UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

SAB-EC-87-030

OFFICE OF
THE ADMINISTRATOR

May 26, 1987

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Thomas:

The Deputy Administrator and the Assistant Administrator for Research and Development requested that the Science Advisory Board (SAB) review the progress made by the Office of Research and Development (ORD) in addressing EPA's needs for extrapolation models. The SAB Executive Committee formed an Extrapolation Models Subcommittee which conducted the review in public session. The Subcommittee's full report, which is attached, describes: 1) the problem that EPA confronts in developing and using extrapolation models; 2) ongoing work from the perspective of the type of extrapolation; 3) an analysis of the ORD effort organized according to scientific discipline; 4) a perspective on the overall effort of the Federal government in this area of research; and 5) the Subcommittee's general comments and conclusions.

Models that allow one to extrapolate from one set of scientific phenomena or observations to another are an important component of the risk assessment process. The use of extrapolation models is subject to considerable scientific uncertainty, and many such models lack recent scientific review. Given EPA's commitment to using risk assessment in regulatory decision making, it is imperative that the Agency promote efforts to improve extrapolation models.

The subject of extrapolation modeling is complex. The Subcommittee believes that the field can be described as a multidisciplinary matrix so that the work can be viewed from different perspectives, such as the kind of extrapolation process, the stage of model development, the scientific discipline involved or the general approach to modeling. Progress in model development can be analyzed from these different perspectives. The Subcommittee developed the following two principles to evaluate research plans:

1) If research on an extrapolation model is successful, how will the Agency be able to better assess risks? What can EPA do with an improved model that it cannot do without one?

2) Will successful research on a model establish leadership for EPA within the scientific community and promote interest in the model outside of EPA?

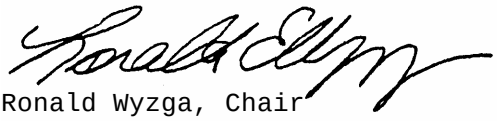
The Subcommittee's major finding is that there is no overall, conceptually integrated Agency research program on extrapolation modeling, but a conglomeration of investigator-initiated projects, many of which are commendable in their design and implementation. The Subcommittee was impressed with the talent of many of the individuals in the research staff within the Health Effects Research Laboratory.

The Subcommittee's major recommendation is that EPA should develop a comprehensive plan for an extrapolation models research program that should: 1) articulate an overall conceptual objective towards which individual projects would aim; 2) enhance EPA's risk assessment-risk management philosophy; 3) develop a framework that promotes more planning and resource stability in support of the research; 4) provide a common nomenclature; 5) improve communication among the Agency's organizational components; and 6) explain to the nonscientist how the research on extrapolation models supports the Agency's regulatory decisions.

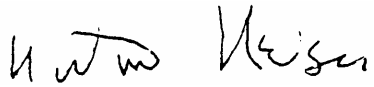
EPA must provide leadership within the Federal government to improve existing extrapolation models. EPA shares with other regulatory agencies a great need for better models, and has some resources to perform research and to stimulate work by the major Federal research organizations. Thus, extrapolation modeling creates a unique research opportunity and agenda for EPA.

The Subcommittee appreciates the opportunity to review EPA's ongoing work in extrapolation modeling. The Science Advisory Board also looks forward to a continuing involvment in the further development and application of this research. We also request that the Agency formally respond to our report.

Sincerely,



Ronald Wyzga, Chair
Extrapolation Models Subcommittee
Science Advisory Board



Norton Nelson, Chair
Executive Committee
Science Advisory Board

SAB-EC-87-030

REVIEW OF RESEARCH IN SUPPORT OF EXTRAPOLATION MODELS BY EPA'S OFFICE OF RESEARCH AND DEVELOPMENT

by the

Extrapolation Models Subcommittee
Science Advisory Board
United States Environmental Protection Agency

May 1987

U.S. ENVIRONMENTAL PROTECTION AGENCY

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I. EXECUTIVE SUMMARY

EPA uses risk assessment as a technical basis for developing regulations and standards. Models that allow one to extrapolate from one set of scientific phenomena or observations to another are an important component of risk assessment. Not all participants in the regulatory process outside of EPA accept the use, or the extent of use, of extrapolation models. Although the Subcommittee members believe that the use of extrapolation models is intrinsically acceptable, to others the choice of a particular assumption or model seems arbitrary. These choices can result in larges differences in risk estimates and thus, regulatory decisions.

All extrapolation models are subject to considerable scientific uncertainty, and many such models lack recent scientific review. To improve public acceptance of the regulatory process at EPA, it is imperative that the Agency promote efforts to improve and validate extrapolation models. The development of accepted extrapolation models can also improve the Agency's use of its resources because these models can be substituted for more intensive (and often more expensive) collection of directly applicable data.

The subject of extrapolation modeling is complex. The Subcommittee believes that the field is multidisciplinary and that the work can be viewed from different perspectives, such as the kind of extrapolation process, the stage of model development, the scientific discipline involved or the general approach to modeling. The Subcommittee developed two principles to evaluate EPA's research on extrapolation models. These include:

1) If research on an extrapolation model is successful, how will the Agency be able to better assess risks? What can EPA do with an improved model that it can not do without one?

2) Will successful research on a model establish leadership for EPA within the scientific community and promote interest in the model outside of EPA?

EPA's Office of Research and Development (ORD) provided a well written briefing document for the Subcommittee. However, limitation of the review to intramural projects within ORD made it difficult for the Subcommittee to evaluate the comprehensiveness and coherence of ongoing work because key elements may have been externally performed. Scientific personnel working in EPA's program offices also contribute significantly to model development. Based on knowledge from other SAB reviews, some Subcommittee members also noted that elements of ORD's ongoing internal work was also not included, particularly in the areas of ecological and dosimetric models, or models that define the movement of pollutants from the environment to a receptor. These omissions, and the time lag in the Subcommittee's preparation of this report, probably have resulted in recommendations that parallel more recent ORD work that is underway.

In their presentations, ORD's scientists emphasized specific projects conducted by various organizational components. Combined with the lack of a comprehensive strategy to direct them, this emphasis placed the Subcommittee in something of a dilemma. The Subcommittee had expected more of a synthesis or overview of the ORD work from the perspective of extrapolation processes. Therefore, instead of commenting on a strategic document and placing more emphasis on reviewing specific models used by the regulatory offices, the Subcommittee has constructed a synthesis of its own.

At present, work on extrapolation models is a small portion of ORD's overall responsibility. In some cases, small pieces of research are carried out with no clear relationship to other research projects or to long-term goals. In other cases, whole areas of extrapolation modeling are apparently ignored. Often, projects are funded for purposes other than the advancement of extrapolation modeling. Such "piggyback" funding permits investigators the time to reorient and refocus their ongoing work onto extrapolation modeling topics. The overall funding level is low in relation to the magnitude of the problem facing the Agency. Given these circumstances, Agency management should not develop unrealistic expectations of ORD.

Support for extrapolation modeling could suffer from EPA's approach to allocating research funds through program-oriented research committees because the work seldom is program or medium specific. However, there are examples which suggest that this is not a uniform problem. The Subcommittee believes that the interaction between ORD and Office of Air Quality Planning and Standards has been productive and could serve as a prototype for other efforts in EPA. The existing research committees and the research initiative on extrapolation modeling revealed by the briefing document provide a start toward a program plan that is responsive to overall Agency regulatory needs.

The Subcommittee identifies ten extrapolation processes that are important to EPA's regulatory efforts. Each process subsumes many specific models. The Subcommittee did not possess a detailed description of models currently used by EPA. It concludes that the scope of ORD's current efforts is uneven, observing specific weaknesses in research on extrapolation between times of effect, structure-activity relationships and pathology/organ systems.

The Subcommittee also reviewed ORD's intramural research on extrapolation models from the perspective of scientific disciplines represented. Its major comments include:

1) ORD's carinogenicity program is well-defined, but the various components of the program are not of equal importance. It was not clear how the research components were selected. Moreover, modification of the planned research could result in significant increases in the value of the work.

2) Extrapolation modeling efforts for mutagencity are clearly warranted. The relevance and validity of the existing research for future risk assessment efforts were not always apparent in the briefing document, and further clarification is desirable. It also appears that this work would be enhanced by increased statistical analysis. The Subcommittee questions whether the results from extrapolations based on the parallelogram model will be useful in predicting adverse human health effects because ORD did not state how chromosome aberrations or formation of adducts relate to human risk. The study

of models that extrapolate from high to low exposures is of particular interest because it is now possible to measure chemically the formation of adducts between genetic material and genotoxic chemicals to provide estimates of internal exposure at much lower doses than previously possible. ORD is participating in this scientific advance. Measurements of adduct formation in animals (or humans) in which toxicity occurs will be of general theoretical importance in extrapolating risks to low doses.

3) The nonionizing radiation research program could contribute information to several extrapolation models that are specific to this source. The goal of the effort should not, however, be just a model with a certain number of cells but an insight into adverse physiological effects in humans as a result of elevated temperature induced by radiofrequency heating. More attention might be given to addressing the significance of physiological effects predicted in humans.

4) The Subcommittee recommends that ORD conduct more of the type of work reported as comparative toxicology and as structure-activity relationships among toxicants.

5) The investigators within the neurotoxicology program appear to coordinate well, and they study the same chemicals under nearly identical conditions. The quality of the research is uniformly high. Indeed, the research group at EPA is widely recognized as a leading neurobehavioral toxicology group in the country. The details of how the developing data base will be applied to the development of extrapolation models needs to be articulated in greater detail.

6) There is a need to develop a methodology for risk assessment in reproductive and developmental toxicology. Some of ORD's work is markedly out of date, whereas other aspects are abreast of contemporary developmental biology as it relates to questions of environmental toxicity. The developmental biology program needs an external, independent source of ongoing guidance and review from senior scientists in the same field. The plans in the briefing document to develop new methods for dermal absorption and reproductive toxicity, although important toxicologically, do not seem to fit with attempts to advance risk assessment in these areas.

7) The research of the inhalation toxicology program addresses issues that are critical to the development of reliable extrapolation models for pulmonary targets. In general, the program is scientifically sound, and it systematically attempts to provide those data needed for accurate extrapolation modeling. The dosimetry studies comprehensively examine important pollutants to provide accurate comparative regional dose estimates for several species. Sensitivity analyses with the developed models can be used to effectively guide further experimental work. However, the species sensitivity aspect of the program is not as well focused and appears to be addressing some important points, while emphasizing some that may not be as critical to extrapolation models. Some refinement is needed to determine which endpoints are of health significance.

8) Most of the projects on systemic toxicants are in the formative stages. The Subcommittee found the lack of integration between this program and the programs in neurotoxicology, inhalation toxicology and developmental biology to be particularly frustrating, since the latter subjects are components of systemic toxicology. Certain organ systems, such as the liver and kidney, receive no attention in ORD's plan. Work in these areas may

lead to new risk assessment guidelines. It seems implausible that the evaluation of test data will generalize much from one organ system to another. For example, EPA could have one guideline for the assessment of neurotoxic substances and another for the assessment of substances that pose developmental risks. This is another reason to establish stronger linkages between the systemic toxicology program and other programs, and to provide research coverage of all major organ systems.

Based on its review from the perspective of scientific disciplines, the Subcommittee concludes that ORD's program has many sound elements, but that the effort is uneven and that omissions exist in some important areas. However, the existing program does provide a good start for a more comprehensives research effort, and stronger planning should make the program on extrapolation modeling more effective in meeting the Agency's regulatory needs.

The Subcommittee also reviewed some disciplinary efforts that cross-cut those described above, particularly pharmacokinetics. Pharmacokinetic approaches within the extrapolation research program range from non-existent to quite sophisticated. For example, the reproduction, teratology and neurotoxicology programs do not discuss pharmocokinetic parameters in the briefing document, while the carcinogenicity and inhalation toxicology programs emphasize dosimetry and modeling at a high level of sophistication. The Subcommittee concludes that certain of the disciplinary programs would benefit by the inclusion of pharmacokinetic experiments and that EPA should develop a systematic approach to pharmacokinetics across all programs of extrapolation modeling.

