. ii) The secretariat note the recent paper from Kirkland DJ et al <i>Mutagenesis</i>, 22, 161-175,2007 which advocates a WOE/MoA approach to evaluate positive in-vitro genotoxicity results</p>
Stage 2 In-vivo tests	Flow diagram and table of tests (other than bone marrow). COM noted need for flexible approach (review of all mutagenicity data and information metabolism and kinetics). Rodent BM, peripheral blood MN assay and BM CA assay identified as first choice (Note made for identification of aneugens if evidence found in stage1). List of tests for second assay (required if positive in any in-vitro test). In general prominence given to rat liver UDS (noted value for compounds which metabolic activation). Recognised that OECD guidelines did not exist for other tests but could be used on case-by case basis. Document notes there are no routine methods for screening gene mutation in-vivo. Noted	<p>Similar scope.</p> <p>Debate required on which tests, and order of tests and circumstances when in-vivo data could offset need for further in-vitro testing. Consideration of need for positive controls in each test.</p> <p>What role would biomonitoring have in this section of the strategy?</p> <p><i>Comment</i> i) As noted above with regard to in vitro tests under comment i). ii) determining top dose levels, relevance of data exceeding MTD, levels of absorption for an acceptable test</p>

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	<p>need for optimising protocols for transgenic assays, and value of these assays as supplementary tests or target organ tests. Use of comet for genotoxins at initial site of action noted. Value of DNA adducts with regard to mechanisms in-vivo noted. Brief comment on value of evaluating why in-vitro mutagenic activity is not expressed in-vivo.</p>	
Stage 3 Germ cell assays	<p>Flow diagram (note table in stage 2 also applies to this stage). Thus far all positive germ cell mutagens have been shown to be mutagenic in somatic cell tests. Germ cell testing undertaken when it is important to do so. Range of possible tests identified in flow diagram.</p>	<p>Similar scope. Is there scope for reconsideration of selection of tests, and under what circumstances there is a need to evaluate germ cell effects?</p> <p><i>Comment</i> <i>It may be possible to eventually combine stage 2 and 3 with exposure assessment being used to determine if germ cell assessment needed.</i></p>
Risk Assessment of in-vivo mutagens	<p>Not in COM guidance, see statement MUT/01/S3. 'The general advice of the COM when considering the risk assessment of chemicals which are mutagenic <i>in-vivo</i> has been that it is prudent to assume a linear, non threshold dose response. Thus it is assumed that any exposure to an <i>in-vivo</i> mutagen is associated with some damage to DNA and consequently an increased risk of mutation leading to an increased risk of adverse health effects albeit that this may be small. In such instances the Committee has recommended that exposures be reduced to a low as is reasonably practicable. The COC has adopted a prudent approach to the assessment of chemical carcinogens which assumes that genotoxic carcinogens have the potential to damage DNA at any level of exposure and that such damage may lead to tumour development. Thus for genotoxic carcinogens it is assumed that there is no discernible threshold and that any level of exposure carries a risk.'</p>	<p>Scope of guidance document to be expanded to include updated review of this area. Noted examples in current statement (eg phenol) may no longer be appropriate.</p> <p>COM consideration of approaches to threshold evaluation (to include Jennings et al) not published as a full statement.</p> <p><i>Comment</i> <i>Need for clear separation of steps (see headings from COC guidance.</i> <i>Hazard identification (COC guidance includes steps 1-3 of COM guidance in this section)</i> <i>Hazard characterisation (COC guidance evaluates dose-response in animal studies, i.e what mode of action is responsible for observed genotoxicity)</i> <i>Exposure Assessment (COC guidance comments on exposure of human populations and limitations of approaches</i> <i>Risk characterisation. The approaches to evaluation of threshold or non-threshold MoA. For Non-threshold mutagens this would involve the development of possible MOE approaches, potency considerations, the use of the TTC. Outcome would be restatement of ALARP and conventional risk assessment for threshold mutagens.</i></p>
Potency considerations	<p>Not included in COM guidance. COC guidance in the section on Risk Characterisation considers QRA approaches. Overall it was considered that QRA for carcinogenicity based on animal data was not appropriate for risk assessment. COC guidance then looks at possible approaches to provide scientific advice which can assist with risk assessment. This included use of potency estimates for ranking (eg T25), the development of minimal risk levels</p>	<p>COM was unable to reach agreement on approach to mutagen potency setting. There is no international agreement on an approach for mutagen potency. Is there scope for debate on some of the areas considered by COC, e.g the TTC approach.</p> <p><i>Comment</i> <i>This is most likely part of Risk Assessment.</i></p>

