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Review of Inhalation Toxicology Research Programs at EPA's Health Effects Research Laboratories Research Triangle Park and Cincinnati

November 25, 1980

Health Effects Research Review Subcommittee
Environmental Health Committee
Science Advisory Board
U.S. Environmental Protection Agency

EPA NOTICE

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BACKGROUND

This review was requested by Mr. Costle, Administrator of EPA, as a follow-up to the Health Effects Research Review conducted by the Science Advisory Board (SAB) in 1978 in response to a Congressional mandate. The Administrator accepted the findings of that report and indicated his desire to have continuing outside review of EPA's research programs and projects as a factor in promoting the high quality of research which is essential to development of sound regulations.

The Environmental Health Committee (EHAC) accepted this responsibility on behalf of the Science Advisory Board. The Committee made two suggestions to modify the procedures used in the original Health Effects Research Review. The latter had been a comprehensive and intensive review, as requested by the Congress, and membership of the Review Group was determined entirely by the SAB. The Committee suggested that EPA's Laboratory Directors be consulted about the selection of program areas for review and that Laboratory Directors be invited to suggest candidates for Review Subcommittee membership, who would be acceptable to the Laboratories. This procedure was followed.

Selected members of EHAC met with EPA representatives in July 1979 to discuss plans for the review. EPA representatives were Drs. Gage, Hunt and Dowd from EPA headquarters and Laboratory Directors Hueter and Garner. A general plan was agreed upon, and Inhalation Toxicology was selected as an appropriate first topic for review by a Subcommittee established for the purpose of accomplishing this task (Appendix A).

More detailed plans were made in visits to the Health Effects Research Laboratory in Research Triangle Park, N.C. (HERL-RTP) in September 1979 and to HERL-Cincinnati in January and February 1980. At HERL-RTP there was planning underway for an Oxidants Workshop in January, and it was considered desirable to postpone the SAB review until after the Workshop (March 20-21, 1980 was later selected as a meeting date). At the Cincinnati meeting it was clear that larger issues were at stake than the quality, relevance, and general well-being of the Inhalation Toxicology Program. Problems in planning and management (related to Research Committee guidance and directives from ORD-HQ) led to great uncertainty about whether there should continue to be an "Inhalation Toxicology Program" at HERL-Cincinnati. The future of the program at Cincinnati and the integration of inhalation toxicology between HERL-RTP and HERL-Cincinnati thus became a concern of the Subcommittee.

The work of the Subcommittee was facilitated by attendance of some of its members at the Symposium on Diesel Exhaust Health Effects in December and the Oxidants Workshop in January. These meetings included research reports by the Inhalation Toxicology Laboratories at RTP and Cincinnati, respectively.

In further preparation for the formal visit on March 20-21, 1980, the Subcommittee asked both Laboratories to respond to a questionnaire, which was designed to elicit a self-evaluation of strengths, research productivity, and institutional obstacles to optimal performance (Appendix B). There were twelve questions divided among 1) work group organization, planning, performance and restraints; 2) publication of research, including reports in peer-reviewed journals; 3) unique capabilities; 4) institutional mechanisms for planning, implementing, and reporting research; and 5) administrative problems.

The material available for review thus included responses to the questionnaire (which were obtained from HERL-Cincinnati but not from HERL-RTP); documentation of scientific credentials and productivity (curricula vitae and publication lists); and presentations at the March 20-21 meeting. Subsequent to the meeting, the HERL-Cincinnati Laboratory submitted a proposal for future facilities and inhalation toxicology research activities of the Laboratory.

FINDINGS AND COMMENTS

Health Effects Research Laboratory-RTP

The Inhalation Toxicology Research Program was presented in two parts, the animal toxicology studies at RTP, on March 20, and the human studies conducted in the Chapel Hill facility, on March 21. Although most of the presentations were very good to excellent, the Subcommittee was very much concerned that the animal studies group, which made its presentation on the first day, was not present for the presentations of human research programs on the second day, and those concerned with human inhalation studies were not present for presentations of animal inhalation studies on the first day. The two groups are very much related, and it is essential that they be completely aware of the work that each is doing. The Subcommittee urges the Laboratory Director to institute mechanisms to promote this exchange.

