United States
Environmental Protection
Agency

Office of Research and
Development
Washington, DC 20460

September 1988
EPA/600/8-88/089

EPA

Research to Improve Health Risk Assessments (RIHRA) Program

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EXECUTIVE SUMMARY

The Environmental Protection Agency (EPA) increasingly relies on quantitative assessment of health risks to make decisions about protection of public health. The utility of the risk-based approach for decision making is dependent upon the availability of an adequate data base that is appropriate for the questions being asked. Insufficient data can lead to large uncertainties that, in turn, allow wide latitude for interpretation. Thus, where the underlying scientific uncertainties are great, the data may support diametrically opposed interpretations, each with dramatically different ramifications for related regulatory decisions.

In 1988, Congress recommended that the EPA's Office of Research and Development (ORD) establish a systematic and integrated Research to Improve Health Risk Assessments (RIHRA) program. Although it was acknowledged that much of ORD's ongoing research focuses on this issue, the Agency agreed that it would benefit from a more formal and structured approach. Consequently, $3 million in FY88 and $10 million in FY89 have been earmarked for development of a targeted, coherent research program to reduce uncertainties in the risk assessment process, including both health and ecological risks.

The primary objective of the health research plan is the development of a systematic and integrated program that would be effective in improving health risk assessments. Moreover, the emphasis is placed on identifying and addressing the significant uncertainties inherent in the risk assessment process. This research program is designed to provide critical data on the relationship between exposure (applied dose), dose to target tissue (delivered dose), and associated health effects. The program emphasizes laboratory and field research that will improve our understanding of basic biological mechanisms, especially as they relate to our ability to extrapolate from one set of circumstances (e.g., animals exposed to long-term, high concentrations) to another (e.g., humans exposed to long-term, low concentrations).

Based on the established guidelines for program development, four general topic areas were selected for investigation. The relationship between the major components in health risk assessment and the principal topics to be addressed by this research program is shown schematically in Figure 1. Two topics, "Analysis of Uncertainty" (i.e., assessment of the major contributors to uncertainty for a given risk assessment) and "Integrated Exposure Assessment" (i.e., improvements in the quality and consistency of data used to assess exposure), are defined to be relatively narrow in scope. Two other topics, "Physiologically Based Pharmacokinetic (PB-PK) Models" and "Biologically Based Dose-Response (BB-DR) Models," are defined to be broad in scope and to include a variety of health endpoints and exposure scenarios. The construction of PB-PK models can be used to establish a quantitative relationship between exposure and dose delivered to a target site in animals and humans under a variety of conditions. The development of BBDR models allows for delineation of a quantitative relationship between the dose and associated health effects. In summary, by focusing the resources through a structured and integrated program, it will be possible to make significant improvements in EPA's health risk assessments.

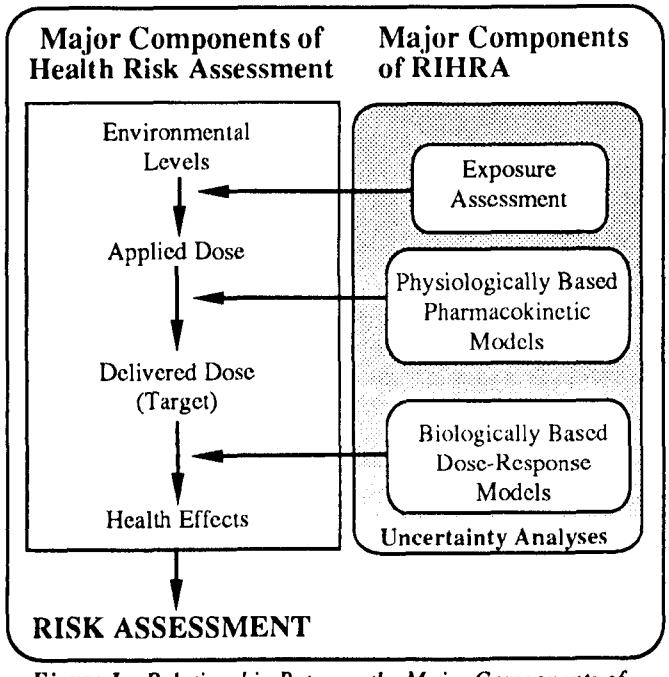

Figure 1. Relationship Between the Major Components of Health Risk Assessment and the Major Components of the RIHRA Program.

INTRODUCTION

This document describes an integrated and systematic research program that will be carried out by the Office of Research and Development (ORD) to improve health risk assessments. It is generally acknowledged that substantial gaps exist in the scientific data bases that underlie the risk assessment process. In many instances, quantitative risk assessment is precluded because of the paucity of appropriate data. Even in cases where quantitative risk assessment is feasible, critical data gaps typically exist and require the application of numerous assumptions, which represent "fall back" or "default" positions. This new program will reduce important uncertainties in health risk assessments through targeted laboratory and field research.

RISK ASSESSMENT FRAMEWORK

The elements of the risk assessment process, as well as the interrelationships between research, risk assessment, and risk management, are shown in Figure 2. Research provides the scientific data bases that underlie the three steps in risk assessment; namely, hazard identification, dose-response assessment, and exposure assessment. The uncertainties associated with these steps, resulting primarily from deficiencies in the quality and quantity of appropriate data, lead to uncertainties in quantitative health risk assessment.

UNCERTAINTIES IN RISK ASSESSMENT

Uncertainties in the risk assessment process are the result of one or more conditions: 1) lack of appropriate and adequate data or underutilization of existing data, or 2) a fundamental lack of understanding of the basic underlying physical, chemical, and biological mechanisms. The most critical problematic areas in risk assessment involve uncertainties about extrapolating observed effects from one set of circumstances (e.g., cancer incidence in experimental animals subjected to high, chronic exposures in controlled experiments) to an entirely different set of circumstances (e.g., individual excess cancer risks in humans experiencing intermittent, low-level exposures). These uncertainties are encountered while extrapolating from species to species, from one individual or subgroup to another individual or subgroup within a particular species, and from one set of exposure conditions to another. The uncertainties arise not simply from insufficient data, but also from a lack of fundamental understanding about the relevant underlying physical (e.g., atmospheric dispersion characteristics, human activity patterns), chemical (e.g., chemical reactions and transformations), and biological (e.g., metabolism, disease processes) mechanisms that affect the validity of the extrapolation assumptions. Research to reduce these uncertainties must focus on development of an understanding of the key processes and how these processes interact to assess either exposure or dose-response.

Basically, risk characterization can be thought of as the combined result of dose-response assessment and exposure assessment (See Figure 2). Thus significant uncertainties in either factor can cause uncertainty in the final risk estimate. In the dose-response area, EPA's Carcinogen Assessment Group (CAG) has estimated that uncertainty in only five "fall-back" or "default" assumptions can lead to three or four orders of magnitude difference in the risk estimate for a carcinogen. Similarly, CAG analyses have demonstrated that incorporation of knowledge about the underlying mechanisms of toxicity and dose-rate information can result in estimates of carcinogenic risk that vary by up to six orders of magnitude. For systemic toxicity, uncertainties of several orders of magnitude are possible. Moreover, a high degree of uncertainty may be introduced by failure to test chemicals adequately over a sufficient range of health endpoints. For example, if a risk assessment is based on an inappropriate or insensitive endpoint, the final estimate may be a significant underestimation of the actual health hazard.