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	and the TTC (Threshold of Toxicological Concern) concept. Overall COC noted that the TTC was not appropriate for some well known categories of carcinogens e.g. nitrosamines. More recently COC has looked at MOE (Margin of Exposure, cf. LOAEL, BMD10, T25 compared to environmental exposure estimates) for carcinogens and has provided generic guidance on this aspect.	
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(summaries were included at end of each section)

COM discussion

4. Members provided a number of comments to the secretariat on the scope table given above. These have been put in the comments section in italics along with some comments from the secretariat.

5. In addition MHRA provided a comment supporting the inclusion of risk assessment. Members will recall that the COM statement on risk assessment of *in vivo* mutagens and genotoxic carcinogens (<http://www.advisorybodies.doh.gov.uk/com/comivm.htm>) covers the provision of data on potential for threshold and concludes on the need for case-by case compound specific data. The MHRA proposal supports including an updated review of this topic in the revised COM guidance document. The key area for discussion is the need for case-by-case data or whether there are sufficient generic data for certain groups of compounds (e.g. low molecular weight methylating agents).

6. Members are asked to consider the outline proposal in table 1 above.

Secretariat May 2008

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**ANNEX 1 TO MUT/08/11
PREVIOUS PAPER FROM FEBRUARY 2008 MEETING.**

MUT/08/03

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

REVISION OF COM GUIDANCE: DISCUSSION PAPER ON SCOPE AND PROCESS.

Background

1. The current COM mutagenicity testing strategy (2000) was developed to update the strategy published in 1989 which had been based on a strategy published in 1981. The COM guidance document published in 1989 contained a number of chapters on the basic science of mutations and their significance for human health as well as a testing strategy (an outline of the structure of the 1989 guidance is given in Annex 1). The current COM strategy was a scientifically based rationale approach to mutagenicity testing intended to update the 1990 strategy. The need to periodically reflect on developments was recognised in the 1989 guidance and prompted the review which was initiated in 1998 which eventually lead to the current test strategy. It was not developed in response to a specific regulatory request. Current regulatory mutagenicity testing schemes applied within the U.K have been developed on an EU basis and in general the term genotoxicity is used rather than mutagenicity testing to reflect the diversity of end points investigated.

2. The rationale outlined during the 2007 horizon scanning process for initiating an update is given below.

i) to provide a current scientifically based rationale for genotoxicity testing for new chemical entities and also for existing substances (e.g environmental contaminants),

ii) to provide updated advice on strategies for Government Departments and Agencies.

iii) to provide an aide when considering problems with regard to the genotoxicity assessment of chemicals.

iv) to provide advice on wider aspects previously not included (such as incorporating COM advice on mixtures and biomonitoring approaches to genotoxicity evaluation).

v) to influence wider debate on the science of genotoxicity evaluation.

Overview of process used for Guidance published in 2000

3. A brief timeline is shown in Annex 1. Initially COM members drafted a number of chapters which were designed to update the 1989 guidance (e.g. on significance for carcinogenicity and use in biomonitoring) but the final document agreed after 6 drafts including a consultation with UKEMS, IGG and internationally based testing laboratories focused on a strategy for testing alone.

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4. Key elements of the strategy which emerged during these discussions were

i) Stage 1 in-vitro tests should be undertaken first to identify mutagenic potential. The use of three in vitro tests (two in situation where there was little or no human exposure (as assessed by relevant Regulatory Authority) was designed to evaluate mutagenic end points (gene mutation, chromosomal aberrations and aneugenicity). The evaluation of potential for aneugenicity was a new development compared to the 1989 guidance. The COM recognised that the strategy could not be based solely on test methods with agreed OECD guidelines. Some elements of stage 1 such as evaluating artifactual positives and the need for independent replication of tests were largely similar to the 1989 guidance.

