UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-89-005

October 15, 1988

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of issues relating to the proposed MALE AND FEMALE REPRODUCTIVE GUIDELINES

Dear Mr. Thomas,

The Science Advisory Board's Environmental Health Committee has completed its review of the issues pertaining to the proposed male and female reproductive guidelines at its meeting July 14-15, 1988 in Washington, D.C..

The major recommendations of the Committee includes; combining the guidelines for male and female reproductivity into one guideline, including illustrative examples in the support document, expanding the weight-of-evidence section to give more detail concerning the relative importance of different endpoints and investigating dose-response models that may be useful additions to the threshold no-observed level approach.

We appreciate the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice provided herein.

Sincerely,

Norton Nelson
Chairman, Executive Committee

Richard A. Griesemer
Richard A. Griesemer
Chairman
Environmental Health Committee

SUBJECT: SCIENCE ADVISORY BOARD'S REVIEW OF ISSUES RELATING TO MALE AND FEMALE REPRODUCTIVE GUIDELINES

SCIENCE ADVISORY BOARD COMMITTEE: THE ENVIRONMENTAL HEALTH COMMITTEE

DATE OF REVIEW: JULY 14-15, 1988

PLACE OF REVIEW: HOLIDAY INN GOVERNOR'S HOUSE, WASHINGTON, DC

Introduction

Reproductive toxicology is a young field, and the process of risk assessment for reproductive effects has yet to be developed. Given the difficult nature of this task, the EHC believes that the Reproductive Effects Assessment Group is to be congratulated for their efforts in preparing this draft of the guidelines. The evolving nature of this field will warrant frequent review and revision of these guidelines to reflect new developments in the science of reproductive toxicology.

Recommendations of the SAB Environmental Health Committee

1. The Environmental Health Committee (EHC) recommends that EPA combine the guidelines for male and female reproductive risk assessment. Eventually sufficient new information may be obtained to justify separate guidelines. We believe the scientific issues are best addressed with a single document.

2. EHC recommends that a technical support document be prepared to provide illustrative examples. These examples should illustrate the type of information available, and the scientific judgments involved in the risk assessment process. These illustrative examples should be used in the guidelines document to clarify the discussion of general principles.

3. EHC recommends that the weight-of-evidence section be expanded to include discussion of the relative importance of the various endpoints, and the quantitative determination of what constitutes a biologically significant change in an endpoint. What, for example, is an acceptable reduction in reproductive performance? Judgment on the relative importance of the endpoints will often be critical in the risk assessment process. Also, a single endpoint may not be sufficient for hazard identification. It will be advisable to consider the weight-of-evidence of related endpoints collectively.

a. EPA should designate as a research need the evaluation of biological relevance of the various endpoints, and the comparison of animal assays with these endpoints in humans.

b. EPA should expand the discussion in the guidelines of how to weigh evidence of reproductive toxicity when other target organ or general systemic toxicity is observed. While the EHC agrees that reproductive effects observed at dose levels affecting other organs should not be ignored, we conclude that the weight of evidence should be substantially reduced if reproductive toxicity is observed only at levels toxic to other organ systems. In any case all endpoints should be mentioned.

4. EHC recommends that EPA refine its weight-of-evidence classifications in Table 2.

a. EPA should establish standards for what constitutes "a convincing body of evidence," for both the positive and negative categories. The technical support document should provide examples on which such standards might be based. Application of the standards may involve many aspects of scientific judgment.

b. The standard for "probable negative" is particularly difficult to define. What set of studies would provide convincing that none of the adverse endpoints occur in humans or in animals?

c. EPA should define what constitutes a minimal data set for a positive, that is, identification of a reproductive hazard based on one or more endpoints.

d. The dose at which the effect is produced must be a major consideration in hazard identification. Because of secondary effects, most substances will test positive at some dose.

e. The "probable positive" category should not include agents for which there is convincing evidence that the mechanism(s) by which an agent causes adverse reproductive effects in one or more mammalian species are not applicable to humans.

f. The difference between the "possible negative" and the "possible positive" categories is not clear, and the distinction between these categories may not serve a useful purpose. We recommend that these two categories be merged into the "no data/inadequate data" category.

5. EHC recommends that the full set of dose-response data be used as the basis for the risk assessment and that EPA not restrict its approach to a reference dose based on a NOAEL. The reference dose approach does not allow for a quantitative risk assessment. Fitting one or more dose-response models in the risk estimation process may be useful in addition to conventional

NOAEL approach. Extrapolation using a model can be based on the full dose-response data set, while the NOAEL reflects one data point. The determination of a NOAEL as the highest level failing to yield a statistically significant response compared to controls implies that this determination will depend on the quality of the test and the sensitivity of the endpoint. Uncertainties in the dose-response estimates should be made explicit by stating confidence intervals around estimates and discussing the assumptions and biological plausibility underlying the choice of the dose-response model(s).

6. EHC recommends that EPA review and revise as necessary the reproductive toxicity testing guidelines, so that the resulting data provide the best possible basis for reproductive risk assessment.

U.S. ENVIRONMENTAL PROTECTION AGENCY
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ENVIRONMENTAL HEALTH COMMITTEE
July 14-15

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