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

EPA-SAB-EHC-90-013

OFFICE OF
THE ADMINISTRATOR

April 23, 1990

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development document Proposed Amendments To The Guidelines For The Health Assessment Of Suspect Developmental Toxicants, 54 FR 9386-9403

Dear Mr. Reilly:

On March 6, 1989, EPA proposed amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants. These amendments expanded and clarified points made in the original guidelines and added new information based on advances in the field.

The Science Advisory Board (SAB) was asked to focus on the major proposed amendments to the Guidelines, and to comment on other aspects of the Guidelines. The charge to the SAB's Environmental Health Committee contained the following elements:

a. Assess the technical changes to the Guidelines for sound scientific support.

b. Review the proposal to use broad weight-of-evidence categories.

c. Review the applicability of the (RfD_{DT}) concept of a reference dose for developmental toxicity.

d. Review the proposed changes in the relationship between maternal and developmental toxicity.

e. Discuss alternative approaches to risk assessment for developmental toxicity.

The Environmental Health Committee met on October 27, 1989, in Bethesda, Maryland to receive briefings from Agency officials involved with the development of the proposed Guidelines revisions, and to discuss in detail the issues noted above.

With two exceptions, the Committee considers the proposals to be adequately founded in toxicological and teratological science, and to reflect the current status in these fields. There are minor technical points which the Committee believes could be improved or presented more clearly. Such items need attention, but do not detract from the overall competency of the proposals. Consequently, comments on these points have been supplied separately to the Agency, and are not addressed in the report.

As noted, there are two areas in which the Committee suggests the need for significant rethinking and revision. First, the weight-of-evidence classification scheme tends to be confusing vis-a-vis current Agency and general usage, and still reflects too strongly its origins in the classification of carcinogenicity as an unitary endpoint, rather than the multiple possible developmental outcomes of exposure to developmental toxicants. Functionally, it does not provide a more powerful conceptual basis for risk assessment in the developmental area than now exists. A more powerful system or scheme would provide a biological, functional basis for assigning priorities to the questions which arise during an assessment by offering a closer coupling between dose and the nature of the expected outcome(s).

The possibility of a decision analysis-based approach, as noted in the report, is attractive, and is offered for consideration with the understanding that considerable effort would be required for implementation. The Agency is advised to consider it, along with any other methodology which could move towards a more conceptually powerful, yet more economical, biologically-based approach to developmental risk.

The same rationale underlies the Committee's thoughts on the subject of the RfD_{DT} and alternative approaches to assessment. The traditional LOAEL/NOAEL process ignores available data, is somewhat insensitive to trends in the data, and ignores the uncertainty in the level of risk at the NOAEL. It tends to reward less statistically precise studies by translating their results into

higher RfD levels and so provides a disincentive to better science. The benchmark dose approach discussed in the report avoids these problems, and is the subject of a growing body of literature (including some fine contributions by EPA staff scientists). It seems to be the next logical step towards uniform risk assessment, and the Agency is urged to begin moving in this direction by incorporating such an approach in the Guidelines to be used in conjunction with the current approaches.

The Science Advisory Board is pleased to have had the opportunity to review the proposed revisions to the Guidelines and to offer its advice. We would appreciate your response to the major points we have raised.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Arthur C. Upton

Dr. Arthur Upton, Chairman
Environmental Health Committee

EPA

U.S. Environmental
Protection Agency

Washington, DC
EPA-SAB-EHC-90-013

Report of the Environmental Health Committee

Review of Proposed Revisions to the Guidelines for Health Assessment of Suspect Developmental Toxicants (54 FR 9386-9403)

A SCIENCE ADVISORY BOARD REPORT

April, 1990

U. S. ENVIRONMENTAL PROTECTION AGENCY

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1.0 Executive Summary On March 6, 1989, EPA proposed amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants (Proposed Amendments To The Guidelines For The Health Assessment Of Suspect Developmental Toxicants, 54 FR 9386-9403). These amendments expanded and clarified points made in the original guidelines and added new information based on advances in the field.

