



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

July 19, 1984

OFFICE OF  
THE ADMINISTRATOR

Dr. John A. Moore  
Assistant Administrator for  
Pesticides and Toxic Substances  
Environmental Protection Agency  
Washington, D.C. 20460

Dear Dr. Moore:

This letter responds to your memorandum dated April 18, 1984, in which you requested Science Advisory Board comments on a paper prepared by your office titled "Design Options for a Retrospective Validation Study of PMN Health Hazard Assessments." This paper was discussed by the Science Advisory Board's Environmental Health Committee (EHC) at a public meeting on May 9-10, 1984. A summary of the Committee's positions, recommendations, and questions as prepared by Dr. Ronald D. Hood and accepted by the Committee at its meeting on June 7, 1984, is attached. Also attached are additional comments by Dr. James G. Gibson. A copy of the transcript of the May meeting has been sent separately to you and your staff with a cover note dated May 14, 1984.

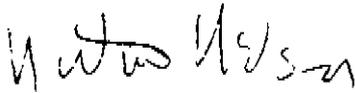
Given that the dialogue between the Office of Toxic Substances (OTS) and the EHC is in process and at an early stage (for example, the discussion has not yet focused in detail on which chemicals to test or how to analyze the data statistically), the EHC summarizes its advice as follows:

- (1) The Committee supports the concept of an experimental validation study.
- (2) The Committee concurs with the OTS approach taken to validation. The EHC feels that the proposed tests also could be used to generate useful new information to improve the screening process.
- (3) The Committee is concerned that the proposal places relatively too much emphasis on carcinogenicity and teratogenicity, while not sufficiently addressing other health effects.
- (4) The Committee suggests that OTS look for assistance to concepts developed in the fields of decision-making under uncertainty and/or artificial intelligence.
- (5) The Committee advises OTS to look towards improved information management procedures.

The Committee appreciates the opportunity to comment on this paper and stands ready to provide further consultation.

Sincerely,

  
Herschel E. Griffin, Chairman  
Environmental Health Committee

  
Norton Nelson, Chairman  
Executive Committee

Attachments (2)

Summary of the SAB's Positions, Recommendations, and Questions Regarding "Design Options for a Retrospective Validation Study of PMN Health Hazard Assessments"

compiled by Ronald D. Hood

The SAB was in agreement with the concept of a validation study with regard to the use of Structure/Activity Relationships (SAR) in the EPA's Premanufacturing Notification (PMN) program. An attempt will be made in the following to present major points raised by SAB members.

#### General Approach

There was general approval of the proposed basic approach to validation. It was also said that the proposed tests could be used to generate useful new information in addition to merely validating the EPA process. It should be stated as an objective that the new information generated would be used to improve the overall screening process rather than merely to validate the process now in use. Additional concern was voiced that the proposal placed too much emphasis on carcinogenicity and teratogenicity, while slighting other health effects.

#### Study Design and Test Selection

It was suggested by OPTS that an appropriate starting point would be to ask what type of information is actually needed and then decide how to best get the relevant data. SAB members suggested that it is important that this opportunity be used to clearly define and improve the decision making process of "judgement under uncertainty" and that methodology based on decision theory, "artificial intelligence" concepts, and the like could be incorporated into the evaluation process used by OTS. Also, a formal information management system would aid in effective use of the large amounts of information generated. Questions were raised such as: 1) will the OPTS study be coordinated with test development efforts of the NTP,

2) will any kind of information regarding metabolism or pharmacokinetics be included at any test level, 3) is prediction of metabolism a goal of the SAR Program, and 4) will the OPTS look into the costs associated with misclassifications, as did the NAS? Further, it was proposed that chemicals evaluated in the PMN system be given a numerical rating that expresses the degree of confidence in that chemical's toxicity assessment.

It was also suggested that even though use of too many tests or tests that were too costly would be prohibitive for the PMN program, OPTS should use whatever tests were needed in the validation study, and that the validity of the present SAR approach was inseparable from individuals doing the assessments. It was thought that an appropriate use of the tier system would be to apply low level tests first and follow up with specific higher level (and presumably more definitive) tests as needed, and that OPTS should test where the most information appears to be needed. It might further be possible to make use of the extensive and detailed toxicology data accumulated by other agencies, such as the FDA. Such data, if made available, could be plugged into the SAR formula development and should be particularly informative with regard to presence and types of biological activity to be expected from a wide variety of molecular structures. This could in particular yield information on structures with little or no toxicity - the sort of "negative data" that seems to be in short supply. OPTS also raised the question of how judgements could be made regarding the accuracy of the calls made by the SAR method and how such accuracy could be rated; the need for written guidelines was expressed.