The program of the Clinical Studies group appears, finally, to have gotten moving. The general direction seems appropriate; however, it is uncertain whether the group has the necessary strength to generate its own research program. Additional staff is needed to provide the critical mass necessary for development of a program that generates its own momentum and research direction. Although the program must always have a strong regulatory orientation, the present program seems somewhat stifled by excessive orientation to establishing exposure response relationships. Possibly, the human studies program could move toward a broader view of pulmonary disease produced by inhaled materials if it would work more closely with the animal toxicology program.

The staff of the clinical research group is not large enough to make adequate use of the facilities available. The present facilities would probably support a staff at least twice, and perhaps three to four times, as large. In considering size, it is appropriate to recognize that good research requires not only the time to conduct experiments but also time to conceptualize and plan, analyze, and write. The loss of Dr. Joel Ginsberg, Health Scientist in the Human Studies Division's Clinical Research Branch, will be a serious blow. The roles of some supporting personnel (clinical chemistry and immunology) are not clear and probably should be reduced in favor of providing positions for personnel who can contribute more directly to the program. Those services needed to document the health of subjects could be readily purchased from the University of North Carolina (UNC) Medical Center. The

understaffing of research physicians has been a continuing problem and should be corrected. The option of placing the facility substantially under the direction of the UNC Medical Center appears to warrant further serious consideration.

The Chapel Hill physical facilities for human inhalation studies are unique, although they are becoming dated. The result is a facility that may be one of the least cost-effective to operate of any now in existence. The facility is over-engineered, without updated computer units, and requires an excessively large supporting staff. Because these facilities are so expensive to operate, their use should be better coordinated with the research at other facilities around the country, and they should be used primarily for those purposes for which they are uniquely suited and for which other less expensive facilities cannot be used.

In general, the animal inhalation research at HERL-RTP is of a high quality. The majority of the staff presented material well and responded vigorously and knowledgeably to searching questions by the Subcommittee. The modeling work presented by Dr. Miller was excellent and at the forefront of such efforts in the United States, and perhaps in the world. This work should be encouraged and expanded. Description of the particulate research program, however, demonstrated a lack of insight into the properties of particulates. The decision to utilize a coarse and fine mode for evaluating particulates in air was based as much upon the methods of formation of particulates in the atmosphere as it was upon the mechanisms by which particulates may cause effects on health following inhalation.

The Inhalation toxicology research in the pesicide area lacks a sense of direction. The presentation was unclear. Obviously, there is a history of uncertainty with this program; a history our group was not briefed on. The Subcommittee cannot be expected to understand all of the institutional history associated with the research program. Nevertheless, the Subcommittee wishes to convey to the Laboratory Director that this program cannot withstand even casual scrutiny by a visiting group of peers. It would seem that it must be straightened out or dropped.

A source of major concern was the tacit assumption conveyed by the presentations that the best way to approach current EPA Research Committee demands for health effects data is to develop the broadest possible spectrum of screening tests. HERL-RTP individuals have expended a considerable effort to bring these tests to an efficient operating level, and they can undoubtedly

apply them routinely. It was not clear from the presentations that many of the individuals understood the limitations and strengths of these tests. Reorientation of objectives is needed to assure that staff are applying scientific judgment, are aware of the previous literature, and can restrict testing to those studies where there is a high probability of yielding results appropriate to the hypothesis under test. The cardiopulmonary test battery program may serve as an example for this needed reorientation. Under this program, a battery of tests was developed and described, including EKG, arterial blood pressure, venous blood pressure, cardiac output, blood gases, blood chemistry, body weight, wet and dry heart weight, and histology. There was no evidence that any thought had been given to specific circumstances or purposes for which each of the tests was to be utilized. Rather, it was asserted in a general way that this assortment of tests had been developed "in order to respond adequately to various Research Committee needs."

The staff of the animal studies group is very competent in the areas of toxicity of ozone, NO_x, and SO_x. They have broadened their outlook in recent years and show promise of developing into a broad-based, first class inhalation toxicology group. To reach this goal it is critical that the group be increased in size and develop capabilities relating to the toxicity of particles. It is also important that the group include several comparative pathologists who are knowledgeable and interested in both classical and quantitative morphological pathology. This should help the group to continue developing its competence in studying the late effects of inhaled materials. The professional development of the individuals in the group is at an important juncture. Most of the individuals in the group probably could benefit from further substantial "bench-type" research; however, they are becoming increasingly committed to involvement in administering contracts and grants and providing in-house consultation. This problem could be remedied by increasing the size of the group and by spreading the "non-research" workload. Recognizing the Agency's continued responsibilities to consider the health effects of airborne materials, increased staff in this area appears not only warranted but imperative.