In addition to pharmacokinetics, there are other disciplines, such as statistics, that also integrate information from different organ systems or extrapolation processes. They also will help to provide coherence to ORD's extrapolation modeling research effort. Work to refine and improve extrapolation models is inherently statistical in nature. Laboratory research aimed at this objective requires the application of statistics for such topics as data analysis, testing of hypotheses, modeling of dose-reponse curves, experimental design and interpretation of statistical variation. Risk assessors can use statistical approaches to analyze large data bases and gain insight into fundamental methods. Although such work is difficult and often demands a multidisciplinary effort, statistical approaches provide, for example, the default assumptions used by regulatory agencies when precise data are not available. Given the emphasis of the briefing document on human endpoints, the absence of epidemiology research also was notable.

Relative to the available resources, the current research program is scientifically promising. ORD has developed a number of worthwhile projects that could improve Agency risk assessment practices and has recruited a group of talented investigators. However, ORD lacks a strategic plan. The current plan brings together independent projects well before the establishment of a compre-hensive extrapolation modeling program. An overall strategy towards which the individual scientist can aim does not exist.

The Subcommittee recommends that EPA initiate work on the plan by making an inventory of the extrapolation models actually used by the various regulatory programs and evaluating them. This specific task has merit on it own, not only as part of the broader planning effort. It could identify areas in which improved extrapolation models are needed and aid in determining the implications for research planning. Development of such a plan should involve all parts of the Agency which make use of extrapolation models, particularly the program offices.

A comprehensive plan for an extrapolation models research program should: 1) state an overall conceptual objective or framework towards which individual projects would aim; 2) enhance EPA's risk assessment-risk management philosophy; 3) develop a framework that promotes more planning and resource stability in support of the research; 4) provide a common nomenclature; 5) improve communication among the Agency's organizational components; and 6) explain to the nonscientist how research on extrapolation models supports the Agency's regulatory decisions.

EPA must provide leadership within the Federal government in improving existing extrapolation models. EPA shares with other regulatory agencies a great need for better models, and EPA has some resources to perform research and stimulate additional efforts by the Federal research organizations. Thus, extrapolation modeling creates a unique research opportunity and agenda for EPA.

II. INTRODUCTION

The charge to the Extrapolation Models Subcommittee was to advise the Administrator and other senior officials of EPA on the status of research on extrapolation modeling within EPA's Office of Research and Development (ORD). The Subcommittee focused, in-particular, on the integration of existing research efforts and their relevance to EPA's regulatory requirements. It also addressed the future needs of the research program. Given the importance of extrapolation models to EPA, other Federal agencies and the scientific community, the Subcommittee has broadened its charge to include a survey of research needs and opportunities that each of these groups, working individually or collectively can address. In support of this review, the Subcommittee received a briefing of two days duration and a report with two appendices. The review is one of a series of SAB efforts intended to independently evaluate ORD's progress in developing data and methodologies for use in regulatory decision making.

Dr. Richard Schlesinger was unable to attend the meeting in person but contributed comments by mail after telephone interviews with appropriate EPA personnel. Dr. Sergio Fabro attended the meeting, reviewed all materials related to developmental or reproductive effects and created the structure of sections V and VI of this report. Unfortunately, Dr. Fabro died while the report was in preparation. Dr. Marshall Johnson, who did not attend the meeting, volunteered to assume responsibility for completion of the developmental and reproductive effects subsections of section VI.

A. DEFINITIONS

As the Subcommittee views the subject, a "model" is an abstract, conceptual description of an object or process that imitates or describes essential features of the object or process, often in mathematical or statistical terms. Models usually are neither well validated nor broadly applicable, but intend to represent components or examples of a specific phenomenon. Models often inexactly describe a complicated, poorly understood object or process. A model can be physical, conceptual or mathematical. For example, a rodent can be used as a physical model of a human in toxicological assessment. The idea that a rodent is an analogue of a human can be expressed diagramatically as a conceptual model. EPA often extrapolates quantitatively from rodents to humans on the basis of body surface area, estimated as a function of body weight. This overall concept can be expressed as a mathematical model, as follows:

$$\frac{(\text{rodent weight})^{2/3}}{(\text{rodent potency})} = \frac{(\text{human weight})^{2/3}}{(\text{human potency})}$$

Although the above is illustrative of extrapolation model concepts, most models that EPA uses are more complex than this example.

Extrapolation is the process of projecting beyond the available data on the basis of the available data. When the model is mathematical, equations

are developed that are consistent with the phenomenon and other scientific information, and equations are fitted to the data to develop parameters. New solutions are then developed with inputs beyond the range of the data. Following common usage in the discussion below, reference is made occasionally to "extrapolation" to untested doses outside of the tested range, which is similar to the other processes discussed. In reality, EPA interpolates between doses since an estimate is made within the range of doses, including an undosed control (or baseline) observation.

B. AGENCY USES OF EXTRAPOLATION MODELS

Extrapolation models are important for EPA because the Agency rarely has fully conclusive data on the "cause" of a public health and environmental problem that is the object of a proposed regulation. Thus, the scientific assessments, on which regulatory and enforcement actions rest, frequently derive from one or more extrapolation models. EPA currently uses extrapolation models in the absence of human data for at least ten sets of scientific activities. These include extrapolating:

1) Quantitative potency between species.

2) Effects in a "normal" population to subpopulations with different sensitivity due to a prior disease state that may be genetically and/or environmentally caused.

3) Qualitative pathology or organ system involvment.

4) Low dose effects from high dose data (with inherent or empirical control data).

5) Effects with one route of administration from data on another.

6) Effects from different times of exposure (and dose rates).

7) Times of effect.

8) Effects at different developmental stages.

9) Effects of untested chemical structures from data on related chemical structures.

10) Whole animal effects from test tube or cell culture results.

After their initial development, new extrapolation models are subjected to technical peer review and sometimes to public comment. They may become widely used if they withstand this scrutiny. The development of accepted extrapolation models can also result in significant economies to the Agency because these models can be substituted for more data intensive (and often more expensive) methods.

In general, the Subcommittee believes that EPA clearly needs to use extrapolation models to discharge its responsibilities.

C. THE COMPLEX NATURE OF EXTRAPOLATION MODELING

As each model develops, work on any of the ten processes of extrapolation described above proceeds in stages. The stages might be described as follows:

1) Physical model.

2) Conceptual model.

3) Mathematical model.

4) Experimentation and validation.

5) Statistical analysis.

6) Iteration of the above steps.

However, this description of the stages uses terms that are overlapping and not independent of each other. For example, a physical model need not be used at all. Statistical analysis sometimes is the first step in model development. At any stage, an alternative model can be posed for investigation. For example, scientists may debate whether mice or rats are a more appropriate physical model to understand some health effect of a substance in humans. As another example, two mathematical models compete as descriptors of the relationship of carcinogenic potency between species. One is body surface area (described above) and the second is body weight, which differs mathematically, as follows:

$$\frac{\text{(rodent weight)}}{\text{(rodent potency)}} = \frac{\text{(human weight)}}{\text{(human potency)}}$$

EPA currently has a cooperative project with the Department of Defense that will attempt to choose between these two (and other) models based on the available human and animal data. This is a very important project for the Agency, as the choice between these two models could result in a re-examination in the level of some environmental standards. (This work was not included in the extrapolation modeling program presented to the Subcommittee because the project is externally funded.)

Extrapolation models will differ depending on the biological endpoint in question. For example, neurotoxic effects and carcinogenic effects are unlikely to develop in a parallel manner under identical conditions of chemical exposure. Most of the various toxicological disciplines differ in their techniques, methods and approaches. From the perspective of laboratory scientists, the technology employed by different disciplines differs so drastically that discussion of the models across these boundaries may seem pointless. For example, the neurotoxicologist focuses on the communication of information by a specialized tissue, using techniques such as measurement of nerve conduction velocity. The oncologist seeks to

understand the phenomena of uncontrolled cellular growth and metastasis, perhaps by measuring alterations in the structure of genetic material. Even if the the same event were examined, for example, the induction of a neuroblastoma, the methods utilized by the two disciplines probably would differ. The examination of the tissue by each expert could involve differing conceptual approaches, pathological techniques and ideas of disease progression, making it unlikely that the disciplines would reach identical conclusions. This latter outcome poses a great challenge for regulatory agencies seeking to synthesize scientific data and methods in a risk assessment.

Another way to view the progress of an extrapolation model is its stage of refinement. To some extent, refinement runs parallel to the stages of development described above. Conceptual models are approximately the same as "default assumptions" in the field of risk assessment. EPA uses default assumptions when specific data on a substance or process are not available. The default assumption is based on reasonable ideas about how substances or processes behave in general. At an early stage, the model may be a vague concept, which later is expressed mathematically> The mathematical expression is more rigorous. However, as work on a model proceeds, a larger data base accumulates that can be used to help evaluate the model for its scientific adequacy. Care must be taken, however, to insure that the same data are not used both to generate and evaluate the model. Particularly when the model is mathematical, it can be fitted to different data sets in order to better state the form of the equation (or its parameters). Discrimination will be gained on how the parameters will change with different categories of substances. Further, confidence in any model will grow as it withstands increasing scrutiny.

The importance of analyzing a model for consistency with the data and accepted theories of physics, chemistry, medicine and biology has not received sufficient attention by regulatory agencies. Often, so many years lapse between proposal of a model and general acceptance that it contradicts our general scientific understanding and should be discarded. In same cases, no known or practical way exists to validate a model.

Eventually, as EPA and other organizations collect better data on a particularly contentious process or substance, it may no longer be necessary to use extrapolation models. The Agency may have exact data on the phenomenon of interest and can provide a more accurate, specific assessment with the result that the uncertainty in risk estimates will decrease in the progression from educated guesses to validated models to exact data on the process in question. This progession contrasts with research on the models themselves, where the effort is to validate the equations or parameters of the model for general use, not to replace it with a description of a single phenomenon. Because the Subcommittee was asked to describe the progress that ORD is making in answering the needs of the Agency to extrapolate, an effort has been made in this report not to confuse work on the models with data acquisition.

The mathematical form, or at least the parameters, of a model will change, depending on the chemical substance involved. For example, the Metals Subcommittee of SAB's Environmental Health Committee has discussed with EPA's Carcinogen Assessment Group the idea of basing the extrapolation between species of carcinogenic potency for inhaled metallic particles on the processes of deposition and absorption in the lung, rather than body metabolic rate. The Metals Subcommittee and the Carcinogen Assessment Group agree that extrapolation based on body metabolic rate can be appropriate for gases.

Despite the complexity of model development, the scientific goal for each model of each biological endpoint is the same, namely to reduce uncertainty to the maximal extent possible. Ultimately, it is desirable not to extrapolate at all, by aquiring and utilizing information on the effect in question by direct observation of the target species of concern and the pollutant of interest at actual environmental exposure levels, and to have these observations supported by well-validated theories of the mechanisms involved. Such information will seldom be available to EPA. Its acquisition is resource intensive for both dollars and equipment and in the use of scarce personnel with special skills and time. Hence, this ultimate goal needs to be replaced by another, more feasible one of having generally accepted extrapolation models with minimal uncertainty associated with their use. These models would enable EPA and other regulatory agencies to achieve their goals through a less resource and data intensive approach.

To better organize the complex task inherent in developing models, the Subcommittee recommends that EPA adopt the idea of a multi-dimensional matrix. Each dimension of the matrix would indicate one of the following ways of viewing the subject:

1) Extrapolation processes, as described above.

2) Stages of model development, as described above.

3) Biological effect or toxicological discipline.

4) Substance(s) of concern.

5) Stage of data aquisition.

6) General approach to modeling or to biological phenomena.

If any two of these dimensions were illustrated as two sides of a chart (or computer spreadsheet), each intersection on the chart would still be quite complex.

D. RELATIONSHIPS BETWEEN EXTRAPOLATION MODELING, PHARMACOKINETICS, STATISTICAL APPROACHES AND RISK ASSESSMENT

Pharmacokinetics is the study of the absorption, metabolism, distribution and elimination of foreign substances (xenobiotics) from the body. Pharmacokinetic information can contribute to any of the ten processes (see page 7) for which EPA uses extrapolation models. However, pharmacokinetic information cannot provide a complete basis for a desired extrapolation process because more factors are involved in each process than absorption, metabolism, distribution and elimination of the external dose (or exposure). For example, in extrapolating between two species, knowledge of the internal (biologically effective) dose of a substance can be gained from a knowledge of the pharmacokinetics of the substance. Indeed, even if the pharmacokinetic data are understood in only one of two species, scientists can make an informed estimate of the internal dose in the second species. However, if the internal dose is the same in the two species, the biological response may differ between them.