The Science Advisory Board was asked to focus on the major proposed amendments to the Guidelines, and to comment on other aspects of the Guidelines. More specifically, the charge to the Environmental Health Committee contained the following elements:

a. Assess the technical changes to the Guidelines for sound scientific support.

b. Review the proposal to use broad weight-of-evidence categories.

c. Review the applicability of the (RfD_{DT}) concept of a reference dose for developmental toxicity.

d. Review the proposed changes in the relationship between maternal and developmental toxicity.

e. Discuss alternative approaches to risk assessment for developmental toxicity.

The Environmental Health Committee met on October 27, 1989, in Bethesda, Maryland to receive briefings from Agency officials involved with the development of the proposed Guidelines revisions, and to discuss in detail the issues noted above.

The Committee supports many of the proposed revisions to the Guidelines; there are, however, areas in which improvements could be made. Detailed comments on specific technical items have been furnished to the Agency. These items notwithstanding, there was a consensus that the proposed revisions were adequately founded in developmental toxicology and represented a step forward for EPA. The Agency is advised to revisit the weight-of-evidence scheme proposed, in order to avoid confusion with more commonly applied

uses of such classifications, and to develop a more powerful conceptual approach. Further, the Agency should begin to move away from the current use of the No Observed Adverse Effects/Lowest Observed Adverse Effects Level (NOAEL/LOAEL) basis for calculating the Reference Dose, to a benchmark dose/confidence limit approach, tied to empirical models of dose-response relationships.

2.0 Introduction The U.S. EPA published proposed and final Guidelines for the Health Assessment of Suspect Developmental Toxicants in November, 1984 (49 FR 46324) and September, 1986 (51 FR 34028), respectively. These guidelines represented a consensus of the scientific community in developmental toxicity on how to interpret data in this area. However, shortly after the final guidelines were published, it became apparent that a good deal of new information had become available that should and could be incorporated into the Guidelines. Therefore, on March 6, 1989, EPA proposed amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants (Proposed Amendments To The Guidelines For The Health Assessment Of Suspect Developmental Toxicants, 54 FR 9386-9403). These amendments expand and clarify points made in the original guidelines and add new information based on advances in the field.

The Science Advisory Board was asked to focus on the major proposed amendments to the Guidelines, in addition to commenting on other aspects of the Guidelines. The major changes are summarized below:

a. The original risk assessment guidance was developed around several basic assumptions that were implicit but not stated in the earlier document; in the proposed amendments, these are clearly stated.

b. Several consensus workshops were held following completion of the 1986 guidelines and the conclusions of these workshops have been incorporated as revisions to the guidelines. Areas affected as a result of these workshops include the relationship of maternal and developmental toxicity, the status of the Chernoff/Kavlock assay, and the development of an approach for a weight-of-evidence classification.

c. A reference dose for developmental toxicity (RfD_{DT}) is proposed which is based on short-term exposure as is used in

assessing developmental toxicity potential. This approach is distinguished from the RfD, which usually applies to chronic or long-term exposures.

d. The functional developmental toxicity section has been expanded to reflect the Agency's recent testing guidelines for assessing potential developmental neurotoxicity.

e. An expanded human studies section now gives more guidance on the use of human data in risk assessment.

f. A number of other proposed minor changes are discussed in the Supplementary Information section of the Proposed Amendments.

3.0 Detailed Charge More specifically, the Environmental Health Committee was asked to:

a. Assess the technical changes to the Guidelines for sound scientific support.

b. Review the proposal to use broad weight-of-evidence categories.

c. Review the applicability of the RfD_{DT} for developing short-term reference dose estimates for developmental toxicity.

d. Review proposed changes in the relationship between maternal and developmental toxicity.

e. Discuss alternative approaches to risk assessment for developmental toxicity. In particular, address alternatives to the National Academy of Science/National Research Council model, as well as more quantitative approaches to risk assessment than the RfD_{DT} approach (It was anticipated that the points in this element of the charge, because of their nature, could best be addressed in concert with the other aspects of the charge listed above rather than as a "stand alone" section. Consequently, these issues are addressed as part of the discussion in section 4.3).