The animal toxicology program is moving, appropriately, to a broader base. Not many years ago, the program was tied to the use of a few test procedures, especially the bacterial clearance systems, developed to a large extent by Coffin and Gardner. The efforts in the areas of pulmonary function evaluation and comparative pulmonary dosimetry (i.e., Dr. Miller's work) are positive steps in the right direction. It is especially

important that the program increase its efforts with inhaled particles, recognizing the extent to which many airborne environmental pollutants exist as particles. It is also critical that the program progress from its present strong orientation toward effects that occur during or shortly after exposure to an orientation toward late occurring functional and carcinogenic effects following chronic exposure.

In both the Clinical Studies and Animal Toxicology Programs, there appears to be an excessive orientation toward developing and using batteries of tests without giving adequate consideration to how and for what materials the tests will be used. A more thoughtful and selective approach is in order.

The diversification of the Animal Inhalation Toxicology Program into new areas, such as the pesticides and hazardous materials areas, should be encouraged. However, it is clear that such programs must be more carefully planned and initiated than was evident. It is especially necessary that a more integrated approach be taken considering the interrelationships between source → exposure → intake → fate within the body health effects.

The animal exposure facilities at RTP are primarily useful for work with low toxicity gases and vapors. They are marginally adequate for use with low toxicity particles and are not suitable for use with high toxicity or carcinogenic materials. With the exception of the walk-in exposure rooms, it is the Subcommittee's view that the facilities are not appropriate for conducting long-term exposure studies.

Health Effects Research Laboratory-Cincinnati

The two visits to the Cincinnati laboratory and attendance at the December Symposium on Health Effects of Diesel Emissions gave the Subcommittee a good mix of informal discussions and formal presentations that provided a good overview of the current inhalation toxicology program. These were complemented by a brief and thoughful narrative presentation that was highly responsive to the questions provided in writing.

The program at HERL-Cincinnati has been, in essence, totally oriented toward the study of automotive emissions. In this area they have made some notable contributions, although the productivity of the group has declined in recent years. This decline can be traced, to a large degree, to uncertainties about the future of the program and inappropriate and excessive program direction from EPA Headquarters. Headquarters

involvement, and especially Research Committee involvement, has extended well beyond problem identification into micromanagement of the research effort. This, coupled with an excessively short-term orientation imposed by Headquarters, has had a devastating effect upon the program. It is tragic that the group was not allowed to start lifespan, multiple exposure level studies with irradiated and non-irradiated diesel exhaust in the fall of 1978. Instead, the research effort was forced into a time schedule dictated by the anticipated date of issuance of standards. The result was an inadequate research effort. It is ironic that a portion of the data used by the Administrator in issuing an interim standard for diesel exhaust particle emissions was developed from a study (influence of diesel exhaust on clearance) that was, mildly put, not encouraged.

The inhalation toxicology facilities of HERL-Cincinnati fall into two broad categories: (1) those uniquely suited for work with automotive emissions (Center Hill) and (2) general use chambers suitable for use with low toxicity, non-carcinogenic materials. The Center Hill facilities are unique in that the capability exists for photoirradiation of automotive exhaust, a capability that does not exist, to the Subcommittee's knowledge, anywhere else in the United States. The other chamber's capability is of limited usefulness because it is restricted to low toxicity, noncarcinogenic materials.

The present staff involved with inhalation toxicology studies at HERL-Cincinnati falls into two broad groups: (1) those involved with generation and monitoring of automotive emissions and (2) pathobiologists.

The first group is quite strong; however, their orientation is rather narrow, and it is doubtful that their capabilities could be readily applied to work other than with automotive emissions. The pathobiology group is in need of strengthening if the Program is to continue. This group appears to have tackled work with automotive emissions in a reasonably competent manner but has failed to conceptualize other problems (and related approaches) in a very convincing way. Taken as a group, the number of individuals involved in inhalation toxicology studies appears marginally to approach a critical mass. If the group is to continue, it would be appropriate to analyze critically the composition of the group and make selections, deletions, and additions to strengthen their collective capabilities.