ii) Stage 2 proceeded based on careful consideration of results of Stage 1. The first recommended test was in-vivo rodent bone marrow or peripheral blood (mouse) Micronucleus assays or bone marrow assay for clastogenicity. The second tests undertaken for compounds negative or equivocal in first was a case-by case choice of a number of assays designed to investigate induction or repair of DNA damage or gene mutations or chromosomal aberrations in a wide range of tissues. This was a new development compared to the 1989 guidance. There was comparatively little guidance on selection of 2nd stage tests (presented in tabular form as attributes and comments on methods) although it was noted that evidence of aneugenicity seen in stage 1 should be followed up in stage 2.

iii) Stage 3 proceeded with a restatement of the conclusion reached in 1989 that compounds considered as in-vivo somatic mutagens should be assumed to have potential as in-vivo germ cell mutagens. However it was recognised that not all somatic mutagens could be demonstrated to be germ cell mutagens and a strategy based on methods for demonstrating germ cell mutagenicity/genotoxicity (dominant lethal assay or other methods for investigating DNA damage). It was considered important to initiate this stage only in cases where it was important to consider the potential for somatic mutagens to induce germ cell mutagenicity. The quantitative assessment of risk of heritable effects in future generations needed strong justification. Stage 3 of the guidance was predominantly similar to the 1989 guidance.

5. A copy of the finalised guidance is appended for member's information as Annex 2. Many of the key comments raised during the consultation related to the role of COM as an independent advisory committee to UK Government Departments as opposed to regulatory agencies with decision making responsibilities who would be assessing conformity to statutory based data requirements (both nationally and internationally required). The preface to the existing guidance document resolved these comments. It is noted that example compounds were included in the various drafts but overall these were removed from the final text which was focused on generic statements of mutagenicity evaluation.

Discussion of some objectives for COM guidance revision

Potential impact of COM guidance

6. The guidance should produce a scientifically based strategy which can be used for screening compounds (not limited to one sector such as pharmaceuticals), evaluating existing chemicals (such as contaminants) and providing case-by case guidance in specific circumstances where specific questions regarding a compound arise (e.g. evaluating genotoxicity mode of action in rodent carcinogen target and non target tissues). The current COM guidance has achieved one of its further key roles which is to influence the development of thinking and strategies by other regulatory groups. Thus US EPA has used COM guidance as a comparator on a number of occasions (cf tables abstracted from Dearfield KL et al Mutation Research (2002), 521, 121-135. and Cimino MC Environ Mol Mutagen, (2006), 47, 362-390. presented in Annex 3).

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7. When the 2000 guidance document was being drafted there were ongoing discussions on genotoxicity testing strategies from a number of international groups. Thus as the COM begins to consider a revision of its strategy there are ongoing consideration of genotoxicity testing strategy by the WHO IPCS, the EU (with regard to the strategy to be used under the REACH regulations) and by ICH (with regard to pharmaceuticals).

8. COM members have commented on the draft WHO IPCS guidance which is predominantly very similar to the COM 2000 guidance.

9. With regard to the proposed EU REACH strategy (draft RIP 3.2-2 RIP3.3-2, dated 30 November 2007 consulted) the basic strategy is predominantly consistent with the COM 2000 guidance. REACH is a new European Union regulation concerning the Registration, Evaluation, Authorisation and restriction of CHemicals. It came into force on 1st June 2007 and replaces a number of European Directives and Regulations with a single system. It is noted that the scope for using QSARs in the total weight of evidence approach is given a higher weight than in the current COM guidance to help confirm results in specific tests, or to help develop a better understanding of mutagenicity mechanisms.

10. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The COM considered the ICH strategy for mutagenicity testing in some detail during the drafting of the COM 2000 guidance. Proposals to update the ICH guidance were discussed at a conference in Yokohama in October 2007. A number of interesting themes are being developed which include;

i) An option to omit an in-vitro mammalian when two in-vivo end points have appropriate data and the weight of evidence suggests that an acceptable in-vitro mammalian cell test cannot be achieved. (This would appear to be inconsistent with the current COM guidance to complete in-vitro testing before considering in-vivo testing.)

ii) Reduce top dose in vitro mammalian cell assays from 10 mM to 1 mM, tighten acceptable toxicity limits and no longer require testing of precipitating concentrations. no need to for duplicate tests with bacterial mutagenicity assays.

iii) Integrate genotoxicity endpoints into routine toxicology studies.

iv) Advice on 2nd in-vivo assay to include comet assay and to decrease emphasis on UDS assay.