Uncertainties may also be large for the assessment of human exposure. EPA's Office of Air Quality Planning and Standards (OAQPS) has delineated some of the uncertainties in the assessment of exposure to carcinogens in the air and the Office of Solid Waste (OSW) has reviewed the magnitude of uncertainties inherent in selected fate and transport models for both ground and surface water. These analyses indicate that there are many potential sources of uncertainty in exposure assessment that can lead to differences of several orders of magnitude in the final risk estimate.

RESEARCH STRATEGY

Substantial uncertainties necessitate the application of appropriate assumptions throughout the risk assessment process. Significant unknowns exist in all aspects of risk assessment,

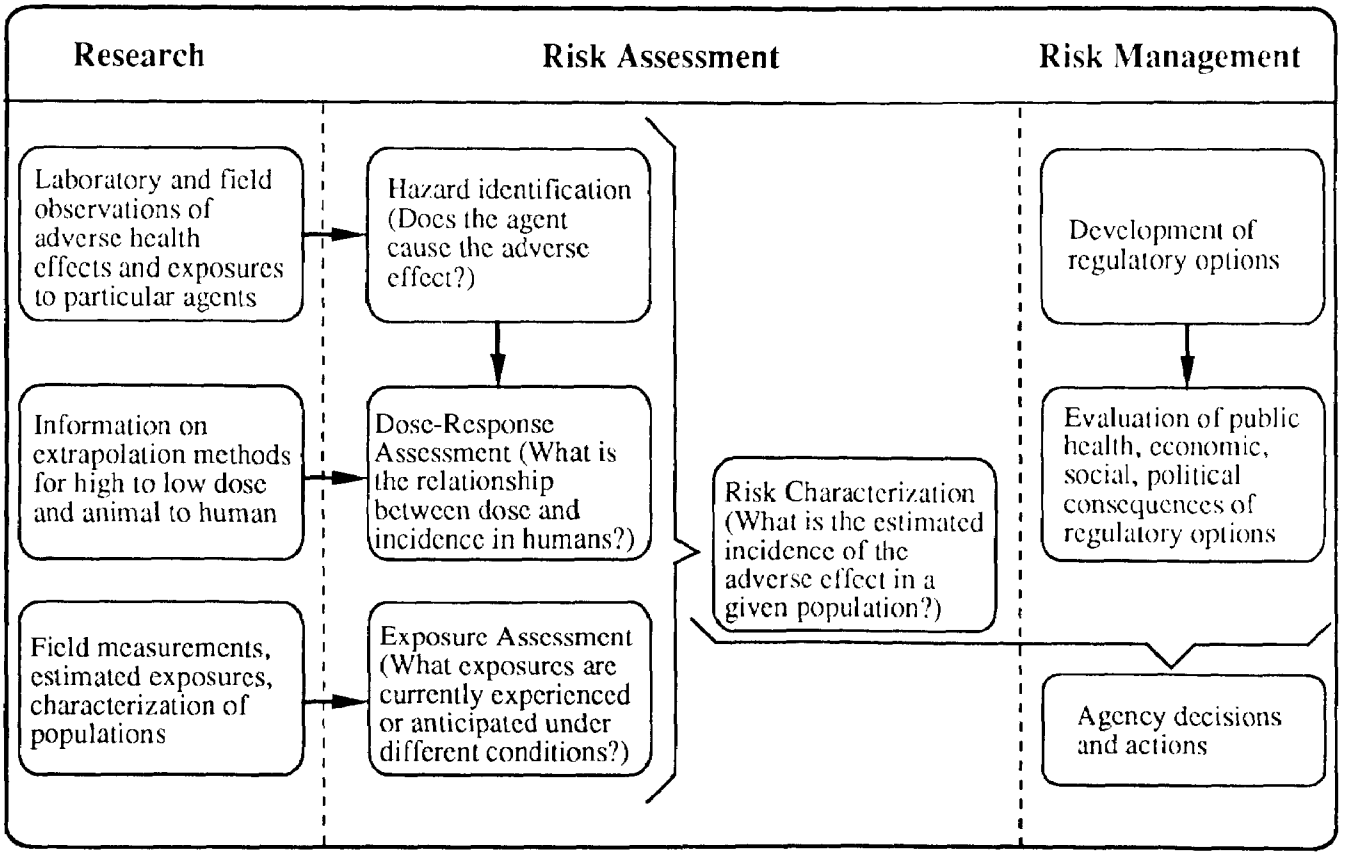

Figure 2. *Elements of Risk Assessment and Risk Management (From: National Academy of Sciences [NAS], 1983.)*

including emission estimates, pollutant fate and transport models, ambient measurements, human exposure estimates, and dose-response assessment. Because the scope and magnitude of these problems are extensive and the resources are limited, it is important that the available resources be focused on the most significant problems.

Based on the goal of developing an integrated and systematic research program that significantly improves health risk assessments, three important decisions were made about the focus of the plan. First, our collective judgment and understanding of the risk assessment process was used to narrow the scope of the program. Accordingly, the RIHRA program will focus on elucidating the relationship between exposure (applied dose), internal dose to the target tissue (delivered dose), and associated health effects (See Figures 1 and 3.). Second, emphasis will be given to non-cancer health endpoints, such as neurological, pulmonary, and reproductive effects. This emphasis is appropriate because EPA is increasingly called on to estimate these kinds of risks for environmental exposures to a variety of contaminants. In general, the risk assessment issues are less well defined and articulated for non-cancer, as opposed to cancer, health effects. Third, much of the research needed to reduce the uncertainties of risk assessment is iterative in nature; that is, the research progresses in multiple stages, with significant outputs at each stage. This dictates that both short-term and medium to long-range research planning and stability are required for this program.

As shown in Figure 3, four major topics were selected for inclusion in the program: analysis of uncertainty in risk assessment; integrated exposure assessment; physiologically based pharmacokinetic models; and biologically based dose-response models. It is important to recognize that the RIHRA program represents a comprehensive overview of the research needs to reduce uncertainties in specific components of the risk assessment process. It provides an intellectual framework to design and implement a coherent research program that will address identified issues within the broad topic areas. Even with this narrow focus, resolution of these issues is likely to require a concerted effort over time. An overview of each topic is presented below.