All extrapolation models are influenced by pharmacokinetic data. In addition, pharmacokinetic data can contribute to an estimate of risk without the necessary inclusion in an extrapolation model. Therefore, extrapolation modeling and pharmacokinetic analysis overlap each other.

Work to refine and improve extrapolation models is inherently statistical in nature. Laboratory research aimed at this objective requires the application of statistics for such things as data analysis, testing of hypotheses, modeling of dose-response curves, experimental design and interpretation of statistical variation. However, "non-laboratory" research activities, which the Subcommittee has defined as "statistical approaches," also play an important role in extrapolation modeling. Risk assessors use statistical approaches to analyze large data bases, gain insight into fundamental methods and develop default assumptions. Such work is difficult, and it often demands a multidisciplinary effort of skilled investigators.

E. OPERATIONAL OBJECTIVES

The Subcommittee has searched for some principles by which progress in research on models could be evaluated. Progress could be said to occur if the research were to:

1) Provide data sufficiently direct and accurate that there is no need to extrapolate.

2) Generate new physical, conceptual or mathematical models.

3) Help focus the acquisition of new data on the most crucial elements of a model and/or improve the parameters of a model.

4) Provide support information that validates, replaces or contradicts a model used by the Agency.

5) Provide critical examples of models (e.g., for a prototype substance).

6) Accumulate sufficient empirical data to stimulate statistical analysis and hypothesis formation.

7) Develop statistical measures of the different classes and impacts of uncertainty, given a set of assumptions for a specific process, substance or model.

An extrapolation model can be evaluated with respect to its function according to the following principles.

1) Is the model efficient? Does it lead to improved risk assessments and aid in rejecting inferior ones? Can it be used by Agency regulatory staff?

2) Is the model accurate? Does it provide answers that are numerically close to measurements in the field?

3) Is the model congruent with (relevant to) the decision at hand? Is it valid?

4) Is the model flexible? Can it be modified easily to reflect a different object or process?

5) Is the model transparent? Will a decision maker distrust or not use a model because it is too far removed from experience?

6) Is the model accepted within the specialized technical community?

While the two sets of principles stated above generally can assist the the scientific community in describing the progress achieved in developing a specific model, they do not easily facilitate the comparison or evaluation of work conducted by ORD on different models. Instead, the Subcommittee developed two principles to guide its discussions, evaluate material prepared by ORD and write this report. They include:

1) If research on an extrapolation model is successful, how will the Agency be able to improve its assessment of risks? What can EPA do with an improved model that it cannot do without one?

2) Will successful research on a model establish leadership for EPA within the scientific community and promote interest in the model outside of EPA?

F. SCOPE OF THE REVIEW

At its review meeting, ORD staff informed the Subcommittee that the review would not include externally funded work. Thus, extramural grant and contract projects supported by ORD were not reviewed. Only work done by ORD employees has been evaluated.

As suggested above, most of risk assessment involves the integration of hazard and exposure estimates. The Subcommittee found that little of the research presented at the meeting or in the ORD documents related to exposure; most emphasized hazard, particularly human health hazard, as the objective. Most assessments of the hazard to human health presented by processes or substances do have embedded in them a variety of extrapolation models. However, the Subcommittee is aware of intramural research done within ORD on models used in expressing exposure and ecological hazards.

III. ORD's APPROACH TO EXTRAPOLATION MODELING

A. EPA's RESEARCH COMMITTEES

ORD and the regulatory offices jointly establish priorities for research programs through a process of extensive consultation within six Research Committees. Four of these Committees relate to the major program offices air, water, hazardous wastes and pesticides/toxic substances. The remaining two Research Committees focus on multimedia energy issues (including acid deposition) and interdisciplinary research. These Committees consist of Agency officials from both ORD and the program offices and are co-chaired by research and program managers from both units. Because the Research Committees serve many clients and address all scientific disciplines that cross-cut the ORD laboratory structure, they focus with difficulty on single initiatives, such as extrapolation modeling.

As the Subcommittee understands it, the potential exists for each Research Committee to give a low priority to research that would significantly enhance the risk assessment process in all program offices because the research is not specific to one environmental medium or program. However, ORD Research Committees do provide an opportunity for program offices to actively develop their own research objectives and introduce scientific initiatives in the planning process. One example of this intervention, the interaction between ORD's inhalation toxicology researchers and the Office of Air Quality Planning and Standards (OAQPS), has led to some of the best (and most easily applied) research on extrapolation models covered in this review. The Subcommittee suggests that EPA as a whole will benefit if it builds upon the ORD-OAQPS interaction.

B. FORMULATION OF THE ORD PLAN

Improving extrapolation modeling is essential to enhancing EPA's risk assessment efforts. ORD's research emerged as a result of projects undertaken by individually creative and ambitious investigators. These early efforts were encouraged by other factors, including: 1) OAQPS staff who understood and supported the relevance of this work to their own programmatic goals; 2) recent recommendations by the SAB in reviews of EPA Health Assessment Documents and Criteria Documents; 3) the Agency's development of new risk assessment guidelines; and 4) the National Academy of Sciences report on "Risk Assessment in the Federal Government: Managing the Process."

Research Committee deliberations and interactions among laboratory scientists and program office staff subsequently led to the identification of a set of major issues in extrapolation research. The overall goal was identified as the need to enhance significantly the scientific basis for risk assessments based on health effects data. The immediate objectives were identified as conducting the research necessary to produce models for important extrapolation processes.

The response of ORD's scientists to this set of objectives was to identify on-going research that appeared to have relevance to extrapolation modeling and to formulate an initiative to the extrapolation of chemical and pharmacokinetic properties to health and ecological effects. (See Appendices to ORD's briefing document). While this effort achieved some early successes, the initial plan omitted some extrapolation models of importance to EPA's direct regulatory needs and lacked sufficient detail to permit evaluation of specific experiments. The Subcommittee recommends that future ORD planning efforts emphasize the specific models currently used in standard-setting, litigation and enforcement, and their relative importance.

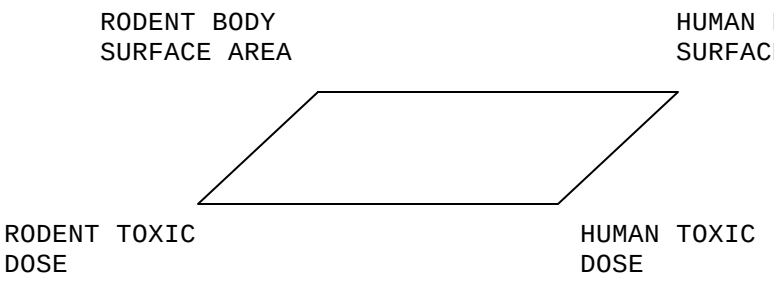
C. BUDGETARY SUPPORT FOR ORD'S EXTRAPOLATION MODELING RESEARCH

The Subcommittee requested and ORD provided a brief summary of EPA's funding for research on extrapolation models. The Subcommittee understands that budget estimates available at the review meeting represent approximations and that individual investigators partition their effort between different projects, many of which are not primarily intended to support extrapolation modeling. This partitioning does not yield precise dollar estimates. The efforts by individuals apparently are added together, and dollar figures are based on the projected cumulative effort.

The "ballpark" figure for total support of extrapolation modeling, about four million dollars for Fiscal Year (FY) 1986, is important in two regards. First, work on extrapolation models is a small portion of ORD's overall responsibility. Second, this level of funding is low in relation to the magnitude of the problem facing the Agency in the area of extrapolation modeling. Unless additional funding is provided, Agency management should not develop unrealistic expectations of ORD.

D. THE PARALLELOGRAM APPROACH

During the course of the briefing, ORD staff from more than one discipline made reference to a "parallelogram" concept which has a certain appeal as a unifying principle for ORD's effort on extrapolation modeling. If used with the rodent to human body weight example described in the introduction (above), a parallelogram would resemble the following:



The Subcommittee believes that the parallelogram approach has both advantages and disadvantages. When the Agency has a detailed understanding of the extrapolation process, the parallelogram approach is an excellent heuristic device, particularly to communicate the work to an audience of lay persons. It also concisely displays the relationships under discussion.

A parallelogram also oversimplifies the information and tends to conceal a number of complexities. In the example above, the Agency actually measures body weight, not body surface area. A parallelogram implies that all relationships will exhibit simple linear proportionality, which seldom will be the case. Most importantly, the parallelogram implies that building extrapolation models is a facile process, leading the uninitiated to believe that relationships between any variables can be derived easily, which is wrong. In several instances, the presentations left the Subcommittee with the feeling that inadequate attention had been given to model formulation and verification. Nothing intrinsic to the parallelogram approach communicates when it is not applicable.

IV. ORD'S PROGRAM FROM THE PERSPECTIVE OF EXTRAPOLATION PROCESSES

The Subcommittee does not intend to provide a project by project evaluation of of ORD's entire program in this section of the report. Instead, the Subcommittee seeks to discuss the applicability of selected ORD research to some important issues facing the field of extrapolation modeling which, in turn, can aid ORD in identifying some future needs of this program. Ultimately, ORD will have to document the extrapolation models in use for a comprehensive evaluation to take place.

A. EXTRAPOLATION BETWEEN SPECIES

Many of the state-of-the-art advances in extrapolation between species originated within ORD's Office of Health and Environmental Assessment, especially in the Carcinogen Assessment Group (CAG) which has pioneered the use in regulatory decision making of animal data to assess carcinogenic risks of substances to humans. Most of these accomplishments have not been funded directly as research projects. Instead, the research developed because existing methods did not work during efforts to assess carcinogens for regulatory purposes. For this reason, much of the creative work of broader significance has been "bootlegged" from the budget to support risk assessments for specific substances.

ORD's Health Effects Research Laboratory is aware of the need to support extrapolation work, and the Subcommittee concludes that ORD has a number of worthwhile projects underway that could further improve Agency practices. The lack of any citation in the briefing document of CAG efforts that address extrapolation issues is noteworthy and suggests that better communication is needed among the EPA groups working on extrapolation models.

EPA basically relies on two approaches to extrapolate between species. These include: 1) body surface area for carcinogenic risks based on the incidence of tumors at different exposure levels, and 2) a safety or uncertainty factor for non-carcinogens, based on an exposure level at which no adverse effects are observed. Both approaches acquire an additional degree of safety through an emphasis on the most sensitive species. During FY'86, ORD has projects underway on the rate of heat loss in response to radiofrequency radiation, computer simulation of radiofrequency effects, determination of the ratio of the dose causing adult toxicity to that causing developmental toxicity, embryo culture, interspecies extrapolation of genotoxicity (especially for molecular dose to DNA), genetic activity profiles, comparative toxicity, dermal absorption, auditory and visual sensory function, male reproduction, uncertainty factors, behavioral/ cognitive studies of animal models for known human effects, studies of animal measures of behavioral/cognitive effects correlated with human effects, inhalation toxicology, predictions of ozone absorption and effects, and pulmonary deposition models for particulates or gases.

Only in a few cases did ORD explain how possible research outcomes might change existing Agency practices of extrapolation between species. One such example is the determination of the ratio of the dose causing

adult toxicity to that causing developmental toxicity. EPA currently assumes that the ratio does not change across species, but the research in progress might show that the average ratio for various substances differs from one species to another. Such information could enable Agency risk assessors to evaluate developmental risks more accurately. Overall, ORD research on extrapolation between species is scientifically adequate and some EPA scientists working on this process are the leaders in their scientific fields.