11. A number of overheads from the ICH conference are included as Annex 4 for member's information.

Scope of revision

12. It is noted from the appended timeline for the preparation of the COM 2000 guidance that the restricting the guidance to testing strategy reduced the workload to a manageable amount over the 2 year period it took to finalise the document. There were a number of generic topics such as biomonitoring and mutational signatures which were not taken forward. The 2000 guidance document was completed at a time when the COM was just beginning (from 1998) to routinely publish statement, discussion papers and minutes. There are a number of important statements which are separate to the 2000 guidance (risk assessment of in-vivo mutagens and target organ mutagenicity testing) which should be incorporated into

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any revision. In addition a number of COM discussions on thresholds for mutagenicity and current approaches to testing for thresholds (e.g. discussions on the approach suggested by Jenkins et al 2005) can only be found in the COM minutes. It is suggested that the minimum approach to revision of the COM guidance would be to bring these important topics into one document. This would also be consistent with the COC guidance (published 2004) which does contain advice on approaches to risk assessment of carcinogens as well as a testing strategy for carcinogenicity. Do Members agree?

13. The proposal from the secretariat would be to leave other topics such as mixtures and biomonitoring as separate stand alone statements. Do Members agree?

Suggested approach to revision

14. Members are asked to consider whether the first draft should be written by COM member(s) or by the secretariat. The first draft for the 2000 guidance was drafted by COM members and then alterations were done the secretariat. Do Members agree?

15. It is suggested that many of the agreements reached on terminology and strategy for the 2000 guidance would still be appropriate for any revision. Thus some time used for these discussions could be used for consideration of the key topics which now need to be considered (such as those raised by the ICH conference at Yokohama). Can Members suggest the areas that need to be considered for the revision of the Com guidance?

16. It is noted that the consultation process used for the 2000 guidance document largely relied on consulting professional groups. The COC guidance document used formalised procedures for consulting a wide range of stakeholders over a 3 month consultation period. It is suggested that this would be an appropriate approach for consultation regarding the revision for the COM guidance. Do Members agree?

COM discussion

17. Members are asked to consider the questions outlined in paragraphs 12-16 of this draft discussion paper.

18. Are there any other topics members wish to raise in connection with the revision of the COM guidance?

Secretariat December 2007

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ANNEX 2 TO MUT/08/11

DRAFT MINUTES OF FEB 2008 MEETING.

ITEM 5: REVIEW OF COM GUIDANCE: DISCUSSION PAPER ON SCOPE AND PROCESS

57. The Committee heard that the terms of reference for the COM included provision of generic advice on testing strategies and risk assessment of mutagens. The COM had previously published generic guidance documents, and this had been accomplished generally at around 10 year intervals. The COM guidance documents (1989, and 2000) had been influential both with regard to national and international approaches to mutagenicity test strategies.

58. Members also heard that the objective of the COM guidance had always been to aim for the highest level of scientific advice possible. It was noted that the operation of regulatory and advisory decision making in genotoxicity within the U.K and E.U. was very different to the situation which pertained in 2000. Thus most guidance on chemical risk assessment was now based at an international level (e.g WHO IPCS, E.U.levels) with relatively little at the national level. Thus it was suggested that revision of the COM guidance would not significantly influence the current approach used by REACH or the revision of the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) review of their guidance on mutagenicity testing (currently ongoing). However, members were informed that the COM was well placed, as an independent scientific advisory committee, to provide 'gold' standard advice, which could subsequently influence regulatory thinking. MUT/08/03 provided a copy of the existing guidance (Annex 2), information on the timeline for the previous consideration of COM guidance (Annex 1), and a discussion on potential scope for a revised guidance document. It was suggested that there was a need to include aspects of generic COM guidance which was not included in current guidance (e.g. approach to risk assessment of mutagens and approach to identification of compounds acting through potential threshold mechanisms).

59. It was also suggested that two COM members could work on an initial draft, which could be discussed at later COM meetings regarding revisions. The drafts and revisions would be published on the internet to allow a fully open process. Relevant professional groups could attend meetings during the drafting process and a consultation document would be produced.

