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Report of the Health Risk Assessment Core Research Plan Review Subcommittee

Review of The Office of Research and Development's Draft Core Research Plan for Health Risk Assessment

A SCIENCE ADVISORY BOARD REPORT

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U. S. ENVIRONMENTAL PROTECTION AGENCY

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ABSTRACT

This report presents the conclusions and recommendations of the U.S. Environmental Protection Agency's Science Advisory Board summarizing a review of the Office of Research and Development's draft research plan for Core Health Risk Assessment. The Board's concensus was that the proposal was well written, and identified many worthwhile subjects for longer-term environmental health research. At the same time, it failed to provide priority-setting mechanisms, did not relate its agenda to on-going national research programs, and seemed overly bound to a risk assessment paradigm.

Key Words: Environmental health research; risk assessment; long-term research; core research.

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TABLE OF CONTENTS

1.0 **EXECUTIVE SUMMARY** The Subcommittee met at Environmental Protection Agency (EPA) Headquarters in Washington D.C. on April 4, 1990 to review the document "Core Research Program for Health Risk Assessment" and heard briefings by Drs. Peter Preuss and Ken Sexton, EPA Office of Research and Development (ORD) staff. The core document represents part of a major initiative by EPA to implement the 1988 Science Advisory Board (SAB) Future Risk report recommendations for a substantial increase in resources (and a concomitant increase in operational stability) for its long-term research efforts. Two other parallel core research program drafts are also being reviewed by the SAB, i.e., on ecological risk assessment and risk reduction (primarily engineering technology and pollution prevention).

The Subcommittee was specifically asked to address the following questions:

a) Is the conceptual strategy clear?
b) Do we have the appropriate major areas for research?
c) Have we asked the right questions?
d) Within each of the major topics, do we have the proper sub-elements? What's missing? What doesn't belong?
e) Is the rationale and need for each sub-element clear and convincing?
f) Are the types of research proposed within the sub-elements appropriate?
g) Does the discussion provide an adequate indication of priorities for future research?

The briefing and document demonstrated a new and very welcome change in ORD and the EPA's vision of its role. We endorse strongly the plans to identify and support a core program with a longer term research agenda, and the plan to have a broad oversight committee guide the program. The core research program will help ORD play a much more important role in developing a better fundamental scientific base for future regulatory and guideline development, as well as a greater ability to anticipate emerging problems and their scope and research needs.

The Subcommittee also found that the document was very well written and constituted a thorough and well conceived description of important EPA and national research needs in environmental health. The authors deserve commendation for developing a document

which is very responsive to SAB recommendations and expands upon them in a constructive and thoughtful way. We found little to criticize vis-a-vis those topics covered in the document, but did note that it failed to address some other significant elements. Among these are:

a) The document, as reflected in its title, is too narrowly focussed on a paradigm for core research on risk assessment. At the same time, it generally ignores research activities on risk assessment methods per se. The core research program can and should address a broad range of EPA needs, but should also deal with the interaction between the health research program described in this plan, and Agency needs for risk assessment methods.

b) The document does not discuss how research priorities are to be set. It outlines a broad range of worthy endeavors, but describes an agenda that would consume far more resources than those likely to be available in the next few years. Thus, it is essential that subsequent drafts describe the mechanisms for priority setting and staging for the most critical needs.

c) The document does not adequately address how the new EPA initiatives will fit into the larger national effort in environmental health research. It should include a description of the mechanisms by which ORD will monitor progress in areas of common interest in the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the National Center for Health Statistics (NCHS), and other relevant institutions, and how its own initiatives will supplement, complement, and utilize the results of these other programs.

Section 4.0, Conclusions and Recommendations, provides additional comment on the issues noted above, and some suggestions for improving future iterations of the draft plan.

2.0 **INTRODUCTION** By the late 1980s, most observers of EPA's Office of Research and Development (ORD) recognized that the program's research "portfolio" was unbalanced, being overweighed with near-term activities directed at specific regulatory problems and issues, to the detriment of longer-term, broader gauge efforts designed to improve (or attain) fundamental understanding of critical areas which underlie EPA's scientific activities--e.g., source-exposure, exposure-dose, and dose-response relationships--needed to improve health risk assessment. At ORD's request, the SAB reviewed the research program's overall directions and strategies and issued the 1988 report "Future Risk"[1]. The report encouraged ORD to place greater emphasis on planning and supporting research on more basic environmental health issues, and to develop and implement "basic core research programs in areas where it has unique responsibilities and capabilities."

ORD's response was to create such an identified program, with a long-term commitment of resources, intended to improve understanding of fundamental environmental health, ecological, and risk reduction issues. To help explicate and direct the effort, draft core research plan documents were prepared for each of the three areas noted, and the SAB was asked to review them.