B. EXTRAPOLATION BETWEEN SUBPOPULATIONS OF DIFFERING SENSITIVITY

Most EPA risk assessments assume a human population that exhibits a variable sensitivity to an environmental exposure to a chemical. If the actual population contains a subpopulation of significantly higher sensitivity, then supralinearity will occur in dose extrapolation, and EPA's usual assessment practices will not protect the subpopulation from the effects of the environmental, exposure. It is appropriate for the Agency to inquire whether such subpopulations exist or whether the subpopulation's sensitivity is subsumed within the normal range of sensitivity of the population. If the subpopulation is not part of the normal population, it also is appropriate to search for some means to identify the sensitive subpopulation.

ORD has several projects underway on sensitive subpopulations. Research on human sensitivity to inhalation of cadmium, phosgene and ozone will help meet some immediate regulatory needs of the Office of Air Quality Planning and Standards and will provide detailed data for more generalized efforts on pulmonary deposition models of gases and particulates. The Environmental Criteria and Assessment Office in Cincinnati has a project on interindividual variability of human response to toxic substances.

ORD's overall efforts on extrapolation to sensitive subpopulations are not integrated and lack focus partly because no definition of sensitive population or set of objectives apparently exists and partly because most of the work in this area is very recent. Research planning will especially benefit from program office input since only a portion of EPA's regulations require a detailed consideration of sensitive subpopulations. However, ORD does have available leadership in this area: the inhalation toxicology program is significantly advancing the state-of-the-art, and efforts of the Environmental Criteria and Assessment Office in Cincinnati are helping to focus the issues from a methodological perspective.

C. EXTRAPOLATION BETWEEN PATHOLOGICAL ENDPOINTS OR ORGAN SYSTEMS

This extrapolation process was omitted from ORD's intial plan. It is, however, a topic of major importance. For example, EPA currently assumes that carcinogenesis in rodent species extrapolates quantitatively to humans, but that the extrapolation is not organ specific across species. This assumption conflicts with most data from models of specific human disease processes. EPA's assumption merits further investigation. As another example, some scientists have shown that, for rodent carcinogens, quantitative measures of acute toxicity correlate with quantitative measures of carcinogenic potency. While this finding is controversial, it is of great importance to Agency standard-setting because, if true, it would provide inexpensive support for the difficult and resource intensive process of evaluating carcinogens, on which EPA places great emphasis.

While extrapolation across pathological endpoints or organ systems was omitted from ORD's plan, the Subcommittee found that some interesting work on this subject is underway. In the neurotoxicology program, five projects (development of a conceptual model of neurotoxicity, development of animal models for human behavioral effects, correlation of animal measures, auditory and visual sensory function testing, and molecular neurobiology) should provide data on the correlation and causal relationships between different neurotoxic endpoints. In the developmental biology program, work on male reproduction should show whether different measures of pathology measure the same or different endpoints. ORD has developed a large data base which profiles the available data on a specific chemical for many genetic toxicity endpoints. The Subcommittee suggests that statistical analysis of these data may determine whether different endpoints are measuring the same thing, or not. The inhalation toxicology program has developed physical models that show how different measures of lung toxicity are associated with each other, and such models should enhance our understanding of the relationship between damage to the lung and to other organs from different kinds of particulate substances. Work in the Environmental Criteria and Assessment Office in Cincinnati on the similarity of target organs and on the severity of effects directly relates to extrapolation between pathological endpoints. All of these projects will produce data that have the potential of changing and/or improving existing regulatory practices.

D. INTERPOLATION BETWEEN DOSES

EPA has developed many of the state-of-the-art practices to interpolate between doses. ORD's Carcinogen Assessment Group has pioneered the use of the so-called "linearized" multi-stage model for the assessment of carcinogenic risks. Apparently, this accomplishment has not been funded as a research project per se. Instead, the work occurred, in part, as CAG responded to comments on proposed guidelines for regulating carcinogens in water. For this reason, much of the creative work on this model has been "bootlegged" from the budget to support regulatory assessments for specific substances. ORD's Health Effects Research Laboratory is aware of the need to support research on interpolation between doses. There is, however, little work underway in this laboratory to address EPA's needs in dose interpolation directly.

More than half of the projects reviewed by the Subcommittee have the potential to influence Agency practices in this area. The project on the risk of chemical mutagens at environmental levels has great potential for the validation of some of EPA's high-to-low dose interpolation models because molecular doses to the genome in humans can be related to the direct observation of the incidence of cancers in exposed persons. ORD should clarify whether this research may duplicate other developments within the Agency addressing the same problem.

E. EXTRAPOLATION BETWEEN ROUTES OF ADMINISTRATION

Although program offices often base their regulatory actions on extrapolation between routes of administration, the ORD program places little emphasis on this process. It is supported only by work in the inhalation toxicology program on cadmium and phosgene and by the pharmacokinetics program.

F. EXTRAPOLATION ACROSS DURATIONS OF EXPOSURE

Extrapolation between different times of exposure is a fairly constant feature of EPA's risk assessments. Usually, the Agency assumes the that fraction of lifespan is equivalent between species. Testing of this assumption merits more research support than currently exists. Even in extrapolating data from the same species to different durations of exposure, the relationship between the different durations of exposure often is not clear. EPA usually assumes a ten-fold increase in potency from acute to subchronic exposure and another ten-fold increase from subschronic to chronic exposure. Additional research is needed to validate these assumptions or provide new ones.

The radiofrequency program has examined extrapolation across time of exposure through computer simulation and experiments. This focus is also a central feature of the pharmacokinetics program. The inhalation toxicology program has projects on pulmonary deposition of particulates and gases that will provide valuable data. The mutational risk project looks at time of exposure in relation to germ cell progression. The Environmental Criteria and Assessments Office has a project on dose duration associations. Overall, research on this topic is well supported by ORD.

G. EXTRAPOLATION BETWEEN TIMES OF EFFECT

Extrapolation of the interval between time of exposure and the onset of effect (latency) has been a particularly difficult aspect of EPA's carcinogenicity assessments. Often the animal data are inappropriate to estimate latency since increased tumor prevalence in a study is difficult to distinguish from reduced latency. Since the Agency's policy is to extrapolate on the basis of tumor incidence without regard to correspondence between organ sites or kind of tumor, latency to the appearance of the animal tumors does not necessarily correspond to the latency of human cancers. The Carcinogen Assessment Group has done some work on so-called "time-to-tumor" models that have been an important feature of risk assessments for a few substances, such as ethylene dibromide. The radiofrequency program and the mutational risk project on germ cell progression also provide some information on latency of effect, but ORD does not appear to do much research in this area.

H. EXTRAPOLATION BETWEEN DEVELOPMENTAL STAGES

EPA typically bases risk assessments on rodent data obtained using standard toxicological protocols. These data are not informative of whether some particular developmental stage is more sensitive, yet the regulatory program offices have to set standards that will protect all developmental

stages and in some instances, such as adolescents employed in agriculture, have to set standards for a specific developmental stage. It often is not clear how to extrapolate in a risk assessment from toxicity data on adults to other developmental stages. Both the neurotoxicology and developmental biology programs have work underway that is generally concerned with this important problem. The dermal toxicology project has already shown that there is no consistent effect of developmental age on dermal absorption. The Subcommittee concludes that the emphasis in this area is appropriate to the Agency's needs for new information, in part because two other research programs have a general emphasis on the extrapolation problem.

I. EXTRAPOLATION BETWEEN DIFFERENT CHEMICAL STRUCTURES

EPA has to evaluate potential effects between chemicals of similar structure in evaluating premanufacture notices, prioritizing lists of substances for detailed assessments, estimating the effects of certain mixtures of closely related substances (e.g. petroleum products) and assessing the weight-of the-evidence for toxic effects (e.g. carcinogenicity). Given this need, the Subcommittee concludes that the ORD effort on this extrapolation process is not extensive enough.

ORD described work in progress within the neurotoxicolgy, genetic toxicology and comparative toxicology programs, but these efforts seem directed at providing raw data on the effects of various substances which others could interpret, as did the short-term cancer models project. If there was any systematic effort to contrast the testing with the generic chemical structures for which the least data exist, ORD did not articulate it; neither was an effort apparent to evaluate the data statistically. ORD did not link the data gathering to the areas in which the regulatory programs experience greatest uncertainty. Only for the dermal toxicity project was an explicit effort to build models underway that was coupled with an effort to improve model building through aquisition of new data.

J. EXTRAPOLATION FROM IN VITRO TEST DATA TO WHOLE ANIMAL EFFECTS

In vitro test systems are rapid, inexpensive and relatively free of ethical considerations in comparison to whole animal toxicity tests. Since EPA often has to regulate with limited data, in vitro test systems hold great promise for carrying out the Agency's mission. ORD seems well aware of this potential, and the Subcommittee concludes that research of fundamental importance is underway for the developing the process of extrapolation from in vitro test data to whole animal effects.

The biological markers program can relate biochemical effects (that potentially can be observed in tissue culture) to the incidence of toxic effects in humans after certain exposures. Hopefully, these biochemical effects are also a part of the pathological mechanism of toxicity. The impact of such systems for Agency risk assessments is profound because causality of a biochemical event in pathogenesis will permit a direct inference to effects of other substances on the same biochemical marker in tissue culture. The work on molecular dosimetry (genetic risk of chemical mutagens at environmental levels) in the genetic toxicology program promises to have a similar power in relating the effects of many substances on cell culture substrates to a few cases in which the incidence of human cancer

at known exposures is linked to the levels of DNA modification in exposed persons. The projects on genetic activity profiles and mutational risk to germ cell stages will improve the ability of EPA to relate in vitro test outcomes to whole animal toxicities. The dermal toxicity program has already shown that human skin does not predict the whole animal absorption of hydrophobic chemicals, counter to the usual assumption of risk assessors. The neurotoxicology program has a project underway to validate the predictions made from in vitro neurotoxicity tests, and the developmental biology program has a similar embryo culture effort underway.

The Subcommittee concludes that ORD has some state-of-the-art work underway on the extrapolation from in vitro test data to whole animal effects, and that some of the investigators within this broad topic are the leaders in their scientific specialties.

V. ORD'S PROGRAM FROM THE PERSPECTIVE OF SCIENTIFIC DISCIPLINES

In the following sections, the Subcommittee has reviewed ORD's work on extrapolation models from the perspective of the scientific disciplines involved. The review does not always follow along the lines of ORD's organization. For example, the Subcommittee preferred to examine several projects on Genetic Toxicology together, although they are housed in different ORD offices and were presented separately.

A. PHARMACOKINETICS

Pharmacokinetic approaches in the extrapolation research program range from non-existent to quite sophisticated. For example, the reproduction, teratology and neurotoxicology programs do not discuss pharmacokinetic parameters in the briefing document, while the carcinogenicity and inhalation toxicology programs emphasize dosimetry and modeling at a high level of sophistication.

The non-ionizing radiation program does not involve chemical administration. Thus, pharmacokinetic approaches have no role. The reproduction and teratology programs focus on the renal, immune and cardiovascular systems for teratology studies and on gerontology and endocrinology for reproductive toxicology studies. Although this program is involved with work on dermal absorption of pesticides, the approach is in vitro and does not involve pharmacokinetics. The program would profit from the availability of pharmacokinetic data. Similarly, the neurotoxicology program places considerable emphasis on species comparisons for extrapolation research. For valid extrapolation, it would seem important to know whether apparent species differences have metabolic determinants.

The genetic toxicology program presents a parallelogram method for extrapolation of in vivo and in vitro data across species which depends on the development of dose-effect data. Although the metabolism of cyclophosphamide is mentioned briefly, and there is a mention of dosimetry under "Future Directions," no systematic approach to pharmacokinetics appears to be a part of this project.

The carcinogenicity program gives considerable emphasis to pharmacokinetics and some of the fruits of this effort could aid other research groups. One series of experiments is directed toward determining the extent to which the data from inhalation toxicokinetic studies can be used to make predictions about the effects of ingested halocarbons. Experiments that attempt to vary both the route and pattern of chemical administration are in progress to determine whether the kinetics and toxicity of halocarbons depend on the route and pattern of exposure. Studies on the toxicokinetics of cadmium involve both pharmacokinetics and computer modeling. EPA uses the data to develop a toxicokinetic model, which is then computer simulated. The simulation is used to predict the consequences of changes in the cadmium level in the food supply. A sophisticated pharmacokinetic approach is the major emphasis of this group.