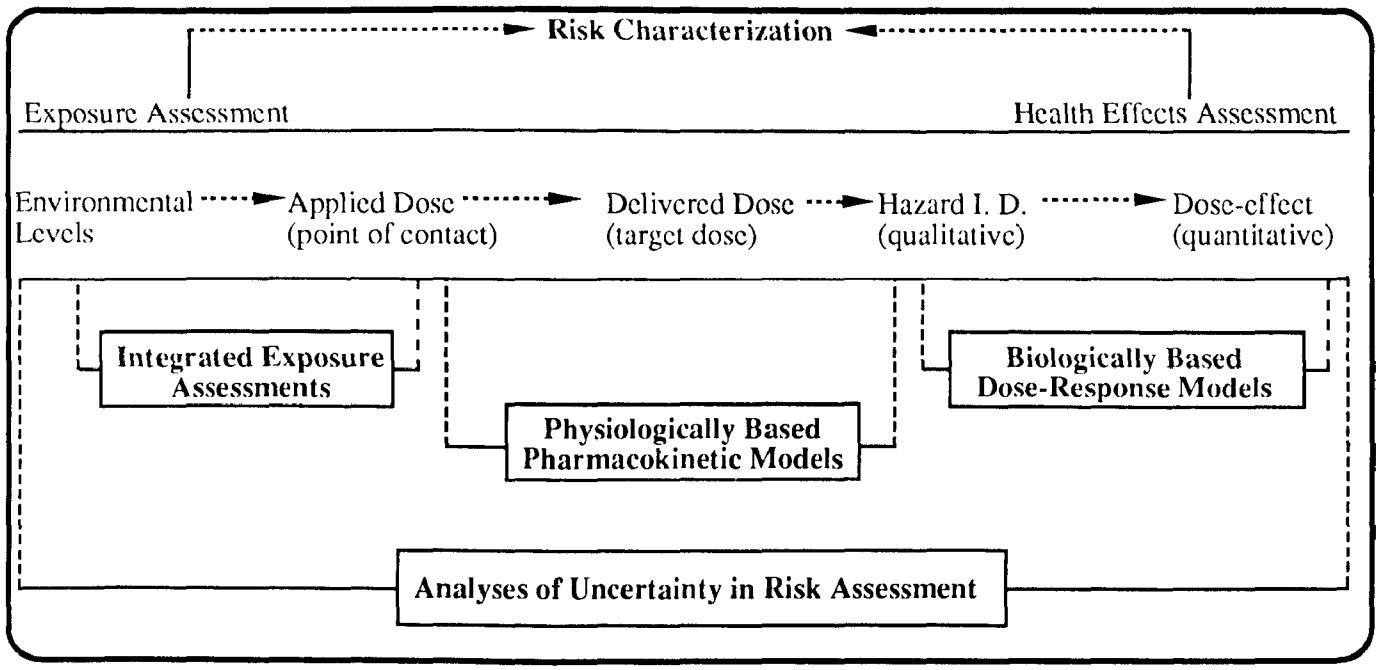

Figure 3. Schematic Representation of the Relationship Between the Four Topics Included in RIIRA and the Major Components of Risk Characterization.

Topic 1 — Analyses of Uncertainty in Risk Assessment

The degree of uncertainty in the qualitative and quantitative aspects of risk assessment is often poorly understood. Research issues related to this topic address the clarification of assumptions and the definition of the uncertainty associated with each of these. Analyses will be conducted to determine which uncertainties are most critical in selected risk assessments and to understand the impact of these uncertainties on the ultimate risk assessment.

Topic 2 — Integrated Exposure Assessment

Exposure assessment (i.e., contact between chemical and humans) is based on either ambient or biological measurements. Ambient measurements can be further subdivided into direct (e.g., individual monitors) and indirect (i.e., combining human activity data with pollutant measurements in important microenvironments) approaches. Research related to predictive exposure techniques will focus on improvement of exposure models through collection of appropriate activity pattern data, microenvironmental pollutant concentration data, and human dose measurements. Another research area will be devoted to improving the quality and quantity of direct exposure assessments, which will be used to generate more realistic exposure estimates. An additional research area will address the uncertainty generated by inconsistent exposure assumptions used in health risk assessments through development of a standardized approach.

Topic 3 — Physiologically Based Pharmacokinetic (PB-PK) Models

Although the trend is to base quantitative risk assessments on dose delivered to the site of toxic action (delivered dose), measurements of applied dose (or exposure concentration) are frequently used as surrogates for the delivered dose, which is usually unknown. Better data on dose delivered to target tissue will help to reduce uncertainties associated with extrapolation from one route of exposure to another, from chronic to acute exposure, from high to low exposure, and from one species to another. While biological factors must also be considered when assessing risk, it is important first to account for the effects of the duration, magnitude, and frequency of the exposure on the dose to the target tissue (i.e., pharmacokinetics).

One area for research will be the accumulation of more experimental data relative to the effective dose responsible for biological effects, including the influence of varying exposure parameters (e.g., duration) on delivered dose. A second research area will address identification of assumptions and conditions for extrapolation from one route of exposure to another. Efforts in this area will focus on reviewing and summarizing information related to route-to-route extrapolations, highlighting critical assumptions and limitations, pro-

viding guidance for risk assessments, and recommending future directions for research. A third research area will concentrate on development of theoretical models and computational methods for making intra- and interspecies dosimetric comparisons. These pharmacokinetic models will depend not only upon physiological parameters of the systems being modeled, but also upon molecular structures and reactivities of chemicals under consideration. Validation of the models will allow scaling of exposure, dose, and effect observed in one situation to a completely different situation (e.g., scaling from animals exposed in a laboratory to humans exposed in an ambient environment).

Topic 4 — Biologically Based Dose-Response (BB-DR) Models

Although a key element in the risk assessment process is estimating the incidence of a specific health effect, human exposure data at relevant levels are not available in most cases. Risk is then generally assessed by high level exposure data from species other than humans and applying an appropriate strategy to extrapolate. A biological mechanism orientation will be used to focus on the conditions under which test species and test systems can be used to predict toxicity in humans. However, since much remains to be understood about the biological aspects of the test species, latitude must be left to incorporate new data into the models. New data will be incorporated into models which will provide insight into the variations that occur in different species and under different exposure situations. The conditions for which data from test species and test systems can be used to predict human toxicity will also be explored. Factors contributing to a health effect of concern will be identified, and directions for research will be dependent upon the current state of mechanistic knowledge for that particular effect.

Research areas address intra- and interspecies extrapolation (e.g., mechanisms of action, species sensitivity), extrapolation of health risk across different exposure scenarios (e.g., variations in route of administration, dose, or dose rate), and incorporation of recent mechanistic concepts into BBDR models (e.g., potential for different biological mechanisms to elicit, initiate, or contribute to health effects). Areas of investigation will include pulmonary, reproductive/developmental, neurological, immunological, and carcinogenic effects.

PROJECT SELECTION

The four topic areas described above constitute the framework for a structured health research program. The desired objective of reducing uncertainties in risk assessment cannot be achieved unless the projects developed to address these topics are supportive of the programmatic goals. To this end four major decision criteria were used to determine the appropriateness of individual projects for inclusion in the program.

1. Projects should focus on major significant uncertainties and knowledge gaps in Agency risk assessments. Important areas for research include assumptions and extrapolations that are used frequently and in which we have little confidence.

2. Projects should have a reasonable probability of success. The proposed work should be technically feasible in terms of existing expertise, resources, and knowledge. The overall program of research should produce a mixture of both short- and long-term products of use to the Agency in risk assessments.

3. Results of the research should directly support the needs of the Agency's risk assessors. Scientists in EPA and elsewhere should be able to apply the results of the research in risk assessments.

4. The results of projects should ultimately have wide application. Results should be widely useful and not be focused on specific situations of limited use. Ideally, the short-term products of this research would be of immediate utility to the Agency, while providing logical building blocks for the long-term improvement of risk assessment methodologies.

Furthermore, the projects must be consistent with the EPA mission and must be the kind of work that EPA (and ORD) are expected to perform; that is, the projects are expected to provide results appropriate to EPA's legislative mandates and regulatory authorities, and to be useful to Program Offices. Since a large amount of the base program addresses other key elements of risk assessment, the ultimate success of the RIHRA program has a direct and, in some cases, a dependent linkage to the ongoing base research program. Finally, although projects selected will have high relevance and a reasonable probability of success, they will not yield instantaneous results. Much of the research needed to reduce the uncertainties in risk assessment is iterative in nature; that is, the research progresses in multiple stages, with significant outputs at each stage. This dictates that both short-term and medium- to long-range research planning and stability are required for the success of this program.