To carry out the charge, the Environmental Health Committee met on October 27, 1989, in Bethesda, Maryland to receive briefings

from Agency officials involved with the development of the proposed Guidelines revisions, and to discuss in detail the issues noted in the Charge.

4.0 Detailed Findings

4.1 Assessment of Technical Support of Proposed Changes It was the consensus of the Committee that the changes generally had adequate rationale and support. It was felt that the changes were not only proper, but that they moved the Guidelines forward in terms of current thinking. Specific comments were addressed to five basic assumptions underlying the proposed revisions.

4.1.1 Assumptions Regarding Adverse Effects in Animals The revisions state that, "An agent that produces an adverse developmental effect in experimental animal studies is assumed to pose a potential hazard to humans following exposure during development." This is a proper, conservative stance. The assumption is consistent with our knowledge of biology, toxicology, and clinical experience to date. If there are exceptions, they do not provide a basis for ruling out this position based on chemical structure of a specific agent under consideration, or the type of response observed in a specific instance.

4.1.2 Manifestations of Developmental Toxicity It is posited that all four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are of concern. Although the relative importance of the four manifestations is not well established, there is general agreement that the assumption is sound.

More specifically, the importance of structural variations is not agreed upon by developmental toxicologists. Some workers feel that variations are as important as malformations or fetal deaths; others regard variation as less predictive of adverse effect in humans than more serious manifestations of developmental toxicity. In addition, we have less experience in detecting functional alterations, as well as less experience in looking at their correlates in the human. Further, the importance of variations is confounded by their common occurrence in the presence of maternal toxicity. Many developmental toxicologists consider that a significant increase in structural variations noted only in the

presence of significant maternal toxicity is a weaker signal than the presence of major malformations or fetal deaths in the absence of maternal toxicity. Thus the assumption stated in the proposed revisions is a generally accepted one, albeit a point of disagreement in the field as to the relative importance of the various subsets of variation or adverse effects noted within these four major manifestations of developmental toxicity.

4.1.3 Animal to Human Correlations The proposed revisions assume that "..the types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans." This is generally accepted by toxicologists, although the supporting data base is not strong. Further examination of this issue is needed, including the generation of proper data to permit a thorough analysis.

4.1.4 Use of the Most Sensitive Species The revised guidelines call for using the most sensitive experimental species to estimate human risk. This is an appropriate default position when more relevant data are not available, but the basic position should be to use the most relevant data to estimate human risk. We would like to see the Guidelines pushing the field in the direction of trying to develop the most relevant data, rather than routinely developing data in rats and rabbits without serious concern about the relevancy to man or the use of other species.

4.1.5 Threshold Assumption The Guidelines assume a threshold in the dose-response function for most developmental toxicants. There is general agreement that this assumption is reasonable, but there is a lack of consensus as to the importance of this assumption in the risk assessment process. For instances in which developmental toxicity is already observed in untreated control animals, endogenous or exogenous factors may be sufficient to produce the developmental toxicity. The addition of substances which augment these factors may produce additional developmental toxicity. For those effects which are caused by non-mutational events, and perhaps even for those caused by mutations, it is important to develop more comprehensive approaches to risk assessment which use the total data available, not just the LOAEL or NOAEL (Lowest Observed Adverse Effects Level or No Observed Adverse Effects Level). This concern is relevant not only to the Developmental Guidelines, but to most of EPA's endeavors in risk assessment, and

has been a continuing concern of the SAB[1]. It is also addressed below (see section 4.3). Risk assessment procedures for developmental effects should be based on our knowledge of the biology of development. The assessment of carcinogenic risk is still usually done with methods based on assumptions for the mechanism of action that have been in use for decades; in developmental toxicology, where we know very little about mechanisms of action, we should be careful not to tie ourselves to mechanistic-based risk assessment procedures where potential errors could be quite significant.