The Health Core Research Plan Review Subcommittee carried out their review on April 4, 1990, at EPA Headquarters in Washington D.C. The charge to the Subcommittee provided the basic structure for the meeting, and contained the following elements:

a) Is the conceptual strategy clear?
b) Do we have the appropriate major areas for research?
c) Have we asked the right questions?
d) Within each of the major topics, do we have the proper sub-elements? What's missing? What doesn't belong?
e) Is the rationale and need for each sub-element clear and convincing?
f) Are the types of research proposed within the sub-elements appropriate?
g) Does the discussion provide an adequate indication of priorities for future research?

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[1] U.S. EPA, Science Advisory Board, Future Risk: Research Strategies for The 1990s, SAB-EC-88-040, Washington D.C., September, 1988.

The following report represents the results of the Subcommittee's analysis of the draft Core Research document, and its discussions with senior ORD management staff during the meeting.

3.0 **DETAILED FINDINGS** The Subcommittee's findings are subsumed into three major categories dealing with: the conceptual structure of the core document; the appropriate content of a core research program; and the setting of research priorities. Within these categories, this report also addresses specific details on program content and the planning and coordination of a core program.

3.1 Conceptual Strategy Because so much of the Agency's current efforts are guided by the conventional risk assessment framework, the core program document adopted what is, in essence, an analogous structure. Although such a model serves the explain to an audience within the Agency the directions the core program seeks to pursue, its scope may be too limited to serve EPA's future needs. Alternative models should be explored, as well. The Relative Risk Reduction Study[2], for example, examined environmental health issues from a much broader perspective, and included facets for which EPA currently has no legal or operational responsibility, such as occupational exposures and their consequences.

The core program draft plan describes a broad program of research, much of which corresponds to prevailing EPA activities. Again, the specific aims are scientifically laudable. EPA, however, is not equipped to pursue all of these laudable aims simultaneously, nor should it do so. Few clues are yielded by the document about the process, or, more importantly, the total framework around which the elements of the program will be fixed. Questions about agents, or classes of agents, cannot be assigned to a secondary role because they help determine how a problem will be structured, nor does the proposal provide guidance to the Agency to call for more research on quantified structure activity research (QSAR), exposure markers, and mechanisms, another possible approach to organizing the program.

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[2]An on-going SAB project to assess the relative risks of various environmental agents/toxicants to health, welfare, and the ecosystem. The project is a review, re-assessment, and extension of an earlier EPA staff effort (U.S. EPA, Unfinished Business, Washington D.C., 1987).

One crucial question that this program might help resolve, and that is a key issue for the EPA, is the compatibility of risk estimates based upon QSAR, biological (molecular) markers, in vitro test systems, animal studies, and/or human data. In fact, the entire core program could be conceived of as a plan for what could be termed vertical integration of these different components. Moving up and down this conceptual "ladder" would offer the possibility of a more economical, immediate risk assessment process. Some strategic vision, albeit not necessarily the one above, is essential if the core program is to enlist interest and support beyond EPA. This is of special importance if these priorities and objectives are to be integrated with the objectives and priorities of other agencies.

Another alternative conceptual model derives from posing the issues from the point of view of society's broader health concerns. That is, what are the major health questions facing our society? To what extent are they linked to environmental variables both directly and indirectly related to EPA concerns and responsibilities? What kinds of information does EPA require to provide such an assessment or to modify the risks? How does it mesh with the needs and objectives of other agencies? Should such an assessment be carried out by an inter-agency task force, and if so, how frequently is such an effort required?

Lastly, this document should articulate why there is a need for a core research program differing from the research activities currently underway within the Agency. In part, it does state that we need basic research on mechanisms and on relationships between the elements of a risk assessment (sources, exposure, dose, etc.). It is clear that such information will help the Agency make informed risk assessment and risk management decisions. The document presents a logical structure for linking not only the elements of risk assessment, but also the interactions among media. What is missing, in the broad conceptual view, is an explicit sense of the objective of this research enterprise. The goal is not just better predictive models or tabulation of the impact of environmental exposures on the health of the nation's population. Ultimately the goal of the core research program should be to provide understanding, methodologies and information to improve the status of the nation's health through more effective and efficient management of all aspects of the environment. This calls for a

more comprehensive vision and explication as to how the research areas will be targeted and how the results will be utilized.

3.2 **Setting Research Priorities** The core research program document provides, as noted above, a comprehensive list of potentially needed health research. The research possibilities mentioned are so vast, however, that even optimistic projections of EPA resources would support only a fraction of the research described. There is a great need to incorporate some mechanism for setting priorities into the draft document. Without such a system the selection of research elements is unclear and the program is at best ambiguous.