PROGRAM IMPLEMENTATION

Formal responsibility for the RIHRA program will rest with the EPA Interdisciplinary Research Committee, and more specifically, with the RIHRA Subcommittee. As shown in Figure 4, the subcommittee will be composed of the Office Directors (and other key designees) from the participating ORD Offices. It will be the responsibility of this committee to

design, implement and manage the RIHRA program. The Subommittee will coordinate the intramural (e.g., Program Offices, Science Advisory Board, Risk Assessment Council) and extramural (e.g., outside peer-review groups) reviews of the RIHRA program, as well as be responsible for ensuring that the reviews are used to strengthen and improve the research program. The Subcommittee will also establish working groups for each of the major topics that are defined in this document. These working groups will be composed of one permanent member from each participating office and a varying number of other ORD scientists. The working groups will integrate input from their respective offices to develop a focused research plan (down to the project level) for each topic. These research plans will be reviewed and approved by the Subcommittee.

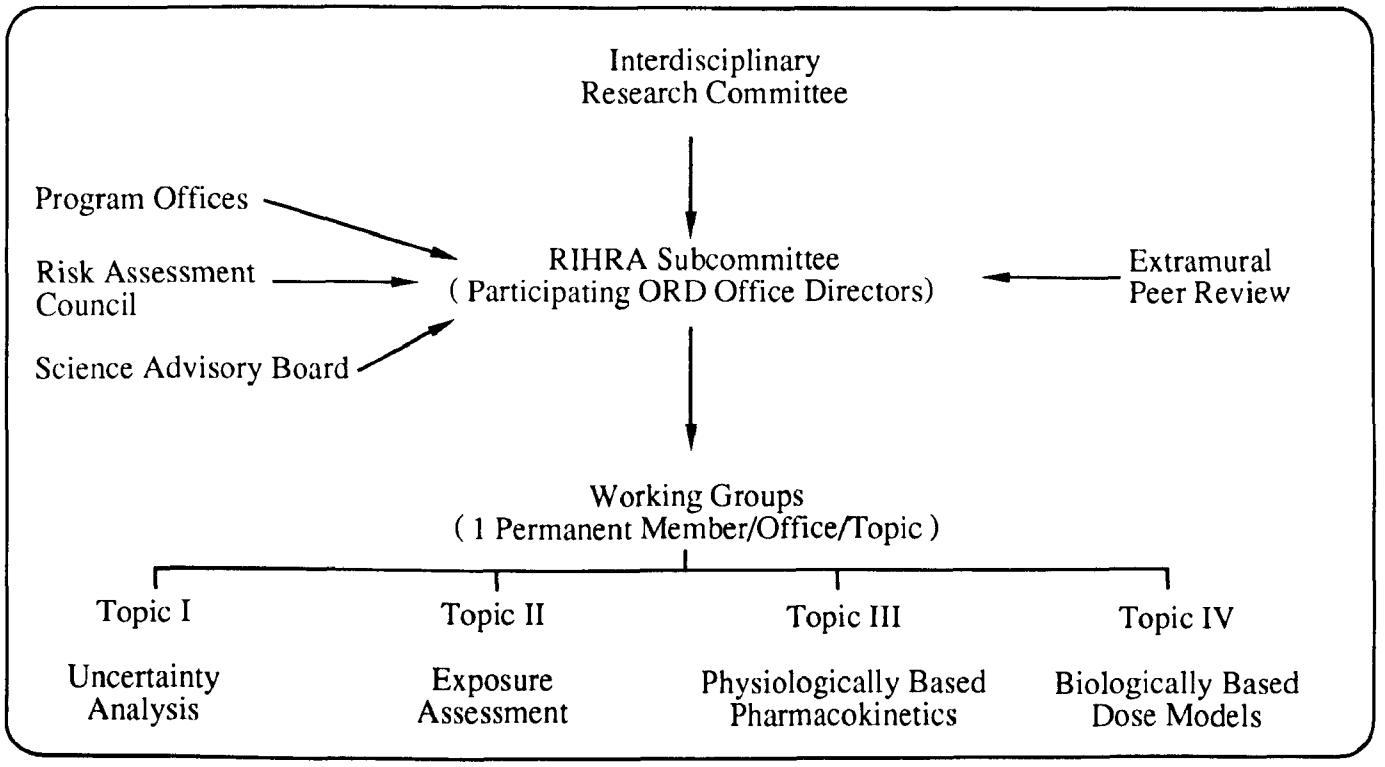

Figure 4. *Proposed Implementation Scheme for the Research to Improve Health Risk Assessments (RIIRA) Program.*

TOPICS FOR RESEARCH

Thus far, most risk assessments have assumed *a priori* that an equivalency of response exists between animals and humans. As one proceeds from the molecular level or biochemical event toward injury at the tissue or organ level, that assumption may become less tenable because of variables such as species differences in repair processes and levels of antioxidant enzymes. If it is sufficiently high, the dose can produce damage at any level from the target molecule to the intact organ, resulting in various disease states. On the other hand, host defense and/or compensatory systems could intervene and might prevent or repair the damage if it is not sufficiently severe. Disease outcome is also heavily dependent upon delivered dose and dose-time relationships. Under some scenarios, defense systems may play a role in the etiology of diseases. The interplay between dose, defense, and outcome is a dynamic one. The lack of information on these interrelated events results in significant uncertainty in current risk assessments and, as a result, the use of a variety of default assumptions.

Due to the paucity of data in many areas, assumptions must be made at various stages of the risk assessment process. Careful consideration of these assumptions for various health effects and exposure scenarios can be useful in the identification of research needs to improve future risk assessments by replacing assumptions with scientifically defensible data. If the research does not refute the assumptions but the new data are not yet sufficient to stand alone, this may lead instead to a more defensible default assumption. In either case, such research will increase our confidence in applying the assumptions used in Agency risk assessments.

In recent years, progress has been made in developing mechanistic models as a means of investigating and improving extrapolations. In such models, the key physiological and biological elements and processes, as well as their interactions, are described. Well constructed models trace the consequences of variation in any key element as it differs among species or dose levels. Such models can reduce the uncertainties in extrapolation in the following ways: 1) The structure of a model embodies a particular theory about what underlying processes are important in the extrapolation and how different elements interact. The model provides a context within which to evaluate the impact of hypotheses about pharmacokinetics or mechanisms of toxic action. 2) Species differences in the underlying biological processes can be determined experimentally, and the impact of these differences on the extrapolation process can then be modeled. This provides a means of developing rational, scientific bases for interspecies extrapolation factors. 3) Differences in the operation of biological processes at different dose levels can be experimentally determined and incorporated into the models. For example, this can allow differences in DNA repair, different levels of cytotoxicity, and various non-linear biological effects to be incorporated into low-dose extrapolation. 4) As new data and theories about special mechanisms of toxic action are developed, mechanistic models provide a means for their quantitative incorporation into extrapolation. For example, the impact of very different levels of chemical stimulation of peroxisome proliferation in different species could be accounted for by modeling the consequences to the chain of biological processes, i.e., carcinogenesis.

In summary, the advantage of the mechanistic approach is that it allows the overall process of extrapolation to be broken up into its biological elements. Experimental data can be developed on independent elements, and the consequences to the overall extrapolation determined. As knowledge of the underlying processes improves, the biological realism of the model improves, and an experimentally testable basis is developed for extrapolations that must currently be done on the basis of assumptions. The models themselves are generic and are applicable to a variety of chemicals, but they can be adjusted to incorporate chemical-specific effects (such as metabolic differences across species or particular mechanisms of toxicity) by the use of experimental data on the effects of a chemical on key biological processes that are elements of the model.

The following sections highlight the specific research topics that are proposed for emphasis in this program. An overview is included to describe why these topics are important, what research they would contain, and where they contribute to the risk assessment process. Although the RIHRA program is presented in a somewhat categorical hierarchy (i.e., topic/issue/activity), it is realized that various research activities may provide important data across these categories (e.g., assessing the effects of varying exposure conditions on delivered dose and health outcome). This will be especially true of projects that are less target-organ specific.

