

Guidance on a Strategy for Genotoxicity Testing and Mutagenic Hazard Assessment of Chemical Substances

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

Response from U.S. Environmental Mutagen Society

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To: Ms. Sue Kennedy

CC: Mr. J. Battershill
Dr. K. Burnett

Ms. Kennedy:

On behalf of the US Environmental Mutagen Society, we would like to thank you for the opportunity to review the draft document: “Guidance on a Strategy for Genotoxicity Testing and Mutagenic Hazard Assessment of Chemical Substances”.

We have reviewed the current draft against the current published recommendations of 2000. We are in agreement with a number of the proposed changes to the current strategy and the background, rationale and workflow presented. Namely:

1. Use of in silico/(Q)SAR tools or assessments to identify probabilities of mutagenic hazards
2. Use of a staged approach
3. Performance-derived decision to reduce the Stage 1 in vitro testing to two assays
4. Inclusion of in vitro micronucleus test as a core in vitro assay to attain mechanistic understanding of the hazard
5. Effort to reduce animal usage:
 - Use of one sex if appropriate
 - Reduction of sample times for in vivo cytogenetics assays
 - Studies where multiple endpoints are evaluated
 - Less emphasis on stage 3 germ cell mutation evaluation as a stand alone

6. Change in emphasis of several tests from core to non-core, such as the mouse lymphoma and the in vivo UDS assay.
7. Inclusion of the peripheral blood micronucleus test using rats as an acceptable core in vivo assay.
8. Rationale and comments on a number of the non-core assays and possible future assays that could be considered, which rounds out the understanding and current state of genotoxicity testing.
9. The flow charts nicely summarize the text

Please see below a few comments and some editorial items for consideration:

Conceptual Comments:

1. Paragraph 15: For many chemicals, in vitro positives will be followed up with a Stage 2 assessment that may consist of multiple tests, such as an in vivo micronucleus assay and a Comet test in one or more tissues. However, it should be acceptable, as mentioned in paragraph 65, to combine multiple in vivo endpoints into one test. Therefore, we suggest some language be added with regard to assessing multiple appropriate genotoxicity endpoints in one set of test animals as being acceptable vs. multiple tests.
2. Stage 0 section (starting on page 11): To facilitate easy reading of this section where there are multiple references to web-sites and listings of (Q)SAR tools, we suggest that the list of available tools be provided in an appendix or table and text of the section describe the major concepts of such models. An example is page 12, lines 15-27.
3. Paragraph 41 (page 19 and 20): we have some concern about the potential for misinterpretation of the intent of Stage 1 studies using metabolic activation. While no in vitro test system perfectly correlates with in vivo hazard, we have a concern with the language used in paragraph 41 that well-conducted, routine in vitro assessments that are negative, especially if (Q)SAR or other expert analysis indicates the potential for mutagenicity with metabolic activation, will be deemed inadequate and Stage 2 tests be requested by regulatory authorities. We feel a

stronger suggestion that these misleading false negatives are rare and additional measures to investigate negative responses through the standard metabolic conditions should be equally as rare.

Minor Editorial Comments:

Page 15, line 28: remove the period after the word “compounds” to keep consistent with the syntax for references.

Page 21, line 9: remove the word “Thus”. Otherwise, you’ll be starting consecutive sentences with “Thus”

Page 23, line 8: reverse word order: “historical negative control data” rather than “negative historical control data”

Page 32, paragraph 65, line 25-26: Since this is the first time in the document that the in vivo comet test is being mentioned, in relation to integrating the comet end points we suggest a change in wording “Integration of in vivo genotox endpoints into repeat-dose studies (see section 79-80) or something similar.

Figure 3, in the stage 2 box: spelling of “rationale”