The definition and choice of priority-setting mechanisms is the responsibility of the EPA staff; however, these mechanisms should probably incorporate some of the following features:

a) The magnitude of the environmental health problem addressed should influence the research priority; the formulation of such estimates would benefit from broad-based participation from the scientific community and public interest groups in a stable and on-going relationship.

b) The ability of the research to reduce uncertainty about environmental health risks should be a significant factor in the priority assessment.

c) Managerial input is clearly needed to define a cohesive research program, but input is also needed from researchers who can identify specific research opportunities which could contribute greater than usual benefits. To accomplish this, we suggest that a group composed of appropriate agency staff officials be designated to communicate with appropriate governmental agencies involved in basic research related to the environment and health. Many of the basic research issues put forth in the draft document are being addressed in other research programs, e.g., NIOSH, NIEHS, NCI, ATSDR, etc. The charge of this "Research Communication Committee" would be to react individually with scientific personnel in other agencies, share EPA's plans and results and explore each agency's basic research plans and findings related to the U.S. EPA's goals and objectives. These basic research data are to be communicated to those implementing the core research program and

to scientific personnel in the EPA actively engaged in related investigations.

3.3 **Appropriate Areas for Research** We are all keenly aware of the shifts in our society; for example, the marked changes in age distribution. Is such a factor likely to alter our relative emphasis on different aspects of environmental health, such as how we evaluate exposures, mechanisms, and effects? This is one example of the kinds of questions that should guide a program designed to propel the Agency's future research agenda.

The proposed agenda, described in the core program document, is clearly written and conforms to what we expect of a solid scientific enterprise--within the areas it addresses. Perhaps the problem is its very solidity. A more extended perspective, even one marked by speculation would have afforded both EPA and its presumed audience a much better grasp of the possibilities.

Looking at specific program content, it is obvious the implementation of the proposed core plan would consume far more resources than those likely to be available in the next few years. Thus, choices must be made in the allocation of available funds. One basic decision in this regard, is whether to spread the resources among a broad variety of research options and in-house competence building or, alternatively, to focus the program on a smaller set of options in order to have a more visible yield in a few high priority areas. In the latter case, exploratory efforts could be devoted to some areas that would be candidates for future high priority research efforts.

The Review Committee favors the latter option, and believes that productive efforts in the initial target areas will build support for the further development and maintenance of a productive core program in health research. In selecting research areas for focused research, consideration should be given to those targets of opportunity where relatively modest levels of support could yield very substantial yields of research results on population exposures, dosimetry, and exposure-response relationships. Among the activities deserving of consideration in this regard are:

a) Systematic acquisition, quality-assurance, organization, and utilization of data sets on environmental concentrations, biomarkers, health outcomes and their interrelationships. This

activity can demonstrate the extent and magnitude of health effects associated with environmental exposures in some cases, and generate hypotheses for further research in others. Specific opportunities for research in this area are well described in Section 5 of the February Draft supplied to the Subcommittee.

b) The development of methods and means to extrapolate results from animal and in vitro studies to humans. A considerable portion of the scientific discussion of human health effects is based on laboratory studies of animals and of animal tissues in vitro. Given the difficulties of conducting human clinical and epidemiological research, animal and in vitro research will continue to provide the most significant health information in many areas. If in vitro data are ever to be utilized in quantitative risk assessment, there is a strong need to develop methods to extrapolate results from these studies to the human condition. A particularly fruitful approach could be to collect data from animal and in vitro studies for chemicals where good human data are available. Toxicants that exert their effects via similar mechanisms may be quantified by in vitro studies. One potentially useful approach is to set up a mechanism for acquiring the large data bases on biomarkers and exposure levels among industrial workers. Many large companies have historic as well as current data that can become an exceptionally rich and useful data base for studies of biomarker validation and exposure-response. With the proper safeguards and means of protection of confidentiality and data source, it is possible that the EPA could acquire data from many cooperative companies.

An understanding of how human risks for various measures of dose are expressed in animals could also greatly enhance future efforts to predict human risk from animal studies. Within this broader context, the core document should more explicitly address reproductive toxicity. We learned from the thalidomide experience in 1960 that there are agents which are considered "safe" on the basis of adult toxicity, but which have a unique capability to interfere with the developmental process at doses below those which adversely affect maternal health. If the EPA is to deal with this issue, a research effort must be designed to identify families of agents that have this property; to develop a concept of the quantification of selectivity; and to determine whether or not one can detect patterns of toxicants which fall, or do not fall, within this group.

c) A systematic acquisition and exploitation of toxicological data bases relating organ toxicity and toxicological dose in animals and humans (as discussed in the draft core document on pages 4-6 and following), is a logical and cost-effective target of opportunity. Such data are valuable for risk assessment based on interspecies extrapolation.