4.2. Weight of Evidence Categories The Committee believes that the revised guidelines reflect a commendable attempt to structure and conceptualize risk assessments for developmental toxicants so that they fit neatly into a regulatory framework. They represent the thoughtful application of toxicological principles and insights to a set of difficult, even volatile, issues.

The Committee sees two significant problems, however, one rooted in current usage within the Agency, and the other rooted in the conceptual approach employed in weight-of-evidence (WOE) schemes *per se*.

Assessing the completeness and quality of the data base for a specific agent is an important part of the risk assessment process. The term "weight-of-evidence" as used in the proposed Guidelines may be inappropriate, since many in the field tend to think of the WOE as the total composite of the information that is available on which to make a judgement about risk, rather than to assess the quality of the data base. Within the Guidelines themselves, and as evidenced by the comments submitted by the public, there is confusion about the term WOE as applied to the data base, compared to the application to a specific chemical agent.

In terms of the underlying conceptual structure, this proposed WOE scheme (like others), is encumbered by ambiguities. Recall, for example, the repeated discussions within the Agency about the proper labelling of carcinogens, and how to differentiate, say,

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[1]See the recent SAB Environmental Health Committee letter report on modifying and uncertainty factors in RfD calculations (EPA-SAB-EHC-90-005).

categories B2 and C. Those discussions, moreover, are circumscribed by their focus on a single endpoint--carcinogenicity--albeit an endpoint manifested in many ways.

The proposal is sensitive to the web of complexities surrounding the WOE classification scheme, and takes care to recognize its multiple facets. Following a fundamental tenet of toxicology, it stresses the need to incorporate dose into the scheme. The exposition stops short, however, of offering guidance on how to do so. Further, it fails to provide guidance on how to evaluate the contribution of maternal toxicity; on how to define the dimensions of "adequate evidence;" or how to construct a coherent model of functional endpoints. The exposition fails to provide guidance on how to structure an inquiry about developmental toxicity that does not extend over the entire realm of possibilities--with the concomitant potential to consume enormous resources--in the application of the WOE classification scheme.

Each of these questions suggests many others; we note them here out of the disquiet that WOE designs arouse. This particular WOE approach seems tightly bound to its origins in cancer. We urge EPA to develop an approach suited to developmental toxicity that can be implemented with available resources.

Given the above comments, we should at least touch on some other approaches or schemes. If one considers the major difference between developmental and carcinogenic risk assessment, the significant factor is that in dealing with the developmental area, many different outcomes, as opposed to one, are possible. For example, the guidelines distinguish the four major manifestations noted above: death, malformations, growth alteration, and functional deficits. Is there some way in which these are linked? Does embryolethality imply the other possibilities at lower doses or at other exposure times? Do malformations imply growth alterations at lower doses? Is there an element of intransitivity or a directional bias in these mutual relationships? As noted above, are they all considered to be of equal importance? If not, how should the relative importance of these endpoints be evaluated?

An approach borrowed from decision analysis may clarify this dilemma. If one considers each of the major manifestations described in the guidelines as a primary category, each primary category would encompass a set of associated aspects. Death, for

example, might include embryolethality, stillbirths, reduced litter size, early neonatal mortality, and even premature death after maturity. Malformations would include all of the indices described in the guidelines. Functional deficits, although spanning an almost infinite number of measures, could be assigned to a much smaller number of primary categories. Even growth alterations may be expressed in many ways; for example, prenatal methylmercury exposure revealed an influence on growth in monkeys only when they approached sexual maturity.

One could then conceptualize the relationships between the major categories in terms of an estimate of the dose ratio required to evoke such an effect. The same scheme may be extended to elements within each of four major outcomes, and to the influence of maternal toxicity as well. Is it reasonable to try to guess the extent to which some functional measure, based on preweaning tests in rats, might portend the value of another functional measure based on adult performance?

