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Dr. Jerry Smrchek
U.S. National Coordinator for the
OECD Test Guidelines Program
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Mail Code 7403M
Washington, DC 20460

Dear Dr. Smrchek:

On behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), we are pleased to provide the enclosed general comments on the revised version of the proposed draft OECD Test Guideline (TG) 487 "*In Vitro* Micronucleus Test." These comments are in response to your January 4, 2007 notification that the OECD had requested comments on this revised TG.

There are two comments that we specifically want to bring to your attention.

First and foremost, the OECD needs to fully recognize the importance of providing sufficient time for draft TGs to be adequately considered and evaluated by national experts. Providing critical background information with only a few days to consider is entirely inappropriate. It is critical to the success of the TG program and the acceptance of data under MAD that all supporting materials should be made available with sufficient time for consideration. Thus, the review process should be delayed to allow for: (1) the significant issues raised by the ESAC Peer Review to be addressed, and (2) careful consideration of the total data package by member countries. We note that the final and critically important ESAC Peer Review document was received only on 30 January, allowing only one day for consideration, in order for comments from representatives of 15 U.S. Federal agencies to be collated, reviewed, and submitted to the U.S. National Coordinator in time to meet the OECD mandated deadline. Thus, although we provide comments, we request that the OECD delay the 15 February due date to allow for due consideration of all of the supporting documents. We also request that, in the future, the OECD take into account the critical importance of the TG review process and provide sufficient time (at least two months, but preferably three) to ensure an adequate review. Otherwise, it could create the appearance that the OECD cares more about schedules than making sure that a TG meets the needs of GD 34 and the regulatory and scientific community.

Second, the purpose of validation is to determine the usefulness *and* limitations of a test method for a specific purpose. The data used to support validation of the *in vitro* micronucleus (MN) assay leaves several critically important questions unaddressed. These questions include how and whether it is appropriate to use cytochalasin B (CB) for cell lines, the method(s) by which cytotoxicity should be measured when CB is not used, and the maximum level of cytotoxicity appropriate for a valid test. The validation data sets, while more extensive than those used to validate some of the older test methods when their guidelines were first approved, are less extensive than those available for several recently validated test methods and do not cover all product categories (e.g., food additives) or functional classes (e.g., a sufficient number of aneugens,

chemicals that require metabolic activation). Use of the protocol described in this guideline is clearly appropriate in certain circumstances (e.g., as a preliminary screen or as a follow-up test in the case of an ambiguous result in another assay or battery). However, the available published data do not support the substitution of the *in vitro* micronucleus assay for *all* current uses of the *in vitro* chromosome aberrations assay. In particular, we do not agree that it is, at this time, appropriate to substitute this test guideline for TG 473 in standard batteries designed to detect agents that interact with DNA to cause genetic damage. In fact, because the two different assays each provide unique information, the *in vitro* MN test, even when adequately validated, should not be considered a replacement for the *in vitro* chromosomal aberration test but rather as another test that might be used to evaluate the mammalian cell genotoxicity of a test compound. In any case, it is not the role of an OECD TG to determine how the results of the test should be used within an overall safety evaluation. Such comments should be eliminated or altered to make it clear that the TG does not include a recommendation of how the results of the test are to be interpreted beyond the finding that the test article does or does not induce chromosomal damage under the conditions of the test. However, we do agree that it is useful to describe the context for why this test might be conducted. We also agree with the comment from Canada that the purpose and intended use of the test should be clarified.

We appreciate the opportunity for the ICCVAM to provide comments on this draft TG. If you have questions or concerns regarding these comments, please contact me or Dr. Marilyn Wind (301-504-7246).

Sincerely,

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Director, NTP Interagency Center for
the Evaluation of Alternative
Toxicological Methods (NICEATM)

Marilyn L. Wind, Ph.D.
Chair, Interagency Coordinating
Committee on the Validation of
Alternative Methods (ICCVAM)

Enclosure

cc:
Dr. Michael Cimino, EPA
ICCVAM
ICCVAM Genetic Toxicity Working Group