The inhalation toxicology program also emphasizes sophisticated pharmacokinetics. As with many inhalation studies, dosimetry across species is a major concern. The Agency's investigators have developed ozone dosimetry models to simulate local absorption of ozone in the lower respiratory tract. Thus far, dose delivery to the lung has been emphasized. The program has considered local distribution and metabolism of chemicals and plans to combine pulmonary dosimetry models with pharmacokinetic models for extrapulmonary dosimetry.

The toxicity mechanisms program attempts to quantify and predict toxicity through structure-activity relationships in fish. This project does not emphasize toxicokinetic parameters. The comparative toxicology program also concentrates on fish models, particularly extrapolation from fish to higher vertebrates. The program compares the pharmacokinetic relationships of different species. Although specific pharmacokinetic procedures are not presented in any detail, an excellent opportunity exists for collaborative research between these two groups.

The program on genetic risk of chemical mutagens at environmental levels develops micro-techniques for the detection of trace mutagens. Such work necessarily involves some consideration of drug metabolism and drug distribution. Dosimetry methodology will be used to study the sensitivity of developing germ cells to possible mutagens. Although the briefing document presents few methodological details, this program appears to be heavily involved in micro-toxicokinetics.

The program on systemic toxicants and chemical mixtures has developed pharmacokinetic data in humans, emphasizing the exposure pathology and age of the subjects. Pharmacokinetic models are being developed for extrapolation purposes, and their utilization in risk assessment is a major direction of EPA research.

EPA should develop a systematic approach to pharmacokinetics across all programs of extrapolation modeling. The sophisticated approaches of a group primarily involved in pharmacokinetic modeling need not be universally applied, but an apparent lack of comparability exists across programs. If the Agency does support a program with a direct emphasis on pharmacokinetics, that new program can provide support to the other programs and lead the coordination effort.

B. CARCINOGENICITY (MAMMALIAN)

At the time of the Subcommittee’s review ORD's carcinogenicity program has three objectives related to extrapolation. These include: 1) developing methods using the results of short-term tests to detect and determine the relative potency of carcinogens; 2) examining the distribution of toxic substances and metabolites (singly or in a mixture) in the human body and whether route of administration influences distribution; and 3) estimating the concentration of cadmium in the human body for various key organs, given estimates of exposure.

The value of the proposed research varies with the objective. For the first objective, current estimates of carcinogenic risk are largely based on animal bioassays. These experiments, which compare the percentages of animals demonstrating cancer at two or more exposed levels, are costly and time-consuming, as they generally continue over most of the lifespan of the test animal. Short-term tests, which could yield the same information in much less time for far less cost, would be immensely useful to predict the carcinogenicity of previously untested chemicals and mixtures. Different formulations of mixtures could not practically be tested using long-term animal bioassays.

Three short-term in vivo bioassays will be studied. The class of genotoxic chemicals to which each bioassay is sensitive will be determined by literature review and experiment. The research will investigate the ability of the short-term bioassays, both individually and as a group, to rank substances according to their carcinogenic potency. Potency measures will be determined for short-term tests singly and in combination. These rankings will be compared with rankings from long-term bioassays.

The Subcommittee recommends that the carcinogenicity program evaluate the short-term tests in terms of both sensitivity and specificity. This objective requires a knowledge of both false positive and false negative outcomes, if a short-term test is to be useful. Hence, non-carcinogens of various chemical classes should be tested as well. The tests should be performed in combination with a larger set of short-term tests than the three under study. Three different short-term in vivo bioassays are to be used to discriminate carcinogens from non-carcinogens and to estimate relative activity. This discrimination can be made statistically, but it is probably best to test for discrimination with each bioassay separately.

Similarly, long-term bioassay data from rats and mice probably should not be combined because these species often differ in potency for the same substance. In some cases, a substance is positive in one species but not the other, or has only been tested in one species. Comparisons may have to be made among substances within one species, rather than by combining data from different species. There is a large data base ("TD50") of tumor incidence data in different species that might be useful. What organs and tumors will be used to determine potency in long term bioassays? The Subcommittee suggests that in some situations the carcinogenicity program will inadvertantly test simultaneously for extrapolation between organ sites or pathological endpoints. Potency differs substantially across organs and tumor types. For example, will the results from the mouse lung adenoma bioassay be expected to correlate with cancer in mice at any site? The Subcommittee did not understand how the potency of complex mixtures will be determined.

For the second objective, studies of the distribution of toxic materials are useful because experimental data often exist only for one route of exposure. It is not clear how to use the results from a feeding study to estimate risks associated with inhalation exposure. The results from this study could help the Agency extrapolate better between routes of administration. Given the higher costs and greater experimental difficulty of inhalation experiments, the carcinogenicity program might consider substituting feeding bioassays, where possible.

The Subcommittee recommends that the carcinogenicity program perform selected experiments on species other than the rat to see if the rat results extrapolate to other species. The U.S. Air Force has developed physiological pharmacokinetic models for several halocarbon solvents that are well-validated by experimental data. The carcinogenicity program should consult these models to ensure that no duplication of effort occurs and that the data are gathered at dose levels that will provide the greatest amount of information about pharmacokinetic variables.

For the third objective, a risk assessment for cadmium will be more accurate if it considers the delivered dose of a toxicant at the site of toxicity rather than the dose administered in an experiment. There also is a need to examine the influence of dosing pattern (for example, continuous versus intermittent) and variability of human response for a given level of exposure. Pharmacokinetic models and data can help resolve these issues. The SAB Environmental Health Committee has commented on the problem of deposition and absorption of cadmium particles in the lung in a separate report of December 5, 1984.

The carcinogenicity program plans to formulate a physiological pharmacokinetic model for cadmium in humans. Probability distributions for the model input variables and parameters will be derived empirically. The initial application of the system will be for cadmium ingestion. Exposure distributions will be entered into the systems to predict the population frequency distributions of accumulated cadmium in key organs, such as renal cortex.

ORD's carcinogenicity program is, in general, well-defined. However, specific elements of the program are not of equal importance and it is unclear how the elements were selected.

C. MUTAGENICITY

ORD presented two programs in genetic toxicology, both with several projects, that are primarily oriented to mutagenicity as an endpoint. Much of the work in this program also will provide useful results for the carcinogenicity program. However, the Subcommittee agrees that mutagenicity is an appropriate toxicological endpoint of concern for EPA.

The program uses the parallelogram method extensively. In one project, the investigators extrapolate genotoxicity data from *in vitro* (rodent and human cells) to *in vivo* levels of cellular organization (rodents; humans, if data are available). This approach will be useful to regulatory programs when human *in vivo* data are not available. This method has been used under a number of different names, as various investigators have tried to apply the results of short-term tests to the prediction of genetic and carcinogenic hazards. The approach outlined in this proposal is useful and has been used successfully in other laboratories. For example, the parallelogram method was applied to use frequency of chromosome aberrations in blood lymphocytes of mice and humans exposed to radiation to establish a usable ratio between the slopes of the dose-response relationships between the two species. These types of studies have enabled investigators to predict the frequency of aberrations that would be produced in humans and the genetic risk for humans exposed to ionizing radiation.

The next major step involves using the parallelogram approach with data for which the dose-response relationships in animals and humans have been developed, to define the dose at the cellular and molecular level. This is relatively simple to do in the case of ionizing radiation, where extensive theoretical work exists on the dose-response relationships, the dose is well-defined and the response can be readily measured. For chemicals, however, only the exposure is known, dose-response relationships are poorly understood and what happens at the cellular and molecular level must be investigated carefully before the parallelogram approach will be useful. For example, the concentration to which the intact animal, cell, or human is exposed may have very little relationship to the actual biological dose to the target tissue, target cell or target molecule. The investigators need to identify adducts in the target tissue following chemical exposure. Quantification of adducts will insure that more appropriate dose-response relationships are utilized in the parallelogram approach. It is evident from the literature that chemical exposure will result in many different kinds of adducts and not all of them may be responsible for the toxic effects of interest. A very important question that needs to be addressed is what level of adduct formation actually is harmful. Is there a threshold level of adduct formation below which no toxic effect will be observed?

The Subcommittee concludes that a major problem in the approach outlined is that the investigators propose, for the most part, to measure only changes at the level of the chromosome. Many chemicals are not potent clastogens but do cause point mutations. In contrast, radiation is a relatively potent clastogen but a poor inducer of point mutations. Most of the radiation induced mutations seem to be the result of chromosome deletions and not point mutations. The investigators should be encouraged to use other endpoints for the approach to be complete for the other chemicals under study.

The approach used with cyclophosphamide is to use the biological response (i.e., induction of sister chromatid exchange) as a measure of real dose and compare the level of exposure needed to double the response in both human and animal systems. This approach may help in understanding if the exposure concentration has a simple relationship to the amount of biological damage observed. However, it has been demonstrated for some chemicals that the exposure, degree of interaction with DNA and the biological response are not well-related, especially when dose-rate changes. The investigators seem to understand these problems and should be encouraged to delve deeper into the relationship between chemical dosimetry and biological effects.

While it is not explicitly stated, it should be clear that the investigators understand that their efforts are directed toward understanding exposure (dose) - response relationships. A key to this work is to make sure that dose-to-target-tissue is investigated. While the work with peripheral blood lymphocytes is appropriate for ionizing radiation, the investigators need to be careful in using chromnosome aberrations in peripheral blood lymphocytes following exposure to chemicals. Although these data will indicate target tissue dose better in some situations, in the extreme case damage to peripheral blood lymphocytes could occur that has no relationship to specific damage in a different target tissue. The investigators need first to establish, for a substance, what the relationship is between "dose" as measured in peripheral blood lymphocytes and "dose" to target tissues.

One of the major criticisms the Subcommittee has with the program is that the investigators are relating their studies to the parallelogram concept for human health effects. While the parallelogram approach is useful for specific lesions or endpoints (e.g., sister chromatid exchange or adduct formation), the Subcommittee questions whether the results from extrapolations based on the parallelogram model will be useful in predicting adverse human health effects. ORD did not state how chromosome aberrations or adduct formation relates to human risk. For example, once all the relationships are elucidated between animal and man in terms of genetic damage, how will this information be used to predict the toxic potential of a compound to people?

The parallelogram concept, as developed within this program, needs to be tested statistically. In particular, the assumption of linearity should be examined. ORD has scattered data for gamma radiation in vitro in humans, and fitting a dose-response model to such data is questionable. The investigators may need to increase the sample size since the number of dicentrics per cell seemed low. They might also utilize measures of potency that are more robust than the estimate of the linear coefficient in the model for gamma radiation. Is the applicability of the parallelogram concept for genetic toxicity being tested with different species of rodents? What measure of potency is best to use? (The doubling dose?) The investigators sometimes use the linear coefficient from the multi-stage model instead. It was not clear what measures of potency and dose were used for studies of peripheral blood lymphocytes in mice. Repeated experiments may be required to test the parallelogram concept, and the investigators should determine how much testing is required to give estimates within a prescribed degree of accuracy.

The practice of pooling data is open to criticism since conditions are never constant across different experiments. How would the results compare if the studies were used separately to estimate the model? Since extrapolation constants varied with dose (but were similar for the corresponding sides of the parallelogram), how will one predict human in vivo response for doses not tested?

Even while recognizing the difficulties involved, the Subcommittee recommends that the investigators address complex chemical mixtures. While information on single chemicals or radiation is very useful for the parallelogram approach to genetic toxicity, the Subcommittee questions whether this approach will apply to exposure to complex mixtures. Humans are exposed to mixtures of chemicals, each of which may have toxic potential.

The mutagenicity program has another project that will use animal data in which the exposure levels of mutagens are high and the incidence of mutagenic effects can be observed in small groups of animals to extrapolate to the lower mutagen doses to which humans are typically exposed. The animals will receive a wide range of exposures. This is an important area of research on high to low dose extrapolation which, in this program, appears to focus on genetic risk rather than on carcinogenic risk. Much of the conceptual approach, however, applies just as well to the problem of carcinogens that act by chemically modifying DNA. The approach that the investigators are using is appropriate and should yield valuable information for use in extrapolation.

The Subcommittee believes that another important aspect of this program is research directed toward developing methods to detect very low DNA adduct levels. The investigators should be encouraged to continue these lines of research since exposures to low concentrations of a toxicant will probably result in very low levels of DNA modification. The Subcommittee was pleased to see that the investigators realize the utility of this approach for investigations of complex chemical mixtures.