#### Selection of Chemicals

A number of comments were made about selection criteria for test chemicals, as this was considered a very important yet somewhat weak area of the OPTS proposal. Concern was expressed regarding the proposed exclusions. For example, chemicals excluded on the basis of low volume might later become high

volume chemicals, and many of the current low volume chemicals may be useful for inclusion, as there is a considerable existing body of toxicological data associated with them. The elimination of chemical intermediates was also challenged on the grounds that such compounds may appear as residues in finished products or may be released in industrial accidents resulting in unplanned human exposure. It was also suggested that perhaps even high molecular weight, relatively insoluble polymers be tested as representative of the presumptive universe of non-toxic materials. OPTS responded to these concerns with comments that even though certain categories of compounds were omitted, the variety of chemicals among those remaining should be an adequate sample of molecular structures. In addition, finite resources would not allow for the testing of all possible compounds in a validation study.

COMMENTS ON  
DESIGN OPTIONS FOR A RETROSPECTIVE VALIDATION STUDY  
OF PMN HEALTH HAZARD ASSESSMENTS

BY  
JAMES E. GIBSON  
CONSULTANT TO EPA-SAB  
MAY 10, 1984

I agree with the objective of OPTS to validate the extent to which "SAR provides an adequate basis for evaluating the potential health hazards of 'new' chemical substances." The weakness of the present biological data base for effectively using SAR clearly supports the need to strengthen that data base. The OPTS proposal would seem to fulfill that need. Certain problems with the proposed study design may prevent achievement of the objective, however.

First of all the proposal refers to SAR as "a combination of submitted toxicity data, data available on analogous substances, and the professional judgments of scientific assessors". This presents several problems as follows: 1. Less than 50% of PMN's are submitted with accompanying toxicity data; 2. There are no methods outlined for assessing the available data on analogous substances; and 3. The credentials of the "professionals" that will be the "scientific assessors" are not outlined or described in any way.

Regarding point 1. there can be no input if data do not exist. On point 2. it must be appreciated that the volume of literature from which the data must be drawn is so large "as to defy the ability of any individual to recall an adequate expanse of data" as pointed out by Golberg in a 1983 monograph entitled STRUCTURE-ACTIVITY CORRELATION AS A PREDICTIVE TOOL IN TOXICOLOGY; FUNDAMENTALS, METHODS, AND APPLICATIONS (Hemisphere Publishing Corporation, Washington). Further on this point one finds no reference to this work in the OPTS proposal although it deals with exactly the same subject. Moreover the OPTS proposal seems to have missed an opportunity to capitalize on the findings and advice of the many experts in this important research field that contributed to the Golberg monograph. Point 3. really needs no comment so long as the personnel charged with the important assignment proposed are sufficiently trained and experienced for the task.

Two issues overlooked in the OPTS proposal are as follows: 1. Biochemical mechanisms underlying toxic actions in whole animals, and 2. The use of the relationship between molecular structure and biological activity. Both of these subjects are dealt with in depth in the Golberg work.

For example one wonders how OPTS will utilize the chemical and toxicological data bases for assessing SAR relationships. There must be a firm proposal as to what the data bases will be, how they will be searched, how complete they will be, and in what way correlates between structure and toxicity will be made. Since the present proposal does not cover these topics, it is judged inadequate with respect to this point.

On the point of biochemical mechanisms one wonders why the proposal does not suggest the use of metabolism and pharmacokinetic studies somewhere between short term tests and subchronic or chronic bioassays. There is much to be learned here. Certain chemicals may be readily excreted or inactivated. Perhaps they are not absorbed. The in vitro tests proposed do not address these points. Since one presumes that the concerns for the potential toxicity of PMN chemicals is largely related to human health, or at least whole animals, this is not a trivial issue.

The emphasis on, and concern for, "false negatives" in the proposal is interesting. Understandably these are to be minimized, or eliminated, if possible. However, it is equally important to validate means by which to minimize, or eliminate, false positives. The proposal should be responsive to this concern. It need not be more expensive, or time consuming, to focus on both issues simultaneously.

The selection of the toxicity tests raises important technical concerns, as suggested in the proposal. As presented there are no innovative ideas put forward. The approach is entirely standard with the same old tests that have existed for years. At a minimum some effort should be made to parallel the testing programs being implemented by the NTP. Of course the status of the NTP program is not presently set. A draft entitled REPORT OF THE AD HOC PANEL ON CHEMICAL CARCINOGENESIS TESTING AND EVALUATION OF THE NATIONAL TOXICOLOGY PROGRAM: BOARD OF SCIENTIFIC COUNCILLORS addresses some fresh approaches that might form the basis of a revised proposal. In the Ad Hoc Panel draft the use of metabolism and pharmacokinetic data is discussed and a recommendation is made that such data be collected. As discussed above the information may be useful in ascertaining the "delivered dose" at target sites following an "administered dose".

On the subject of Selection of Chemicals a few comments are in order. It is agreed that the test set chemicals could exclude those recognized for various reasons to have "low hazard potential". While it is true that the selection of chemicals for study from the those remaining could be random, this misses an opportunity to explore the utility of existing SAR methodology. In other words these known methods should be used to develop a stronger basis for stating the "potential presence or absence of a toxic effect".

At present this reviewer cannot recommend an option, from the options presented, the one that is best for the proposed validation study. It is agreed however that such a validation study is needed. A restructuring of the proposal with an eye toward the comments mentioned above could lead to an appropriate study design to accomplish the study objectives.