60. The committee considered the potential scope of a new guidance document. Members recalled that previous guidance had been based on the use of well validated methods as the primary approaches to genotoxicity testing. Members agreed that the rationale for revising the COM genotoxicity test strategy and new test methods would have to be evaluated in light of recent testing developments e.g. proposals to update the ICH mutagenicity testing guidance. Members agreed that it would be important to be aware of the new approaches recommended by other authoritative bodies such as the US EPA, OECD, and UKEMS, and that views could be sought during an open committee process of producing a new guidance document.

61. Members noted a number of initial aspects which could be considered including proposals made by the ICH, e.g. an option to omit an *in vitro* mammalian test when two *in vivo* end points have appropriate data and the weight of evidence suggested that an acceptable *in vitro* test could not be undertaken, the proposal for reduction of the top dose in *in vitro* mammalian cell assays from 10mM to 1mM, the need for duplicate tests with bacterial mutagenicity assays, the integration of genotoxicity endpoints into routine toxicology studies, updating advice on the choice of a 2nd *in vivo* assay to include the comet assay (with a decreasing emphasis on the UDS assay), and the proposal that a concurrent positive control could be omitted as a routine part of *in vivo* genotoxicity assays. Members noted that

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although these were appropriate aspects to review, much of the ICH process and data evaluation was not open to scrutiny

62. The Committee agreed that it was important to emphasise in any new COM guidance document that a testing strategy could be developed with the 'three Rs' in mind (Reduction, Refinement and Replacement of animal tests).

63. Members agreed that there was a need to include advice on the use of QSAR data in any proposed revision of the testing strategy for mutagenicity. Members were aware of proposals for greater use of QSAR information as part of the REACH strategy for chemical risk assessment. The committee also recommended that advice on the use of human biomonitoring data, which had been the subject of extensive COM consideration over the past few years, should be included. This would include inclusion of biomonitoring data within a genotoxicity testing strategy and also the use of biomonitoring data in the risk assessment process.

64. The chair suggested the secretariat circulate a proposed scoping paper between meetings and that the scope of the COM guidance document was considered at the 12 June 2008 COM meeting. It was noted that the proposals to include more information on consideration of the evaluation of potential thresholds for genotoxicity and biomonitoring would make the proposed revised COM guidance more similar to the current COC guidance document (Guidance for the risk assessment of chemical carcinogens) which had been published in 2004.

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ANNEX 3 to MUT/08/11

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OVERALL SUMMARY

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APPENDIX A:

A suitable procedure for use of the in-vitro micronucleus test

to for detection of clastogenicity and aneugenicity

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APPENDIX B:

List of Members

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ANNEX 4 to MUT/08/11

COMMENT FROM MHRA

Committee on Mutagenicity

Scope of revision of COM guidelines

I note that the evaluation of evidence for threshold mechanisms of mutagenicity is one of the topics proposed to be included in the review of the COM guidelines. I strongly support this proposal and consider this to be an important and timely topic for consideration, particularly in light of recent published literature:

In vitro evidence for pragmatic threshold of genotoxicity of EMS in human cells; Doak et al. *Cancer Res* 67, 2007, 3904-3911

Background

It has been assumed that a linear relationship exists between exposure to DNA reactive genotoxins, the induction of DNA lesions and their conversion to mutagenic alterations. However, mammalian cells have some homeostatic mechanisms that provide protection to a certain extent e.g. DNA repair. These mechanisms initially prevent damage from becoming a permanent defect until they become saturated, thus resulting in a no observed effect level (NOEL), the experimental concentrations below which no statistically significant increase in mutations is detected. However, the existence of such a threshold effect for compounds with carcinogenic potential is still controversial. Currently, there is only limited data with regard to the kinetics of mutation induction in the low-dose region.

DNA-reactive chemicals have been assumed to have a non-threshold mode of action, as they directly induce DNA lesions that have the potential to be fixed as point mutations or chromosomal aberrations. However, homeostasis in mammalian cells allows them to adapt to chemical insults, which may be predicted to limit genetic damage, therefore introducing a range of low doses that have biologically insignificant effects (i.e. NOEL). Determining the existence of threshold dose responses for genotoxic compounds has important implications because exposure to low concentrations within the NOEL would carry little carcinogenic risk as DNA aberrations are not fixed, thus they have no biological significance or further consequences on the cell.