The mutagenicity progam will have to overcome some obstacles. A model development problem exists in incorporating the low dose data into a dose-response curve since linear extrapolation does not fit the data well. It would appear that the embedded problem of species-to-species extrapolation remains. The Subcommittee does not understand the extent to which dose rate will affect the interpretation.

This mutagenicity program within the Office of Health Research can make useful contributions to extrapolation modeling, but the Subcommittee had a difficult time understanding from the briefing document and oral presentations where the program is going in the future or how it related to other efforts elsewhere. The Subcommittee also had difficulity trying to determine if the approach is going to be sufficiently unique that it will add understanding to the mechanisms of damage from chemicals and radiation. Such understanding would facilitate making the large extrapolation jumps between radiation and chemicals, between in vitro and in vivo measurements of genetic damage and between animal data and man.

D. NON-IONIZING RADIATION

Non-ionizing radiation is discussed on four pages of the ORD briefing document. The Subcommittee also reviewed recent reports by other SAB panels concerning non-ionizing radiation and interviewed experts in the field, including the SAB panel chairmen.

The first of these reports (January 31, 1984) is a review of a major EPA risk assessment source document, Biological Effects of Radiofrequency Radiation. The SAB Biological Effects of Radiofrequency Radiation Subcommittee noted that a considerable portion of the scientific results reported in the assessment originated from EPA's own laboratories, and it urged that the EPA research program be maintained. A number of research topics were suggested as potentially significant for future decision making, including the effects of chronic versus acute exposures, partial body versus whole body exposures, and evaluation of the thermoregulatory capability and concomitant physiological processes of various populations exposed under extreme environmental conditions. The SAB Radiation Advisory Committee prepared a letter report on April 26, 1985 to restate the same list of research topics, stressing the potential importance of these topics for future EPA decisions.

Previous SAB reviews directed at this area have endorsed the quality and the appropriateness of the research work. The work of Spiegel and coworkers is explicitly summarized on pages 4-38 to 4-44 of EPA's assessment document. The main directions of EPA's subsequent research, extension of

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1 R. J. Spiegel, D.M. Deffenbaugh, and J.E. Mann, "A Thermal Model of the Human Body Exposed to an Electromagnetic Field," Bioelectromagnetics 1 (1980) pp. 253-270.

the heat transfer model to three dimensions and the validation of the thermal calculations using data from suitable experimental animals, are also delineated in this document on pages 4-45 and 4-46. While the discussion in EPA's extrapolation models briefing document of the motivation for this research might be improved, it essentially addresses research needs identified in the EPA radiofrequency assessment document and the two SAB letter reports.

The discussion of "Future Directions" on page 7 of the briefing document could be improved considerably by recognizing that the goal of the effort is not just a model with a given number of cells but insight into the adverse physiological effects in humans as a result of elevated temperature induced by radiofrequency heating. If the largest energy deposition occurs in the neck and lower head areas, leading to a temperature increase of approximately 3° C at levels of radiation currently accepted as safe, what physiological impacts does temperature increase imply? What organs or sensitive tissues could be affected? In refining the model, it would seem appropriate to achieve a finer resolution (by using smaller cells) for the neck, lower head, and other areas of the body where large temperature increases may occur, and to use larger cells elsewhere. In this fashion, it may be possible to achieve high resolution for assessing the physiological effects of potential regulatory significance without the extensive computational resources needed to use small cells throughout the body.

In many areas of toxicology, risk assessors estimate human response by using the results of the most sensitive among small laboratory animal species that can be tested at low cost, and by scaling the dose from animal to human using a simple mathematical formula. For non-ionizing radiation this approach might underestimate the extent of adverse human response. More accurate methods have been developed based on an understanding of the biological mechanisms involved and how they differ among species. As our understanding of biological mechanisms advances, it will be appropriate to apply this modeling approach to other types of toxic agents as well.

The non-ionizing radiation extrapolation efforts appear to fit previously cited needs. More attention, however, might be given to the significance of physiological effects predicted in humans as well as the validity of these predictions for humans.

E. COMPARATIVE TOXICOLOGY

The Subcommittee recommends that ORD conduct more of the type of work reported as comparative toxicology and as structure-activity relationships among toxicants. It is in these areas of fundamental research where a good potential exists for discovering answers to the applied questions posed by extrapolation modeling.

The effort in comparative toxicology is important to the development of the structure-activity relationship concept at EPA. It is clear that different species do exhibit different tolerances to a given toxicant. Is it not possible, then, that some species may have evolved mechanisms for the amelioration of the effect of a toxicant or group of toxicants? Identifying these mechanisms among species is a logical step in building the empirical base to 1) test the structure-activity relationships hypothesis, and 2) initially build extrapolation models.

Although the research generally is moving in a logical direction, it is open to some criticism. The briefing document implies that an understanding of the underlying control mechanisms and more complete models will somehow result from the data to be collected, but ORD needs to explain the logic and procedures by which this synthesis will be accomplished. The 10 by 10 matrix testing regime designed to test the sensitivity between diverse taxonomic groups may yield disappointing results if the group relies solely on major taxonomic groupings (genera, families, orders) as the distinction among species. The model should depend on the properties of the organic agent and the species tested. It is not clear that an effective target dose in one species would predict another species because the target organ may differ by species. Taxonomic classification is a history of origins and not necessarily of environmental experience. Sufficient examples of evolutionary divergence exist within families and genera to cast doubt on a scheme that uses either families or genera as a category of species classification for the purposes of determining sensitivity relationships. The family Cyprinidae, for example, contains species that vary in sensitivity' to a toxicant by several orders of magnitude. The effort would be better served with a matrix that considers classification of organisms based on environmental experience rather than taxonomic relationships.

In summary, current efforts are reasonably well conceived, but might be improved by placing more emphasis on environmental experience rather than taxonomic relationships in developing the research agenda.

F. NEUROTOXICOLOGY

Neurotoxicology is at a stage as a research field where the emphasis is on establishing and validating methods for detecting and measuring the consequences of chemical insults to the nervous system. ORD's neurotoxicology program has concentrated its efforts on developing rat models for determining the effects of potential toxins on behavior, neurochemistry and neuropathology. The neurotoxicology program then attempts to validate the animal model by comparing the rat data with that available from humans, with a particular interest on behavioral measures since behavioral parameters can be measured non-invasively in man.

The neurotoxicology program has performed an excellent job in developing methods and procedures for measuring neurobehavioral toxicity. The development of the neurotoxic esterase assay as a measure of delayed neurotoxicity produced by organophosphate insecticides should have an immediate impact on regulatory processes, as it should allow for replacement of the hen test with the conventional rat model in use for most other types of regulatory testing of agricultural pesticides.

The approach of the neurotoxicology program has been to jump directly from the rat to man for model validation. Although man does represent the ultimate validation, the program may be relying too heavily on the rat model. The Subcommittee recommends that the neurotoxicology program place a greater emphasis on cross-species comparisons (allometry). Another area where the neurotoxicology program could use additional emphasis is pharmacokinetics. The general needs for the development of pharmacokinetic capability in ORD are documented elsewhere in this report. The use of pharmacokinetic data as possible explanations for species differences in neurobehavioral responses to chemical insult could be of great benefit to this research group.

Members of the SAB Environmental Health Committee have previously pointed out that some neurotoxic effects clearly do not occur in relation to blood levels of the neurotoxic agent. (See, for example, comments on the drinking water health advisory for acrylamide.) For some substances of environmental concern, processes in nervous tissue are of greater apparent importance as determinants of human toxicity than tissue dose. Such examples are of great importance in setting limits on the utility of pharmacokinetic analysis for risk assessment.

The groups of investigators within the neurotoxicology program appear to coordinate well, and they study the same chemicals under nearly identical conditions. The quality of the research is uniformly high. Indeed, the research group at EPA is widely recognized as being a leading neurobehavioral toxicology group in the country.

The neurotoxicology program has been concentrating on the effects of neurotoxins on sensory, motor and cognitive processes and the molecular mechanisms underlying these effects. In sensory systems, the neurotoxicology program has taken the approach of developing rapid electrophysiological and behavioral methods for measuring effects of chemicals on the visual and auditory systems. They have used the pattern-reversal-evoked potential (PREP) as a model for studying visual acuity in the rat and the brain-stem-auditory-evoked-response (BSAER) as a model for studying auditory thresholds in the rat. At a mechanistic level, the effects of specific lesions in the visual system on the PREP and the effects of cochlear lesions produced by known ototoxicants on the BSAER are being studied with neuropathology observations made in the same animals.

With respect to cognitive function, the emphasis is on behavior measures. A microprocessor-based system for use in field studies of human cognitive function, as well as sensory-motor function, has been developed, although not yet used to measure cognitive function in toxicant exposed humans. Most of the other studies involve animal models. These models include place learning, flavor aversions and operant conditioning procedures. The program has emphasized comparisons across these behavioral measurements, with comparisons of animal responses with human responses given special attention. Future developments in this area will focus on the development of additional learning and memory tasks in animals, with special emphasis directed toward those tasks which can be studied in animals and humans under comparable conditions.

On a mechanistic level, research is conducted relating to the neurochemical and neuropathological basis of functional changes produced by toxic chemicals. One such effort involves determination of the extent to which nervous system-specific proteins can be used as biochemical markers of neurotoxicity. Animals are being exposed to known neurotoxins, and the effects on nervous system-specific proteins are measured by biochemical and radioimmunoassays. Preliminary data suggest that these proteins predict the cytopathological changes associated with toxicant exposure and that they may ultimately be sensitive and accurate predictors of human neurotoxicity.

Another mechanistic approach concentrates on neurotoxic esterase and its involvment with the delayed neurotoxicity produced by organophosphorous compounds. The degree of inhibition of this esterase is highly predictive of the symptoms of delayed neuropathology produced by these compounds, and ORD is suggesting the measurement of the enzyme inhibition as a replacement

for the hen test currently used within the Office of Pesticides and Toxic Substances. The advantage of replacing the hen test includes the opportunity to incorporate the enzyme inhibition test into conventional rodent toxicity test protocols.

The future directions of the research program include: 1) a focus on cross-species extrapolation of sensory test procedures, particularly to humans; 2) the use of the micro-processor based system for field studies in humans; 3) the development of learning and memory tasks in animals that can be directly compared with human tasks; and 4) further refinement of the cellular and molecular studies on nervous system-specific proteins. The briefing document notes that the neurotoxicology program has concentrated on the effects of chemicals on motor behavior, in addition to effects on sensory and cognitive processes, but the results of the experiments on motor behavior are not discussed, nor are the directions of future research in these areas. Some of the issues that may be relevant to discuss include: 1) How is motor function assessed in animal and/or human models? 2) Are molecular tests being developed to study the mechanisms underlying changes in cognitive functions in animal models? 3) What species are used to make neurotoxicity comparisons? How do laboratories approach the problem of extrapolation across species with respect to neurotoxicity? 4) Measuring the inhibition of neurotoxic esterase inhibition and nervous system-specific proteins are very specific mechanistic tests. Are other types of mechanisms planned for future study, and if so, which ones? 5) Do the cross species comparisons really involve similar processes or only analagous processes? 6) Is there any attempt to study pharmacokinetic parameters of different neurotoxins? Do species differences perhaps depend on different metabolic pathways in different species, or differences in drug delivery? Would dose--modeling studies be appropriate in making species comparisons? 7) Does an adequate collection of baseline data exist in nontoxicant exposed humans to validate the use of the micro-processor system in "normal humans" before studies begin on toxicant exposed populations? 8) Is the neurotoxicology program examining problems of acute versus chronic exposure, and reversible versus irreversible changes? 9) If bioassays of nervous system-specific proteins are to serve as predictors of neurotoxicity in humans, a model for extrapolation from animals would appear to be necessary. 10) How will the hypothesis that nervous system-specific proteins are sensitive indicators be tested? How will prediction be accomplished? 11) How is the test for assessing visual acuity in rats to be extrapolated to humans?