One advantage of such an approach might be that it helps us to "map" the location of important gaps in knowledge. Such a map might enable us to apply a probability value to an un-evaluated outcome, which despite its grossness, might be better than no information at all.

A basis for assigning priorities to questions will be required if regulations and resources are to enjoy even modest compatibility. The volume of data implied as necessary by the guidelines is so overwhelming that it is likely to arouse fierce resistance or, worse, evasion. The decision analysis approach involves new concepts, and would require further development. Care is needed so that this approach also does not require an unreasonable amount of data and analysis. However, the type of scheme outlined above may offer a closer coupling between dose and the nature of the expected outcome(s), which, after all, is the aim of risk assessment.

4.3 Applicability of the RfD_{DT} Concept The proposed Guidelines substitute the use of an RfD_{DT} (Reference Dose for Developmental Toxicity), based on the use of short-term or acute developmental toxicity data, for the RfD, which is usually based on chronic data. This substitution is appropriate, given the endpoints considered, but the use of the RfD concept has weaknesses that are recognized

in the Guidelines; specifically, the value of the RfD can be influenced by the characteristics of the experimental design used to generate the toxicity data. Hence, an RfD based upon a study with low statistical power may be (inappropriately) considerably greater than one based upon a study with greater power. For that reason, RfDs based upon very limited studies may not be sufficiently protective. In addition, the current procedure makes no explicit use of any trend in response to dose.

Alternatives to this approach require some assumption about an underlying dose-response model. Not enough is known about the biology of a specific case to know which model(s) properly represents that case. This is particularly problematic if there is need to extrapolate response to a level of risk much lower than that observed in the experiments used to generate the data. Moreover, it is often supposed that developmental toxicity is associated with a threshold phenomenon, yet there are no clear-cut models which can be used in a risk assessment.

Both the choice of models and the existence of threshold doses need to be addressed in the generation of developmental toxicity guidelines. The latter are discussed and used to justify the use of the RfD_{DT}. Some of its weaknesses are acknowledged and there is some indication that the weaknesses are factored into the RfD estimate (although no specifics or examples are given). It generally is not recognized that the incidence of developmental toxicity at the NOAEL, which is the starting point for calculation of the RfD, may be as high as 6%[2]. Hence, at the RfD, there exists a non-zero baseline risk, which is independent of exposure.

An alternative which may overcome some of the difficulties with the RfD applications of the above approaches has been presented. A recent paper by Kimmel and Gaylor[3] suggests the use of a benchmark dose associated with a response level of 10 percent. The benchmark dose, defined by the lower confidence level for the ED_{10} (the dose level at which a 10 percent risk is associated), is estimated through use of an empirical model that makes use of all dose-response data. If we choose the lower confidence limit to the

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[2]Gaylor, D.W., Environmental Health Perspectives 79:243-246, 1989

[3]Risk Analysis, 8(1), 15-20, 1988

ED_{10}, denoted by LED_{10}, then studies with higher statistical precision generally will yield larger values for the LED_{10} and larger RfDs than studies with lower precision. Hence, the greater uncertainty associated with limited data (and thus lower statistical precision) is factored into the benchmark dose.

The model used to estimate the ED_{10} is less critical than when extensive extrapolation is required because the ten percent response is likely to be in the range of dose levels used to generate the toxicity data. Thus, any empirical model which fits the data well is likely to provide a reasonable estimate of the ED_{10}; in fact, several models could be applied to suggest how robust the estimates of the ED_{10} actually are. It is realized that the nature of developmental toxicity data presents specific model problems; e.g., individual data derived from a given litter are not independent. Suitable models are available to account for this lack of independence, and they should be applied. Since the model is only used to extrapolate (or interpolate) to the ED_{10}, no assumptions about the existence (or non-existence) of a threshold are needed.