TOPIC 1: ANALYSES OF UNCERTAINTY IN RISK ASSESSMENT

In characterizing the health risks of environmental pollutants for Agency decision makers, the degree of uncertainty in the qualitative and quantitative aspects of risk is often poorly understood. A framework is needed to delineate clearly the various assumptions and alternatives and the degree of uncertainty associated with each. The following research issue related to this topic will be pursued.

Issue 1.1: Uncertainty Analyses

Evaluation of major uncertainties in the risk assessment process as a whole is needed. A rigorous evaluation of where uncertainty is most critical in risk assessments that are used for decisions would improve planning and implementation of research. Granted that much uncertainty exists, this activity will address whether these uncertainties are of such magnitude as to make potential differences in decisions. If so, the types of uncertainties (extrapolation, source assessment, etc.) will be described and, if possible, quantified. This activity also will include investigation of what the end users of risk assessments (i.e., decision makers) would like to see in the way of uncertainty assessment, including both quantitative and qualitative aspects.

Activities within this issue will be a continuation of the current Estimating Assumptions in Risk (EAR) Project initiated by the Risk Assessment Council and an extension of the Risk Assessment Forum projects on uncertainties in exposure assessment that will be initiated in FY88. These activities will include further efforts to identify major assumptions and to assess the magnitude of each. New efforts will be initiated to develop the data base supporting the qualitative and quantitative work described above, with case studies being developed to illustrate the numbers and impacts of the uncertainties in specific risk assessments.

Projects under this issue might include several which explore possible approaches to the problem of uncertainty analysis building upon such formal disciplines as decision analysis theory or evaluating the use of Monte Carlo simulation for assessing environmental sources of risk as compared to other sources (food, lifestyle, etc.). A number of such approaches have been recognized as potentially useful, but further work will be needed to select those better suited for this task.

TOPIC 2: INTEGRATED EXPOSURE ASSESSMENT

Over the past several years, exposure assessors at EPA and elsewhere have approached the problem of assessing the exposure (contact between chemical and organism) or dose (amount entering the organism after contact) in three ways, one direct and two indirect. The direct measurement approach involves real time measurements of contact intensity through the use of personal monitors such as radiation badges or active devices that pump and trap volatile chemicals, through analysis of the amounts and contamination levels of food and water ingested, and through methods to measure dermal exposure. The indirect methods can either be predictive, using models for pollutant behavior or human (ecological) behavior or, under limited conditions, they can be reconstructive, using body burden and knowledge of pharmacokinetics to back-calculate what the exposure must have been to result in the observed levels. All of these methods have strengths and weaknesses, and all have associated uncertainties for their intended uses. Reducing uncertainty in the reconstructive approach is discussed separately under Topic 3.

Predictive exposure assessment techniques have been particularly appealing to a regulatory agency such as EPA, since they allow the evaluation of the impacts that regulatory options have on risk. Predictive techniques need not only estimate (or measure) concentrations of pollutants but may also relate those media pollution levels to what is being contacted by the target populations. Clearly, living organisms are mobile in the environment and the assumption of constant levels of exposure over time for an individual or population is at best an approximation, at worst a major misrepresentation of the actual situation. In the case of human exposure, knowledge of human activities, activity patterns, and ways to incorporate this information into the assessment has long been a weak link and thus the origin of much uncertainty in exposure assessment. The first two issues discussed below (2.1 and 2.2) deal directly with reducing that uncertainty.

A second major area of uncertainty is how the data for exposure assessment are taken in the field. For measurements to be used in predictive assessments and also for measurements for directly determining exposure, the methods used to collect the data are particularly important if the data are to be used appropriately in an assessment to reach conclusions with minimal uncertainty. Of particular recent interest in this area, for example, is the question of how a series of short-term duration exposure peaks would differ in a risk context from equivalent lifetime long-term exposures at fairly constant but lower levels, and how this information can best be measured in the field and incorporated into the exposure assessment. Issue 2.3 addresses this topic, which is related to the work proposed under Issue 4.3 (which addresses how information from different exposure conditions would be used in a dose-response relationship). Taken together, Issues 2.3 and 4.3 will reduce uncertainty in risk assessments by making the assessments more closely describe what happens in the actual environment.

A third major area of concern in reducing uncertainty in exposure assessments is the inconsistency in assumptions used

by various assessors for similar exposure situations. This often leads to two assessments of the same situation done by different assessors (for example, an Agency assessment of a Superfund site and an assessment sponsored by a potentially responsible party) which use somewhat different methodology and parameter values, and thereby reach estimates of exposure or risk that are substantially different. Issues 2.1 to 2.3 will also address the way EPA approaches exposure assessment, both by developing data that can be used consistently across many assessments, and by standardizing the approach to estimating population exposures related to certain commonly evaluated situations such as incinerators, waste sites, or indoor air.

In summary, the proposed program in exposure assessment focuses on three major areas of uncertainty: acquiring better information on human activity patterns as they relate to exposure estimates, improving methods to obtain exposure assessment data, and standardizing the ways the Agency uses these data. The following paragraphs discuss the issues in more detail.

Issue 2.1: Human Exposure Models

More work is needed to develop and validate human exposure models which can generate realistic predictions of exposure to chemicals using human activity patterns and source information. Human exposure models seek to combine the concentrations of pollutants people experience in various microenvironments (microenvironmental exposures) with the time spent in those microenvironments (human activity patterns), and to integrate this information with the resulting doses experienced from those microenvironments. Such models should address all the microenvironments in which people visit or reside (homes, stores, schools, subways, buses, automobiles, workplace) and must include multiple routes of exposure (air, food, drinking water). In particular, they should take into account indoor and in-transit microenvironments. The research problems to be addressed in human exposure model development lie not only in development of improved exposure models based on existing data (2.1.1), but also in validating these models (2.1.2).

2.1.1: Development of Human Exposure Models.

Research on this topic will proceed by first constructing human exposure models for a family of important pollutants that EPA regulates (e.g., respirable particles, volatile organic compounds, semivolatile organics, formaldehyde) using the best microenvironmental data and the best activity pattern data available. For those pollutants for which microenvironmental field data are missing, special microenvironmental field investigations will be conducted to construct the needed submodels. The human activity pattern data and resulting microenvironmental concentration data will combine human activities, time budgets (See Issue 2.2), and microenvironmental concentrations using a generalized exposure equation. Suitable pharmacokinetic models will be incorporated into the resulting exposure models to estimate body burden and dose from these chemicals.

2.1.2: Model Validation.

Once the models are developed, they will be validated by testing them with field data collected in total human exposure field studies for a variety of situations. Uncertainty ranges around the predictions will be characterized. After the uncertainty of the model is characterized (validation phase), guidance for the risk assessor in the use of human exposure models will be incorporated into guideline documents. The guidelines will include discussion of the appropriateness of various exposure situations and the expected accuracy/uncertainty of the models.

Issue 2.2: Human Activity Patterns

More data are needed on human activity patterns to improve exposure analyses in risk assessments. Human activity patterns, sometimes called "time budgets," are records of what people do, where, when, and for how long. Recent findings from field studies of human exposure, such as the Total Exposure Assessment Methodology (TEAM) studies, have shown that an individual's activities are critical in explaining the exposures of the population to environmental pollutants. Current predictive exposure assessment methods often use assumptions that essentially treat an entire population as a homogeneous unit rather than a collection of individuals. This is done for the most part because the aggregate data on population activity patterns are unknown. Development of these data will allow the Agency to advance to a much more realistic way of predicting exposures using probabilities. For example, instead of using a worst-case scenario, activity pattern information will allow exposures to be presented as a frequency distribution, allowing statements to be made about the average case, the 90th percentile exposure, etc. Thus current exposure assessment methods will be replaced by a new generation of techniques.