G. SYSTEMIC TOXICITY

The purpose of the systemic toxicants program is to develop the assumptions, appropriate modifications and, when necessary, new approaches to risk assessment for systemic (non-carcinogenic) toxicants including chemical mixtures. The approach proposed recognizes the need to take into account both theory and reasonable assumptions, and emphasizes the importance of understanding the mechanism of toxic action in the test system relative to the expected outcome in humans. The staff plans to evaluate the component parts of the various existing extrapolation models and make revisions or produce new methods. If new methods evolve, the staff plans to test and evaluate the newly proposed method. Among the tools employed will be literature searches, data base creation, scientific workshops and symposia.

The following specific projects are proposed: 1) an assessment of the reliability of animal data for predicting human risk; 2) a statistical model for species extrapolation using categorical response data; 3) estimation of the impact of human inter-individual variability of humans on response to toxic substances; 4) pharmacokinetic methods for improved estimation of effective dose; 5) development of quantitative methods to assess toxicity of chemical mixtures; 6) development of a severity-of-the-effects ranking scheme; 7) development of reference values for risk assessment; and 8) study of dose duration associations: extrapolation and interpolation procedures.

Most of these projects are in the formative stages. However, a number of specific examples of research products are cited to indicate progress.

The Subcommittee found the lack of connections between the excellent programs in neurotoxicology, inhalation toxicology and developmental biology and the systemic toxicology program particularly frustrating, since the former subjects are components of systematic toxicology. Certain organ systems, such as the liver and kidney, receive no attention in ORD's plan. Ultimately, work in this area may lead to the development of new risk assessment guidelines. This is an additional reason to establish stronger linkages between the systemic toxicology program and other laboratory programs to provide research coverage of all major organ systems.

The Subcommittee recommends that the program use specific chemicals as examples to explore the proposed techniques. At the time of the Subcommittee's review meeting, the work was not sufficiently applied nor specific to fully evaluate research progress or to contribute to needed risk assessments on important problems.

H. INHALATION TOXICOLOGY

The objective of the inhalation toxicology program is to improve the quantitative extrapolation of inhaled, airborne toxicants, primarily criteria air pollutants, to pulmonary effects. This objective allows the direct use of animal inhalation toxicity data in risk assessments by developing quantitative cross-species interrelationships. To this end, the inhalation toxicology program seeks to examine two parameters that are needed to develop such relationships, namely dosimetry and species sensitivity, as well as to provide judgments as to those specific health effects which merit extrapolation.

The goal of the dosimetry studies is to determine dose to target sites. The approach employed is the development of mathematical models, for both gases and particles, which incorporate parameters of lung structure and physiology as well as the specific properties of the toxicant of interest. These models will be used to predict dose by region within the respiratory tract.

Current work on gas dosimetry is aimed at predicting the local absorption of O_3 in the lower respiratory tract of experimental animals and humans; defining the reactions of NO_2 following deposition in the lung; refining knowledge on the composition of mucus in animals and humans so as to improve estimates of oxidant reactivity; and determining the removal of O_3 in the upper respiratory tract so as to provide more accurate input into the lower respiratory tract model.

For particle dosimetry, the program is building mathematical models to predict the deposition of hygroscopic particles. These will be tested by studying the deposition of both hygroscopic and nonhygroscopic particles in humans. Deposition is also examined in casts of the respiratory tract of experimental animals and humans, including children. Lung morphometric analyses are performed to refine this essential component of a dosimetry model.

The stated aim of the particle dosimetry studies is to assess the regional deposition of chronically inhaled particles. It is, however, not clear how the studies outlined in this area address this issue. They appear to be aimed solely at studying sites of particle deposition in model systems which will provide important input into the development of empirical models.

It is important that the inhalation toxicology program make full use of the available data base in the particle deposition area and design studies that will complement rather than repeat those already preformed. For example, data are needed on the deposition pattern of ultrafine particles (<0.1 um), and this could be obtained both in cast systems and in vivo. In addition, these deposition studies should be conducted in experimental animals to expand the data base to allow dose extrapolation in this important ambient particle size range.

If the data are available to perform extrapolation of delivered dose of insoluble particles from animals to man, a need exists for a greater modeling effort. The program assumes a simple linear relationship but should verify the fit to data statistically. A poor fit will suggest that further efforts to develop an appropriate model are needed; data analyse alone will not suffice.

The goal of the species sensitivity studies is to examine interspecies differences in sensitivity to equivalent toxicant doses, and to quantitate these differences. To these ends, various approaches are used, largely employing three test materials: O_3, phosgene, and cadmium. Specific studies include: examining pulmonary macrophages after both in vitro or in vivo exposures; in vitro exposures of respiratory tissues for comparison to in vivo exposures; assessment of effects of phosgene inhalation in various species over a range of exposure concentrations; comparison of acute pulmonary function responses to O_3 in various species; determination of the concentration response relationsip for O_3 induced alterations in alveolar epithelial permeability; and assessment of the effects of oxidant gases upon collagen metabolism and turnover.

The projects concerned with determining species sensitivity do not seem to be as integrated, or as consistently relevant, as those in the dosimetry area. EPA staff have chosen various test endpoints, but the Subcommittee questions the relevance of some in the total picture of the program.

Another area of critical importance in extrapolation modeling which does not appear to be addressed in the inhalation toxicology program is analysis of interspecies clearance rates, both short-term, i.e., mucociliary clearance, and longer-term, alveolar clearance. EPA should conduct these analyses in a methodologically consistent manner to allow direct extrapolation between species.

It is not clear how the study involving in vitro exposure of human respiratory tissues will aid in extrapolation modeling. Although it is anticipated that results in vitro will be compared with results obtained in vivo, the importance of this project needs to be clarified. Unlike the area of macrophage biology where there is a large data base on in vitro exposures, which should be scaled to allow extrapolation of in vivo effects, there are few systems using respiratory tissue in culture, and the procedure is not amenable to widespread use.

Also unclear is the importance of the studies of phosgene sensitivity, especially since any scaling factors for this material are to be likely different than those for other gases, such as O_3 itself. The briefing document does clearly state how results with phosgene will help the inhalation toxicology program in the extrapolation modeling of critical ambient pollutants.

Another study is aimed at assessing collagen turnover and metabolism in humans and experimental animals. This is important in assessing the role of air pollutants in producing fibrotic lung disease, and will allow development of a scale of the sensitivity of various species to this important effect of oxidant pollutants.

The construction of an integrated dosimetric biological model for hazard assessment is an important step in providing accurate, up-to-date and state-of-the-art extrapolation methods for ambient toxicants. It will, hopefully, facilitate better use of existing experimental animal toxicologic data and new data in the standard-setting process.

The inhalation toxicology program has addressed an important issue for which there are few available data, namely deposition and morphometry in children's lungs. This is a critical activity since children may receive a greater dose for an equivalent exposure level than adults. These studies should be performed with models of lungs of other sensitive populations--for example, persons with chronic lung disease.

The inhalation toxicology program is scientifically sound and is addressing critical issues in extrapolation modeling. The dosimetry studies are systemically examining important pollutants to provide accurate interspecies regional dose estimates. Sensitivity analyses with the models developed can be used to guide further experimental work effectively. However, the species sensitivity aspect of the program is not as well focused, and appears not to be addressing some important points, while emphasizing some that may not be critical to extrapolation models. Some refinement is needed on determining those endpoints which are of health significance.

I. REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

The objectives of the developmental biology program are to establish means for risk extrapolation to humans from data obtained under experimental laboratory conditions. The program addresses a wide range of potentially adverse effects on human reproduction and development including effects on fertility, pregnancy outcome, and long-term postnatal functional effects.. The program seeks to increase the sensitivity and specificity of reproductive toxicity testing. Plans are incorporated in the program to develop more sensitive methodologies able to detect lesions that cannot be identified with the presently available testing techniques. There is a need to develop a methodology for risk assessment in reproductive and developmental toxicology. However, plans for developing methods for dermal absorption and reproductive toxicity, although important toxicologically, do not seem to fit with the plan that attempts to advance our knowledge in these two areas of risk assessment.

In teratology response studies, the problem of general maternal toxicity in the formation of birth defects is addressed. The issue is fundamentally important for identifying agents that produce developmental effects at maternally toxic exposure levels. In any proposed methodology for quantitative risk assessment, there must be an evaluation of the dose-effect relationship irrespective of the mechanism(s) by which these effects occur. To assess the role of maternal toxicity in the formation of birth defects is an important objective, but it does not directly contribute to the development of a quantitative risk assessment methodology.

In presently available teratologic testing systems, a number of problems are recognized: 1) a variety of organ systems are not evaluated because of technical difficulties; and 2) for several effects with high background incidence it is difficult to assess the exact toxicologic importance. The developmental biology program has approached these problems by assessing any long-term significance of "non-teratogenic fetal toxicity" and by the postnatal evaluation of organ systems (e.g. renal, immune, and cardiac functions) in the neonate. Beyond a few isolated studies of diverse organ systems, the only substantial literature of potential manifestations of perinatal insult is of effect on parameters somewhat related to central nervous system function. Good, clear examples of effects produced in functional capacities at exposure levels below those able to produce other signs of altered in utero development in Segment II evaluation are not available. This topic merits further investigation.

The program supplies three approaches to the problem of interspecies risk evaluation. The first approach is to develop in vitro sytems that possess the metabolizing functions characteristic of different species, including the human. The program plans to observe rodent in vitro embryo development in the presence of metabolizing systems which possess different capacities characteristic of the different species. The aim is to enable examination of the effects of human metabolites on the developing rodent embryo. This may be useful for a general understanding of the toxicologic importance of same class of chemicals to the rodent embryo developing in vitro and for increasing our knowledge of the relationship, if any,

between chemical structure and reproductive toxicity. The likelihood that this type of approach will significantly contribute to the establishment of a quantitative reproductive risk assessment methodology is meager. By testing the effect of various metabolizing systems from different species on the development of one species, this approach addresses the important problem of species difference in teratogenicity, but only indirectly.

The second approach is to evaluate whether the A/D ratio (defined as the ratio of the dose of a chemical exerting adult toxicity to the dose that causes developmental toxicity) is constant in different species. The A/D ratio is an important observation for quantitative risk assessment methodology. The usual assumption is that the A/D ratio does not vary across species. However, A/D ratio appears not to be constant across species, based on this group's preliminary studies. The ratio may need to be defined statistically, as has been done elsewhere. For example, A is the dose that is toxic to percent x of the adults, and D is the dose that is toxic to percent y of the embryos. Perhaps for the right choice of x and y, the ratio is constant across species. The development of mathematical models for dose response in animal studies is difficult because of the complexity of the maternal-fetal system and litter effects. This group is proceeding with the project with outside consulting support, which is commendable.

Currently, the no-observed-effect-level plus margin-of-safety method is used for species extrapolation. The value of the A/D ratio work depends on the accuracy with which the biochemical lesions used are predictive of teratogenesis.

The third approach to interspecies risk evaluation is to use molecular markers of teratogenic action (such as the formation of DNA adducts by alkylating agents, effects on microtubular function, or changes in biochemical pathways) in order to extend the lower measurable bounds of the dose-response curve. The developmental biology program hopes that, by quantifying biochemical lesions which putatively precede teratogenic effects, it will be possible to define the shape of the dose-response curve with actual data. This approach is interesting, but it implies that the detected biochemical abnormalities are causally related or linked in some way to the teratogenic action. This may not be a general rule since biochemical lesions unrelated to teratologic action are likely to be detected. This also assumes that the wide spectrum of teratogenic effects will have a commonality of biochemical mechanisms, which is an unlikely proposition.

In research on reproductive toxicology, the developmental biology division has three projects. The first is general reproductive effects extrapolation. In an attempt to increase the ability to extrapolate between species, rats and hamsters exposed to a selected agent are followed with morphological and behavioral tests from weaning through puberty, breeding and gestation, up to the Fl generation.

The approach to endocrine and aging effects is to implement specific neuroendocrine measures necessary to identify the mechanisms and/or the sequence of events mediating the disruptive effects of toxic substances on reproductive function in the young-adult-geriatric animal. At the same time,

attempts will be made to 1) identify mechanisms reponsible for reproductive aging, and 2) determine how age-related changes alter the organism's risk following exposure to xenobiotics.