The choice of uncertainty factors applied to the LED_{10} could be similar to those applied to a LOAEL. If the data are adequate to estimate the ED_{01}, which is closer to a threshold dose if one exists, the choice of uncertainty factors applied to the LED_{01} could be similar to those applied to a NOAEL. Another advantage of the benchmark dose over the current approach is that benchmark doses likely allow upper bound health risk estimates. As Gaylor[4] has argued, since dose-response relationships are often sub-linear in the low dose range, decreasing the dose by an uncertainty factor will generally lead to a proportionately greater reduction in risk. Thus, if a maximum risk is indicated, a dose level can be estimated through the benchmark/uncertainty factor procedure such that the dose level is a lower bound for dose levels associated with the risk.

The above approach is not entirely new (in 1984, Crump suggested replacing the NOAEL with a benchmark dose[5]), but it

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[4]Journal of Toxicology and Environmental Health, 11, 329-336, 1983

[5]Crump, K.S. Fundamental Appl. Toxicology, 4:854-871, 1984.

offers some advantages over the NOAEL/LOAEL approach. We recommend that it be considered for incorporation into the health assessment guidelines for developmental toxicants, to be used in conjunction with other currently "standard" techniques. This will facilitate understanding of both approaches and allow them to be compared.

4.4 Maternal Toxicity One of the major points of uncertainty in developmental toxicology today is the relationship between maternal and developmental toxicity. With the exception of some specific, minor technical points (which have been separately transmitted to the Agency), the Committee endorses the proposed revisions, and considers them to be a good explication of the basic tenets of the teratological literature.

The proposed revisions do not (and probably cannot) "solve" the question of the relative weight or significance to be placed on the manifestation of developmental toxicity in the presence of observed maternal toxicity. This subject elicited considerable comment from the public, and was the source of considerable discussion by the committee. We suggest that the Agency retain the current statement in the proposal, i.e., "..when adverse developmental effects are produced only at maternally toxic doses, they are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity," making only those modifications which do not weaken the thrust and basic sense of the proposal.

5.0 Conclusions and Recommendations On the whole, the proposals are adequately founded in toxicological and teratological science, and reflect the current status in these fields. There are numerous minor technical points, ranging from considerations of utilizing human epidemiological data, to the use of *in vitro* testing (perhaps the technically weakest element of the proposals) which the Committee feels could be improved or whose presentation could be clarified. Such items need attention, but do not detract from the overall competency of the proposals. Consequently, comments on these points have been supplied separately to the Agency, and are considered beyond the scope and purpose of this report.

There are two areas in which the Committee suggests the need for significant rethinking and revision. First, the weight-of-evidence classification scheme tends to be confusing vis-a-vis

current Agency and general usage, and still reflects too strongly its origins in the classification of unitary endpoint carcinogen effects, rather than the manifold possible outcomes of exposure to developmental toxicants. Functionally, it does not provide a more powerful conceptual basis for risk assessment in the developmental area than now exists. A more powerful system or scheme would provide a biological, functional basis for assigning priorities to the questions which arise during an assessment by offering a closer coupling between dose and the nature of the expected outcome(s).

The possibility of a decision analysis-based approach as discussed above is attractive, and is offered for consideration with the understanding that considerable effort would be required for implementation. The Agency is advised to consider it, along with any other methodology which could move towards a more conceptually powerful, yet more economical, biologically-based approach to developmental risk.

The same rationale underlies the Committee's thoughts on the subject of the RfD_{DT} and alternative approaches to assessment. The traditional LOAEL/NOAEL process ignores available data, is somewhat insensitive to trends in the data, and ignores the uncertainty in the level of risk at the NOAEL. It tends to reward less statistically precise studies by yielding higher RfD levels and provides a disincentive to better science. The benchmark dose approach discussed above avoids these problems, and is the subject of a growing body of literature (including some fine contributions by EPA staff scientists). It seems to be the next logical step in assessing risk, and the Agency is urged to begin moving in this direction by incorporating such an approach in the Guidelines to be used in conjunction with current methods.