

February 14, 2011

To: Sue Kennedy (Sue.Kennedy@hpa.org.uk)
Committee on Mutagenicity of Chemicals in Food, Consumer Products, and the Environment (COM)

Submitted by:

Kristie Sullivan, MPH, for the Physicians Committee for Responsible Medicine

RE: Comments on: GUIDANCE ON A STRATEGY FOR GENOTOXICITY TESTING AND MUTAGENIC HAZARD ASSESSMENT OF CHEMICAL SUBSTANCES

I. General Comments

We find this document to be an informative and thorough look at the available options for investigations of the genotoxicity potential of a substance. Overall the COM has made an effort to communicate to the reader the importance of the 3Rs and of minimizing as much as possible the consideration of animal use and animal welfare when designing such investigations.

We very much support the discussion in the guidance of a case-by-case approach--a "menu" of tests to consider instead of a list of tests to check off (as outlined in paragraphs 15, 19 and 63. Especially for the *in vivo* tests, the results of *in vitro* tests and other information should guide what *in vivo* tests, if any, will be done. To strengthen this approach, we recommend the suggestion be made to return to *in vitro* or other non-animal investigations (Stages 1 or 0) whenever possible before considering Stage 2 "Supplementary [*in vivo*] tests" (paragraph 82).

The COM makes a distinction between situations in which *in vivo* testing is not allowed and where it is allowed (i.e. cosmetics versus pesticides, etc), and indicates that in most cases, positive *in vitro* findings should be followed up with *in vivo* tests, and in some cases, negative *in vitro* findings should be followed up with *in vivo* tests as well (where such testing is allowed). This is because it is claimed that *in vitro* tests are too sensitive. However, none of the details of sensitivity and sensitivity for *in vivo* tests are provided--was it considered by the COM? In paragraph 18, the clause, "...the use of animals in mutagenicity testing is primarily required when it is necessary to investigate whether genotoxic activity detected *in vitro* is reproduced *in vivo*..." sounds as if all positive *in vitro* genotoxicity results should lead to Stage 2 (*in vivo*). We urge the COM to consider identifying situations in which, even if it is allowed, further *in vivo* testing is not recommended to follow up on potential *in vitro* "false positives."

Finally, we note that there does not seem to be a discussion of whether substances that are positive (either *in vitro* or *in vivo*) are usually tested in the carcinogenicity bioassay. This is an important consideration when determine which genotoxicity tests should be conducted and whether results should be followed up with further testing.

II. Specific Comments

- A. Figure 3 is missing, at least in our copy.
- B. In paragraph 19, Step 4, there is mention of repeating tests. Suggest including or referencing criteria for repeating tests based on identifiable deficiencies in the previous study, such as the Klimisch criteria, urging the reader to avoid repeating studies if at all possible, and consideration of combining results from “less than ideal” studies together in a weight-of-evidence approach in an effort to avoid repeating studies.
- C. The use of “Stage 0” is referred to in Figure 2, but not in the text; we suggest it should be.
- D. There is quite a lot of information on SAR resources, which is excellent. We suggest also referring to resources to find existing data such as the OECD eChemPortal, ToxRefDB, and TOXNET.
- E. In paragraph 26, the sentence referencing Combes et al 2007 (the use of QSAR to aid in interpretation of *in vitro* findings) is an important point and we wonder if this could be emphasized or discussed in more detail.
- F. In paragraph 34, there is discussion of investigation of positive *in vitro* results in *in vivo* tests in order to understand their relevance, except where not possible (i.e. cosmetics). A consideration of Mode of Genotoxic Action (MoGA) investigations using *in vitro* tests should be considered first even for non-cosmetic sectors.
- G. Again in paragraph 37, there is evidence that genotoxicity tests “using human reconstructed skin may provide useful information...” but do not believe it should be limited to “circumstances where *in vivo* testing is not permitted...” In fact these assays can provide information on the metabolism of substances and so could be quite useful for all substances with the potential for dermal contact.
- H. Paragraph 84, line 26: Recommend: “This may involve repeating some aspects of the recommended *in vivo* genotoxicity tests, or performing supplementary *in vitro* or *in vivo* investigations...”

Thank you for consideration of these comments. Questions can be directed to the author at the contact information below.

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