The initial phase will entail a critical review of all previous activity pattern-time budget studies and the subsequent development of an improved activity pattern questionnaire. This questionnaire will focus on those activities which result in exposure to pollutants. Part of this task will include development of an automated data-logging activity diary. (The development of a microprocessor-driven activity diary would be a major innovation in these studies and should result in much improved data.)

Issue 2.3: Data Base on Indirect Exposure Parameters

More work is needed to improve our data base on parameters used to make indirect exposure estimates and to clarify how to use them. More information is needed on the ranges and distributions of parameters used in indirect exposure assessments, such as ingestion rates, exposure durations, contact rates, and short-term vs. long-term exposures. The Regions have repeatedly requested guidance on such topics to improve consistency in risk assessment. Guidance is also needed on how to apply these factors to create different scenarios such as typical and reasonable worst case.

Two topics that will receive special attention under this issue relate to 1) predicting the incidental soil ingestion of children based on site-specific parameters such as ground cover and weather; and 2) determining the contribution of short-term peaks to total exposure. Significant controversy exists about the amount of soil ingested by children, and this is a very significant exposure route in many assessments. Field work will be done to develop the data base needed to establish the relationship among these variables.

Also, it has become clear that for many pollutants, short-term peaks are extraordinarily important contributors to exposure. Besides their importance as contributors to exposure, short-term peaks are important in the dose-response portion of the risk assessment (see Issue 4.3). Methods will be pursued for measuring short-term peaks and then incorporating this information in establishing the dose-response relationships. These data would then be used to supply risk assessors with basic parameters and ways to incorporate these parameters into exposure assessments.

TOPIC 3: PHYSIOLOGICALLY BASED PHARMACOKINETIC (PB-PK) MODELS

The trend over the last few years has been to base quantitative risk assessments on the "delivered dose"—the dose of proximate toxicants, whether parent compound or metabolite, at the tissue site of toxic action—rather than on the applied dose or ambient concentration. The determination of this delivered dose is an extension of exposure assessment, in that the direct exposure of the actual target tissue is examined free of the various physiological fate and transport processes by which the body filters, attenuates, degrades, and modifies compounds absorbed from its environment. Uncertainty will be reduced by knowing more about the effects of different conditions of exposure on the amount and pattern of delivered dose. For example, examination of delivered dose will be very useful in comparing the toxic results of exposures by different routes of administration. In this way, extraneous factors such as different degrees or rates of absorption can be accounted for, resulting in more meaningful comparisons. The ability to estimate tissue-level doses also is necessary for progress in mechanistic biological modeling of toxicity, which will require extensions of exposure assessment to the internal sites where these mechanisms occur.

In risk assessment as currently practiced, measurements of applied dose or exposure concentration are used as surrogates of the unknown delivered dose. The equivalencies among different conditions of exposure are set by assumptions, many of which have little empirical support and, therefore, represent sources of uncertainty. Among the most critical uncertainties associated with extrapolation from experimental to actual conditions are assumptions about: (1) route-to-route extrapolation-comparability of exposure by different routes of administration (by accounting for differences in absorption, bioavailability, and first-pass metabolism); (2) chronic-to-acute extrapolation-comparability of different regimes of exposure, such as the effect of repeated versus single dosing on dose delivery, and the equality of episodic, peak, and chronic exposures totalling the same cumulative dose (by comparing the resultant delivered doses); (3) high-to-low-dose extrapolation-proportionality between external exposure level and the resulting delivered dose for high exposure studies, compared to lower levels typical of environmental exposure (by accounting for sources of non-proportionality such as saturation of metabolism, utilization of different pathways of biotransformation, and non-linear binding); and (4) species-to-species extrapolation -scaling or translation of dose to determine exposures yielding equivalent doses in different species, especially when extrapolating toxic effects in experimental animals to those expected in humans (by examining species differences in the degree of delivery of given applied doses).

One way to reduce these uncertainties is to obtain data on doses at a more biologically meaningful level, i.e. delivered dose at the target tissue. Of course, the examination of delivered dose does not answer all questions about extrapolation in risk assessment, since the equivalency of effects across species is determined not only by relative dose delivery but also by any species differences in reactivity or susceptibility to a given delivered dose. Similarly, the extrapolation of effects to low doses or from acute to chronic exposures depends not only on the delivered dose differences in these circumstances, but also on the relative toxicological effects of different degrees and durations of tissue exposure to the proximate toxicant.

The ability to determine patterns of internal exposure at particular tissue sites focuses attention on the mechanisms of action. For example, it may not be clear at which target site the delivered dose should be described. Depending on the mechanism of action, the toxic response may be a function of quantity of metabolite formed, number of adducts or other covalent reaction products formed with crucial cellular macromolecules, extent of reversible binding to specific receptors, average

toxicant concentration, peak toxicant concentration, or duration spent above a crucial concentration. There may be countervailing repair processes of limited or perhaps saturable efficacy. These other factors can and probably do vary among species, strains, sexes, previous histories of exposure, and physiological condition of the subjects. In summary, although examination of delivered doses can remove a great deal of uncertainty from the various extrapolation processes in quantitative risk assessment, it is not a panacea. The other biological factors cannot be addressed, however, without first accounting for and eliminating the confounding and obscuring effects of dose delivery and pharmacokinetics. Thus, progress in pharmacokinetics is central to performing biologically rational risk assessments.

Issue 3.1: Experimental Absorption and Biological Parameter Data

More experimental and physiological data relative to the effective dose responsible for biological effects are needed for risk assessments. Often both the amount and the biologically active form of the toxicants are unknown. This results in the use of uncertainty factors to a greater extent than would be necessary if appropriate experimental data on the absorption, metabolism, transport, and elimination of the parent compound and its metabolites were available. Such experimental data can be coupled with studies on toxic mechanisms of action to reduce uncertainties inherent in the use of external exposure or administered dose.

3.1.1: Experimental Absorption Studies.

Efforts to develop theoretical models (see below) to study the uptake and distribution of chemicals need to be complemented with experimental studies in which the uptake, distribution, and time course for elimination of the parent chemical and various metabolites are determined in the major body organs for various species. Moreover, the experimental dosimetry studies will support the guidance and design of biological experimentation in a number of organ systems, such as reproductive, nervous, and pulmonary. An integrated approach is needed to encompass oral, dermal, and inhalation exposures for adult, neonatal, and fetal animals with a linkage to human studies where possible.

3.1.2: Physiological and Anatomical Parameters Across Species.

The great advantage of physiologically based pharmacokinetic modeling is that the model structure is common across species—only the scale is changed. The model for one species (and the attendant insights about delivered dose) can be applied to another if the various physiological and anatomical parameters governing the kinetics of the compound in the first species are replaced by those of the other. Physiological parameters describe capacities and volumes (organ weights, blood volume, partition coefficients, lung capacity, etc.) and rates (blood flows, metabolic rates, ventilatory rates, elimination rates, etc.). Anatomical parameters describe the structure of an organ, such as the size and number of airways in the lung, and the number of glomeruli and the structure of the nephrons in the kidney. Once most of these values are determined, they can serve as input data in the construction of models for many compounds. Caution must be exercised when making generalizations if there is any evidence that the chemical being modeled can itself influence the various physiological and anatomical parameters which help to define the model. Metabolic parameters can be very chemical-specific, but even these can benefit by characterization of major biochemical pathways for metabolism of xenobiotic compounds.