After a series of discussions, initiated at the January meeting in Cincinnati, Dr. Vilma Hunt asked the Laboratory to

develop a long-term research plan (three to five years). This plan was prepared in May 1980 and was made available to the Subcommittee in June. Since there has been no meeting of the Subcommittee since then, only individual comments are available. There was general endorsement of the proposal, except for the recommendation that diesel particulates be considered as a model aerosol. Diesel particulates are too atypical in physical and chemical properties to be considered a model aerosol for urban atmospheres.

SUMMARY OF RECOMMENDATIONS

1. The development of a long-term orientation toward inhalation toxicology problems should be encouraged, recognizing more adequately than in the past the extent to which air pollutants will be of concern to EPA for the foreseeable future. This includes better integrated research planning and retention of inhalation toxicology capabilities at HERL-Cincinnati. The result would be to increase EPA's ability to assess health effects of inhaled particles, a complex and long-term problem.

2. Increased collaboration and interaction between the Human Studies and Animal Toxicology groups at HERL-RTP and the Inhalation Toxicology groups at RTP and at HERL-Cincinnati should be encouraged. These laboratory groups should be perceived and dealt with as complementary rather than as competitive.

3. The role of Headquarters staff should be critically evaluated, especially the roles of program office staff and research committees in determining research approaches. There should be greater emphasis on problem identification by the Washington staff, with the details of research protocols and the conduct of research left to the field research staff. A review is in order because the present approach is having a profound effect on EPA research, essentially negative in terms of both morale and research content.

4. Avenues should be pursued by which to create a more effective personnel management system, placing primary responsibility at the laboratory level for management and assignment of research personnel. Identifying personnel slots by specific pieces of authorizing legislation and carrying this identification down to the laboratory level seriously impairs the effective management of research personnel. Changes in enabling legislation may be required.

5. A better balance should be developed between orientation of research toward meeting specific regulatory deadlines and letting the research needs determine the schedule required to carry out the program.

6. The utility of batteries of tests should be critically reviewed, and there should be more selectivity in developing test procedures, carefully matching the test to specific needs and questions.

7. Integrated approaches to studying airborne materials should be encouraged, carefully considering the relationships between source, exposure, intake, fate within the body, and health effects.

8. There should be a strengthening of EPA's capabilities for evaluating late occurring functional and carcinogenic effects of chronic exposure to airborne materials.

9. An increase in staffing, especially additional research physicians, for the Clinical Studies group or, alternatively, a shifting of major responsibility for the program to the University of North Carolina is needed.

10. The strong input to development of criteria documents and management of extramural research should continue. However, there must be more adequate recognition by all concerned of the time demands of the effort and its impact on the contributing staff. Clearly, there is need to increase the size of the staff to do this important work well.

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SAB Review of ORD's Inhalation Toxicology Program

Questions for EPA Staff

Work Groups

1. Describe the rationale(s) for the organization of work groups in the laboratory and the major long term and short term questions addressed by the groups.

2. Describe how the questions addressed by the work groups relate to EPA concerns, in either a general or program specific way.

3. Describe major accomplishments of the work groups during the past three years.

4. Describe major setbacks or restraints encountered by the work groups during the past three years.

Publications

5. Provide a list of projects pursued in your laboratory during the past three years and publications reporting scientific or technical outputs of these projects. Indicate year project started and year of publication. Include papers submitted for publication.

Unique Research Capabilities

6. Describe any research capabilities in your organization which you believe to be unique or rare in the U.S. How are these capabilities being utilized?

Institutional Mechanisms

7. Describe institutional mechanisms now in place which help planning, implementing or reporting research. Are there additional mechanisms which you would recommend?

8. Describe institutional mechanisms which help to improve the scientific/technical capability of your laboratory group. Can you suggest mechanisms not now utilized?

9. Describe ongoing mechanisms which you now utilize to interact with (a) ORD headquarters, (b) other EPA scientific/technical staff and with (c) non-EPA scientific and technical staff.

On items 1 to 9 above include comments on recent changes, i.e., changes which occurred in the past six months.

Staffing and Other Administrative Matters

10. Provide a list of projects and associated staffs and budgets for the current year.

11. Provide a list of position vacancies for the current year. Superimpose on this list your estimate of needs to pursue projects in a satisfactory or outstanding manner.

12. Provide a list showing the contracts, grants, and cooperative agreements which individual staff scientists oversee and their budgets. Indicate whether funding decision was made by ORD headquarters or by laboratory.

Other Topics

Discuss additional topics which you consider important and relevant to this review (e.g. adequacy of facilities, growing demands on personnel, new grants procedures).