The effort on male reproductive function involves assessing testicular function in animal models and humans in an attempt to determine whether changes in the structure and function of the rodent reproductive tract predict impaired reproductive function in humans. These experiments include morphological evaluations and an in vitro assessment of the reproductive functions and how exposure to various xenobiotics modify them.

The developmental biology program evaluates the difficulties inherent in the extrapolation of animal data on skin absorption into the human situation, and has developed a number of interesting in vitro techniques.

The Subcommittee has a mixed evaluation of the status of extrapolation modeling for reproductive and developmental effects. Some of the work is out of date, whereas other aspects are highly germaine and abreast of the contemporary developments in developmental biology as it relates to questions of toxicity. The description in the briefing document consists of a series of questions that apply toxologic questions to on-going research interests. This emphasis is unfortunate and should be changed to address more relevant questions and techniques needed to answer the more important questions. The developmental biology group needs an external, independent source of on-going guidance and review from senior scientists in the same field. The individual scientists involved in the developmental biology group tend to be of high caliber and motivation. The program merits this attention, so that its projects will become less diffuse and not distracted from developing extrapolation models. The group has adequate resources and, if directed rather than diffused, could have a significant impact.

VI. THE OVERALL FEDERAL RESEARCH EFFORT ON EXTRAPOLATION MODELING

Without extrapolation, testing of chemicals in laboratory animals is pointless. Given the critical importance of extrapolation, and the millions of dollars spent by the Federal research and regulatory agencies on toxicity testing, it should be expected that major efforts are underway to develop and examine extrapolation methods. EPA does not have a program that focuses directly on extrapolation method development and evaluation. In its place are exciting research projects on toxicology tests and other efforts directed at extrapolation.

This conclusion was also stated in a recent review of U.S. research directed at examining and improving risk assessment for carcinogens. The review[2], prepared by the Environ Corporation for the ILSI-Risk Science Institute, concluded that less than 5 to 10 percent of the research budgets of institutions involved in risk assessment is directed at improving methods, including extrapolation. The bulk of the latter research is supported by EPA.

Little overlap exists in the material surveyed by the ILSI-Risk Science Institute and the present Subcommittee report. The former studied extramurally funded research on extrapolation of carcinogenic effects by key institutions throughout the entire U.S., whereas the latter reviewed extrapolation of all health effects only in intramurally funded work in EPA's ORD. However, both groups' findings have sane remarkable similarities. Both reviews conclude that extrapolation efforts are insufficiently funded and uneven with respect to the particular scientific issues addressed. The ILSI-Risk Science Institute study also highlights the importance of coordinating research efforts among Federal agencies.

The National Academy of Science Committee on Institutional Means for Assessment of Risks to the Public Health listed fifty-nine "components" of risk assessment that might be improved. Of these, the ILSI-Risk Science Institute survey identified twelve studies that examine the relationship between administered dose and target tissue dose, and seven that seek to identify biological markers of human exposure. Those are important extrapolation processes, and Section IV of the Subcommittee's review has discussed more extrapolation processes that are also important. The ILSI-Risk Science Institute found that no research was funded for twenty-seven components, and only one study was underway for the remainder.

A. NON-ORD EXTRAPOLATION PROGRAMS IN EPA

While research at EPA is focused in ORD, extrapolation modeling also occurs in many of the regulatory offices. These include: 1) the Hazard Evaluation Division within the Office of Pesticide Programs; 2) the Health and Environmental Review Division within the Office of Toxic Substances; and 3) the Criteria and Standards Division within the Office of Drinking Water. Each group uses such models frequently to carry out their respective missions. That ORD requested a review of its own effort is laudable, but the omission of the non-ORD scientific assessment activities from the current plan limits the usefulness of the plan. Beyond the extramurally funded work that is managed by ORD, the Office of Toxic Substances has housed the "Gene-Tox" program, which collates world-wide data on

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[2] J.V. RODRICKS and C. ST. HILAIRE, Review of Current Research Activities to Improve Risk Assessment and Identification of Major Gaps. Prepared for the ILSI-Risk Science Institute by Environ Corporation, November 6, 1985.

bioassay methods for many genetic endpoints and has work underway on structure-activity relationships that has the potential to improve the Agency's practice of extrapolation between similar chemical structures. The Office of Solid Waste and Emergency Response has a support contract with the Centers for Disease Control. Other examples exist that would further demonstrate the necessity to have an Agency-wide plan.

B. OTHER FEDERAL REGULATORY AGENCIES

The need for extrapolation models is felt most strongly in regulatory agencies. Therefore, they should provide the core leadership, direction and support for the Federal effort. At present, EPA appears to carry most of the responsibility, although the Food and Drug Administration has the support of the Center for Food Safety and Applied Nutrition and the National Center for Toxicological Research. To avoid unnecessary duplication and to utilize scare resources optimally, EPA needs to coordinate its research planning with the other Federal regulatory agencies.

C. OTHER FEDERAL RESEARCH AGENCIES

The Department of Energy and the Department of Health and Human Services support research on extrapolation modeling. Within the Department of Health and Human Services a number of organizations are involved, including the Centers for Disease Control (the Center for Environmental Health, the Agency for Toxic Substances and Disease Registry) and the National Institute for Occupational Safety and Health. The National Institutes of Health has several organizations involved, especially the National Cancer Institute and the National Institute of Environmental Health Sciences. EPA's research plans should explicitly take into consideration the contributions of these agencies.

APPENDIX I

STATUS OF EXTRAPOLATION MODELING RESEARCH NEEDED TO EXTRAPOLATE FROM ANIMAL DATA TO HUMAN RISK, FROM HIGH TO LOW DOSES, AND FROM ACUTE TO CHRONIC EFFECTS

VOLUME I

BRIEFING DOCUMENT

Prepared By

Office of Research and Development Staff

To assist the Science Advisory Board panel convened to provide the Administrator of EPA with a programmatic review of extrapolation related research conducted in ORD.

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SEPTEMBER 1985

EXECUTIVE SUMMARY

This briefing document was prepared by Office of Research and Development (ORD) staff to assist the EPA Science Advisory Board (SAB) in their review of research in progress dealing with extrapolation of nonhuman laboratory data to man. Various components of ORD research related to extrapolation are discussed. The findings and recommendations of the SAB will be transmitted to the EPA Administrator and Assistant Administrator.

The overall extrapolation program considers the needs of the various program offices and research committees. This document provides an overview of the extrapolation research projects in the Office of Health Research (OHR), Office of Environmental Processes and Effects Research (OEPER), and Office of Health and Environmental Assessment (OHEA). Here, we describe those elements of the program that relate to major issues in extrapolation research:

1. Extrapolation from in vitro techiques to whole animals.

2. Extrapolation of laboratory animal data to humans.

3. Extrapolation of results from high dose exposure to low dose (ambient) exposure.

4. Extrapolation of results from acute or subchronic exposure to continuous exposure/chronic effects.

The overall goal of the extrapolation research program is to provide a significant enhancement of the scientific basis for risk assessments based on health effects data. Extrapolation of effects using data from ecosystems species is also included in the research program. With improved extrapolation methods, major uncertainties in the health data bases can be better resolved, leading to more precise risk assessments, thereby improving risk management judgments. To these ends, ORD has developed a research plan consistent with program office needs, research committee priorities, available expertise and resources, and state-of-the-art science. In further support of this program the Assistant Administrator for ORD has recommended an increase of 1.3 million dollars and 4.9 positions in the budget request for FY 87. This represents partial funding of a large research initiative on advanced methods for extrapolation; a full description of the initiative may be found in Volume II, Appendix I-8. The increase is designed to strengthen ongoing efforts and to focus on areas which are in the forefront of scientific knowledge.

The research effort has built upon the recommendations of the National Academy of Sciences and needs defined in EPA criteria documents, proposed risk assessment guidelines, and such reports as the NRC "Risk Assessment in the Federal Government: Managing the Process," and EPA's "Risk Assessment and Management: Framework for Decision Making," as well as from various program reviews. Interactions among laboratory scientists, program offices, and research committees also have been important to the development of the overall program. The program is designed to reduce uncertainties and improve the accuracy and precision of risk assessments when sufficient human clinical and epidemiological data are not available.

Neurotoxicology - Techniques for extrapolation between sensory, motor, and cognitive effects of high to low dose, acute to sub-chronic, and cross species extrapolation.

Genetic Toxicology - Mutagenicity test battery for human hazard estimation; molecular dosimetry for comparative mutagenesis, carcinogenesis, and risk assessment.

Carcinogenicity (Mammalian) - Statistical methods for estimating carinogenic potency of organics; utility of route to route extrapolation in risk assessment; predicted probability distributions of kidney cortex and urine cadmium levels; mathematical simulations of pharmacokinetics of drinking water contaminants.

Inhalation Toxicology - Combining dosimetry and species sensitivity data for quantitative extrapolation of animal toxicological results to man. Efforts include developing theoretical models for gaseous and particulate deposition in man and animals, model validation and mechanistic studies, experimental dosimetry studies, comparisons of species sensitivity to oxidants, studies providing improved input data for interspecies comparisons .of delivered dose, etc.

OEPER: Toxicity Mechanisms - This effort attempts to predict toxicity of a chemical to fish on the basis of molecular descriptors and chemical properties. To do so a sequence of measureable histologic, biochemical, physiological, pharmacokinetic, and behavioral responses are measured to define the acute mode of toxic actions.

Comparative Toxicology - The objective of the program is to provide the necessary toxicological data to extrapolate dose responses between invertebrates and lower vertebrates and between lower and higher vertebrates (including man).

OHEA: Genetic Risk of Chemical Mutacens - This research program is designed to provide a scientific basis for risk estimates calculated by using extrapolations from the relatively high mutagen doses used in animal mutation studies to the lower mutagen doses associated with human exposures.

Systemic Toxicants and Chemical Mixtures - This program validates risk assessment assumptions, develops appropriate theoretical modifications, and when necessary, develops new approaches to risk assessments for systemic (non-carcinogenic) toxicants and for mixtures of various chemicals presenting either carcinogenic or non-carcinogenic risks.

INTRODUCTION

A major goal of ORD is to improve the scientific basis for extrapolation which will enhance the precision of risk assessments. Valid extrapolation methods are essential if EPA is to optimally utilize a highly diverse and complex health data base in making risk assessment decisions. The existing health data bases for most chemicals have common problems: in vitro or animal data often strongly suggest potential human hazards, but it is humans who must be protected, most often by regulation of human exposure levels; health data often exist for high doses, but toxicity resulting from ambient exposure is not sufficiently quantified; and many experiments indicate a hazard from acute exposure, but humans may be exposed chronically and experience a different degree or type of effect. Making such extrapolations, as outlined above, especially in a quantitative or semi-quantitative manner, is exceedingly complex and not yet precise.

Multifaceted research approaches must be applied to account for the inherent complexities of the issues. Each key issue must be addressed at a pace consistent with the state-of-the-art of a given issue. For example, animal to man dosimetric extrapolation of inhaled chemicals needs to be approached initially for simple cases of chemicals not undergoing biotransformation to gain basic understanding needed to solve more difficult problems for many inhaled organic chemicals. There are other extrapolation issues needing more elementary approaches, such as cases for which animal models of developmental toxicity and neurotoxicity need to be refined and mechanisms understood in relation to human mechanisms before such models can be applied to collect data for ultimate extrapolations.

Thus, areas of emphasis for ORD's extrapolation program are:

1. Improving the scientific basis for extrapolation.

2. Decreasing uncertainties in risk assessments by improving the precision of extrapolations.

3. Responsiveness to the extrapolation needs of the program offices.

These considerations, issues, and goals were incorporated into the development of the extrapolation research projects to be described. The scope of the overall program is broad, given the expertise, resources, and specific missions of the research groups involved. The chapters of this document are organized by research groups to facilitate the presentation and are as follows:

OHR: Non-ionizing radiation - Scaling physiologic effects of radio frequency radiation exposure and mathematical modeling of thermoregulatory systems.

Reproduction and teratology - Adult vs developing embryo minimal dose extropolation; maternal toxicity in teratogenesis, the role of metabolic regulation during differentiation; reproductive toxicological testing to improve extrapolation of effects.

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