3.1.3: Influence of Varying Exposure Parameters (Route, Duration, Rate) on Delivered Dose.

In Section 3.1.1, experimental dosimetry studies were described that would be associated with health effects studies. High-to-low dose extrapolation is an area with major uncertainties due to a lack of pharmacokinetic and pharmacodynamic data. Also, one of the extrapolations that must be made in quantitative risk assessment is from the experimental dose regimen used in an animal toxicological study (repeated dosing or chronic exposure, usually for extended periods) to the expected human exposure patterns (which may be single exposure or chronic, episodic or continuous). The doses are usually compared on a total cumulative dose basis, e.g., the total mg/kg or ppm/h of exposure. However, both dose rate and dose level can affect the pharmacokinetics of a compound and hence the amount that is delivered to the target site. For example, high dose levels may include pathways that at lower dose levels do not contribute to metabolic conversions which are linked to the toxicity of the compound.

As work progresses under activities 3.1.1 and 3.1.2, investigations will begin to examine the influence of route, duration, and rate of exposure on delivered dose to understand better the uncertainties inherent in extrapolating toxicological data obtained using one exposure scenario and species to that of another exposure scenario and species. Data obtained from such projects will enable guidance to be developed for improving risk assessment methodologies.

Issue 3.2: Route-to-Route Extrapolation

Research is needed to identify the assumptions and conditions for route-to-route extrapolation to be scientifically defensible in risk assessment. There are many chemicals for which risk assessments are needed for a given route of exposure but for which the necessary pharmacokinetic and toxicological

data are not available. Instead, information may be available on toxicological effects associated with a different route of exposure. Route-to-route extrapolation can use such data for the exposure route of interest. Development of PB-PK models needed to perform route-to-route extrapolation would allow the maximum use of data from experiments other than by the route of concern. For example, the derivation of some inhalation reference doses (RfDs) would be facilitated if the conditions under which oral toxicity data could be used were better understood. Having a better definition of the problems in hand, a research program can then be proposed that supports such extrapolations.

Prior to expanding current efforts on route-to-route extrapolation, the Agency will commission the NAS or some like body to assemble a panel of experts to: 1) discuss the critical assumptions and limitations related to route-to-route extrapolation, 2) provide specific guidance for risk assessments, and 3) recommend research areas which would facilitate route-to-route extrapolation in the future. This represents an extension of past activities of organizations like the NAS to emphasize the potential use of pharmacokinetics in risk assessments. Since various EPA Program Offices are engaged in extrapolating oral toxicity data to inhalation, the panel will be requested to focus on this issue. Also, dermal versus oral absorption extrapolations would be a priority. ORD will seek Agency-wide participation to identify questions for the panel to address. Research recommendations arising from this exercise will be incorporated into ongoing ORD research programs.

Issue 3.3: Theoretical Models

Theoretical models need to be developed for a unifying structure upon which intra- and interspecies dosimetric comparisons can be made in risk assessments. Development of theoretical PB-PK models for chemicals will enable better estimates of dose-equivalence across species for various rates and durations of exposure. The development and modeling of pharmacokinetic information from various species will allow for the implicit determination of pharmacodynamic differences among species. Improved mathematical formulations for the disposition of compounds following oral, dermal, or inhalation exposure are needed that incorporate age- and species-specific input parameters, such as partition coefficients and blood flow, and incorporate the properties of the molecules being considered. Validated PB-PK models will permit us to scale exposure, dose, and effect observed in one circumstance (animals in a controlled environment in a laboratory) to completely different circumstances (human beings in an uncontrolled ambient environment). Successful work in these areas offers the potential to reduce the magnitude of the uncertainty factors (e.g., 10-fold interspecies extrapolation) used in various risk assessments.

3.3.1: Theoretical PB-PK Models.

Theoretical PB-PK models provide a foundation for making intra- and interspecies dosimetric comparisons in risk assessments. Although specific chemicals may be restricted environmentally to only some exposure routes, a general need exists to develop models for all routes of exposure (oral, dermal, and inhalation). A major impetus for the application of pharmacokinetics to risk assessment is the suspicion that experimental rodents may have quite different degrees of delivery of an applied dose to the site of action than humans may because physiological and metabolic processes in small mammals occur at much greater relative rates than in humans. While pharmacokinetic differences are not the only source of differences in the potency of a chemical in various species, extrapolation procedures should account for differential dose delivery.

3.3.2: Structure Activity Relationships in Mechanistic Models.

The actions of xenobiotic agents in a biological system are a direct consequence of their molecular properties and are produced by a variety of specific molecular interactions and non-specific processes. They may interact with receptors, enzymes, and macromolecules involved in transport by fully or partially mimicking the relevant properties of endogenous substances or by evoking the detoxification potential of the biological system. The scientific basis for the evaluation of the risk to human health of specific chemicals will be enhanced by computational pharmacokinetic models that depend not only on the physiological parameters of the systems being modeled but also on molecular structure and reactivities. These models will provide important insight into the transformation, distribution, and deposition of the chemicals under consideration as these properties relate to the biological activity of the chemicals. Additionally, as the potential risk of many chemicals first must be assessed when all the relevant data are not available, a computational approach that allows the estimation of the molecular properties in the model has a significant advantage.

3.3.3 Models Linking Exposure to Dose to Biological Outcome.

Once estimates of delivered dose have been made, a great deal of uncertainty still exists about how they should be incorporated into the current quantitative risk assessment methodology. The delivered dose information will aid in the extrapolations, but other factors outside of pharmacokinetics also influence the extrapolations. Species may have different degrees of response to a given delivered dose, not only because

of possible idiosyncratic differences in defenses, but also because the physiological processes interfered with in the course of the toxic reaction are themselves subject to scale differences in different-sized mammals. When focusing on "biologically effective dose," one must also incorporate knowledge of the biological reaction to that dose to make proper use of the pharmacokinetic data. Projects under this issue will examine the interactive role of pharmacokinetic factors and pharmacodynamic factors. For example, efforts might focus on species differences in repair and tissue-dose kinetics as they relate to the overall extrapolation process. The activities in this section are linked to those in Section 4.2.3 (Interaction of exposure parameters on outcome).

TOPIC 4: BIOLOGICALLY BASED DOSE-RESPONSE MODELS

The quantitative component of the risk assessment process entails estimating the incidence of a particular health effect at human exposure levels. Ideally, human data would be available at the relevant exposure levels. However, the data available usually reflect higher exposures, more often based upon experiments in test species than obtained from human studies. As such, the risk assessor is required to select and apply an appropriate strategy (e.g., RfDs or mathematical models) to perform a high-to-low dose extrapolation. The major uncertainty in quantitative risk assessment evolves from this selection process and the often untested assumptions that may guide selection. The final risk estimate may vary by orders of magnitude depending on the approach (model) applied.

The development and application of BB-DR models can greatly reduce the uncertainties in quantitative dose-response assessment. In the BB-DR approach, key physiological elements and processes, as well as their interactions, are described. Utilization of such information facilitates the selection of a biologically plausible strategy upon which to base extrapolations necessary for risk assessments. Moreover, such models may be able to account for the variation in any key element as it differs within and among species or varying exposure conditions. The integration of biologic/mechanistic data into the modeling process can also allow the risk assessor to support or modify "default" assumptions that are often applied in the risk assessment.

Utilizing a biologic/mechanistic orientation, research under this initiative will be directed at determining the conditions under which data obtained in test species and test systems can be used to predict toxicity in humans. Such efforts will reduce the uncertainties associated with existing methodologies as well as lead to the development of new BB-DR models for human health risk assessment. Ancillary components of these activities will be the development of protocols to (1) validate these models and, (2) facilitate their actual risk assessment application.