In prioritizing research needs, the Subcommittee has identified several key areas beyond those denoted as "targets of opportunity." These key areas include:

a) Research on Integrated Exposure Assessment. We recognize the need for multimedia models, as discussed in Section 2.3.4. of the core document. We encourage ORD to examine total human exposure assessment needs, with efforts aimed at improved environmental measurement techniques and biomarkers, and their validation.

b) A strategic Approach to Dosimetry. Section 3.1.1. provides a framework for a systematic examination of the state-of-the-art in dosimetry. The results of this examination can be used to guide future research for developing PB-PK models in particular, and dosimetry research in general.

c) Research on biomarkers. The Environmental Health Committee of the SAB has recently examined the ORD biomarkers research strategy. The following is an appropriate excerpt from their report that refers to both near term and longer range efforts: "EPA's recommendations would be quite reasonable if examined in isolation, and if there were substantially greater resources to implement them. However, even if all the projected resources were available for the development of new, more sensitive biomarkers, it would only permit modest incremental contributions to those already being developed in the Health Effects Research Laboratory of EPA (HERL), NIOSH, ATSDR, NIEHS, and the NIEHS Superfund program project grants at academic centers." Thus, the mechanism for communication with other agencies recommended in Section 3.2 (c) is especially appropriate to the biomarkers program.

d) Development of models for chronic disease etiology. One extremely important research area not addressed in the document is the development of chronic deficits in performance and function

following a repetitive series of acute exposures. Conventional animal models have been ineffective for important endpoints such as: 1) developmental deficits clearly associated with low levels of environmental lead exposure; 2) increased rates of bronchitic symptoms in children living in areas of high ambient aerosol acidity; and 3) reduced rates of lung function growth in children exposed to environmental tobacco smoke. Means of addressing these kinds of slowly developing chronic disease effects from low-level and intermittent environmental exposures should be a major focus of EPA's long-range research planning.

e) Research on risk assessment, i.e., the synthesis and interpretation of health science to provide a basis for risk management decision making by the Agency. Recent reports by the SAB on the revised guidelines for risk assessment of reproductive/developmental toxicants[3] and on asbestos[4] are two cases in which valuable areas for further research are identified.

The Subcommittee suggests that in future development of the core program, additional external input would be of benefit, in terms of improved coverage and depth of coverage. Such input would ensure that various research areas, even though well represented in the core plan, are up to date and not simply a repackaging of the research interests of the Agency scientists. Just because a research area is of long time interest to Agency scientists does not mean that it merits the emphasis perhaps evident in the document.

It is suggested that a workshop or similar means be used to overcome these types of potential problems. Significant input would be useful from leaders, in diverse areas, who are not Agency employees or contractors. In general, development of an Agency/Academic ongoing interaction would be markedly useful to the Agency scientists.

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[3]Review of Proposed Revisions to the Guidelines for Health Assessment of Suspect Developmental Toxicants, EPA-SAB-EHC-90-013, April, 1990.

[4]Letter Report to Administrator William K. Reilly, EPA-SAB-Letter-90-002.

4.0 CONCLUSIONS AND RECOMMENDATIONS The Subcommittee found the draft plan to be well written, and to provide a thorough and well conceived description of important EPA and national research needs in environmental health. The authors deserve commendation for developing a document which is responsive to earlier SAB recommendations and which builds upon them in a constructive and thoughtful way. Little was found to criticize in the content of the document. On the other hand, the document does lack some significant elements. Among these are:

a) The document, as reflected in its title, is too narrowly focussed on a risk assessment paradigm for core research; at the same time, it generally ignores research on risk assessment methodologies, per se. The core research program can and should address the broader range of EPA needs, but should also address the interaction between the health research program in this plan, and Agency needs for risk assessment methods.

b) The document is inadequate as a tool or guide for setting research priorities. It describes a broad range of worthy endeavors, but in doing so creates an agenda that would require far more resources than those anticipated to be available in the next few years. Thus, it is essential that subsequent iterations describe mechanisms for priority setting and time phasing for the most critical needs.

c) The document does not adequately address how the new EPA initiatives will fit into the larger national effort in environmental health research. It should include a description of the mechanisms by which ORD will monitor progress and plans in areas of common interest in NIEHS, NIOSH, ATSDR, NCHS, etc. and how its own initiatives will supplement, complement, and utilize the results of these other programs.

d) The Agency should give serious consideration to the suggestions for specific research areas provided in section 3.3 above--"targets of opportunity," integrated exposure assessment, strategic dosimetry approaches, biomarkers research, risk assessment methodology, and models for chronic disease etiology.

e) Provision should be made for increased external input to EPA research planning by the many other science institutions in the federal government and the private sector. Some mechanisms for accomplishing this are suggested above, but the possibilities for setting up fruitful interactions is by no means limited to those noted.