The development of BB-DR strategies will entail both the utilization of existing data and the generation of new data; the extent to which those options are exercised will, in part, be a function of the state of mechanistic knowledge for a given health effect. The selected issues represent those for which major uncertainties exist. The proposed research will reduce these uncertainties by confirming or replacing assumptions with scientifically defensible data. The specific issues to be addressed are as follows: (1) intra- and interspecies extrapolation; (2) extrapolation of health risk across different exposure scenarios; and (3) delineation and incorporation of recent mechanistic concepts into the development of BB-DR. Research to help clarify these issues will emphasize especially pulmonary, reproductive/development, and neurological health effects with a smaller effort devoted to immunological and cancer effects.

Whereas the primary focus of this research is to better understand the role of various biological processes on chemically induced injury, the models should be flexible enough to incorporate new information as it is obtained.

Issue 4.1: Inter/Intraspecies Extrapolation

Considerable uncertainty exists as to the factors responsible for differences in response within and across species. Research is needed to elucidate the critical physiologic and mechanistic factors that contribute to the health effects of concern in the risk assessment process. Such research will improve the basis on which to adjust for intra- and interspecies variability in dose-response extrapolations.

4.1.1: Homologous Models.

To determine the extent to which effects observed in one species can be extrapolated to another, research will be performed to ascertain whether effects in animals are analogous (i.e., superficially similar) or homologous (i.e., resulting from a common mechanism of action) to those in humans. Research emphasis will be placed on evaluating species similarities and differences in both mechanism and expression of a given outcome. As such, these efforts will not only attempt to confirm the existence of homologous mechanisms for inducing specific toxicities (i.e., disease), but also the degree of homology in the expression of such disease (i.e., comparable outcome).

4.1.2: Interspecies Sensitivities.

Using pharmacokinetic models (Topic 3), we will be able to determine the effective dose at a given target site. However, given equivalent target doses, we are still left with questions regarding interspecies differences in sensitivity that need to be addressed independently. Research will focus on the degree to which dose-effect functions for a given health effect (e.g.,

reproductive failure) differ across species, as well as the degree to which the relative sensitivity of different health effects (e.g., reproductive versus neural) vary across species at a given dose. A component of this activity will determine the appropriate dose metric for expressing and comparing a given dose across species (mass/unit volume, mass/unit area, etc.).

4.1.3: Intraspecies Sensitivity.

This research will characterize the factors that may contribute to differing sensitivities in response to chemical exposure among individuals of the same species. Variables to be evaluated include age of the individual (developing, adult, or aging organism), previous or current health status, and genetic makeup. Such data will allow for a better estimate of the differential probability and extent of a given health risk for particular subpopulations. An important aspect of efforts under this activity will be determining how these factors interact with pharmacokinetics to produce intraspecies differences in sensitivity.

Issue 4.2: Exposure Scenarios

Major uncertainties exist in our knowledge of how variations in dose-rate, intensity, and duration of exposure to environmental pollutants affect toxicological outcomes in humans. Research efforts in this risk assessment issue are needed to determine the effects of varying route, dose, dose-rate, duration, and cumulative dose on health outcomes. Attention also needs to be directed towards defining the continuum of effects and their toxicological significance as a function of exposure. The intent of these efforts is to develop biologically based dose-response models wherein the data and assumptions that are utilized realistically reflect human exposure scenarios. Because of the nature of this research, some activities are expected to be crosscutting with Topic 3 (i.e., characterizing the behavior of the delivered dose under different exposure conditions). Clearly, exposure scenarios are important determinants of outcome for a number of health endpoints. Research in this area is therefore critically important to risk assessment and risk management.

4.2.1: Mechanisms across dose.

Important in any extrapolation effort is knowledge of whether the mechanism of toxicity varies as a function of dose. Testing protocols that evaluate many toxicological endpoints use some approximation of the "maximum tolerated dose" as their high dose with lower doses being mathematically reduced multiples of that level. In evaluating dose-response relationships, it is often assumed that the mechanism of toxicity does not vary as a function of exposure scenario, and that novel or secondary mechanisms do not influence outcome at these very high exposure rates. Yet the experimental subjects may be exposed to conditions that might well exceed their capacity to biotransform and excrete the active moiety, might saturate or cause disruption of natural protective/repair mechanisms, and/or might trigger nonspecific stress responses. Because of the similarity of protocol designs, results from studies on the validity of effects caused by very high dose exposures cut across multiple areas of toxicological significance.

4.2.2: Sensitivity of endpoints as a function of dose.

In describing the full range of effects in a dose-response study, endpoints change in severity from biochemical alterations, to physiological changes, to pathological conditions, to the ultimate effect of mortality. For the risk assessment process it is important to understand the progression of biological effects in terms of adaptive responses, compensatory responses, and overtly adverse or pathophysiological responses. Research efforts should therefore be directed at defining the full extent of responses throughout the experimental dose range, the interrelationships, and biological significance.

4.2.3: Interaction of exposure parameters on outcome.

At one extreme, chemicals may exert their effects when a critical body burden is exceeded, irrespective of the level and duration of exposure. At the other extreme, the toxicity of a chemical may depend on the dose rate or duration of exposure. In these latter cases, the toxic effects of a short-term exposure to high concentrations may be very different from one produced by long-term, low-level exposure. In some disciplines of toxicology, this issue translates into whether it is the peak concentration or the cumulative exposure that is the trigger for inducing toxicity. It is important, therefore, to perform research aimed at improving our understanding of the interplay among rate, intensity, and duration of exposure as it affects the toxicological outcomes.

Issue 4.3: Mechanistic Variation

It has become increasingly apparent that a variety of biological events may contribute to the occurrence of a given health effect. The intent in this area is to develop dose-response models that take into consideration the potential for different biological mechanisms to elicit, initiate, or contribute to the health effects of concern. To date, the primary efforts in this area have been in delineating the role of non-genetic events in the development of dose-response models for cancer. It is envisioned that this effort will continue, while comparable considerations will be given to the variety of mechanistic path-

ways that may contribute to mutagenic events or other target organ toxicities.

This research program will assess risks of nongenotoxic carcinogens including the development of models incorporating biological data on promoters. An initial step would be to review presently used models for carcinogens to determine whether alternative models can be developed. Such a review will attempt to define explicitly the assumptions used in the current models and test the sensititivity of the model to changes in these assumptions. Research focused on promoters will take advantage of some of the known biological activities associated with these chemicals. A promising model that would benefit from this research is the Moolgavkar and coworkers multi-stage model that requires specific experimentally derived constants not currently available. The determination of these constants could help to define and test the Moolgavkar model for its application to risk extrapolation.

SUMMARY

This document presents the objective, rationale, and approach for a research program to improve health risk assessments. The program is designed to improve our understanding of the relationship between exposure (applied dose), dose to target tissue (delivered dose), and related health effects, primarily by providing data on basic biological mechanisms. Four major topic areas were chosen for emphasis: analysis of uncertainty in risk assessment, integrated exposure assessment, physiologically based pharmacokinetic models, and biologically based dose response models. Important research areas within each topic were identified and evaluation criteria for selecting individual projects to address the research needs were established. It is unrealistic, however, to expect that the relatively limited resources devoted to this program will resolve all of the uncertainties inherent in health risk assessment. Nevertheless, by focusing the resources through a structured and integrated program it will be possible to make significant improvements in EPA's health risk assessments.